IATDMCT 2026
645 abstracts reçus à la date du mercredi 14 octobre 2026

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1- Pharmacologie moléculaire, cellulaire, préclinique

00004
Modulation of striatal cAMP levels: A key pathway in the treatment of hyperkinetic movement disorders

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Hyperkinetic movement disorders are abnormal involuntary movements, most notably dystonia, chorea, myoclonus, dyskinesia, tremor. They can impair quality of life. Dysregulation of cyclic AMP (cAMP) pathway and associated striatal dysfunction have been implicated in hyperkinetic disorders, including genetic causes like Huntington Disease, and drug-induced causes like levodopa-induced-dyskinesia in Parkinson. Studying a disorder with primary disturbance of the striatal enzyme

producing cAMP would give a unique opportunity to unravel common mechanisms underlying hyperkinetic movement disorders.

We used a translational approach to characterize ADCY5-related disorders pathophysiology and treatment, for which little is known. ADCY5 encodes adenylyl cyclase 5, key enzyme for striatal cAMP synthesis. Pathogenic variants in this gene result in mixed hyperkinetic movement disorders (MxMD-ADCY5).

Materials and methods

Our translational approach in humans and mice investigates the link between cAMP signaling pathway alterations in striatal neurons and hyperkinetic movement disorders.

To prove the putative effect of caffeine on MxMD-ADCY5, we conducted a first-in-class, proof-of-concept, prospective double-blind randomized crossover trial in two patients. To understand underlying mechanisms of therapeutic effects, we generated an MxMD-ADCY5 mouse model, that we characterized with behavioral, pharmacological, biochemical, -omics and cellular imaging studies.

Results

We proved in a clinical trial that motor phenotype of two patients with MxMD-ADCY5 was significantly improved by caffeine. Abnormal movements were inversely correlated to caffeine blood levels. We then investigated the underlying mechanisms to explain this therapeutic effect in the MxMD-ADCY5 mouse model. An increase of striatal AC5 specific activity was associated with Adcy5 disease-causing mutation. Motor phenotype of mutant mice and cellular consequences were partially reversed by caffeine. We demonstrated this positive effect occurred through A2AR blockade in indirect pathway striatal projection neurons.

Discussion / Conclusion

Our translational experiments provide new insights into pathogenesis and treatment of hyperkinetic movement disorders. Fine modulation of cAMP levels in these neurons represents a key pathway in hyperkinetic disorders treatment, especially dystonia/dyskinesia

Reference(s)

Yuan, Ruiyi, Emmanuel Roze, Mohamed Doulazmi, et al. s. d. « Modulation of striatal cAMP levels: a key pathway in the treatment of hyperkinetic movement disorders ». iScience. https://doi.org/10.1016/j.isci.2025.114457.

Keywords

Movement Disorders, ADCY5, cyclic AMP, Adenylyl cyclase 5, striatum, adenosine receptor

00085
Alteration of α1-adrenergic signaling in TPC-deficient mouse aorta

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Two-Pore Channels (TPCs) are non-selective cation channels known to release Calcium (Ca^{2+}) from endosomes and lysosomes, upon Nicotinic Acid Adenine Dinucleotide Phosphate (NAADP) stimulation. The two isoforms TPC1 and TPC2 are ubiquitously expressed in the vasculature. Here, we evaluated the role of TPC-dependent Ca^{2+} signaling in mouse aortic vasoreactivity.

Materials and methods

Aortas, harvested from wild-type (WT) and TPC1/TPC2-deficient (TPC KO) male mice, were mounted in an organ bath system to assess responses to several contractile agents [a 60 mM KCl depolarizing solution, an α1-adrenergic agonist (phenylephrine, PE), or a Thromboxane A2 mimetic (U46619)]. Some aortic rings were frozen for Western Blot analysis.

Results

Among the contractile agents tested, only the response to the α1-adrenergic agonist PE was impaired in the absence of TPCs. The maximal contractile response to cumulative PE concentrations was significantly increased by 55% in TPC KO compared with WT aorta.

When PE was applied at a single concentration, the contractile response displayed a biphasic profile. In the absence of TPCs, the initial phasic component, attributed to IP3-dependent Ca^{2+} mobilization, was unchanged. In contrast, the amplitude of the sustained tonic phase, reflecting Ca^{2+} influx through L-Type calcium channels (LTCC) and store-operated calcium entry (SOCE) was markedly enhanced compared with WT.

Pretreatment with the NO-synthase inhibitor (L-NAME) potentiated the PE-induced contractile response to a greater extent in WT than TPC KO aorta, thereby abolishing the observed difference between genotypes.

Western blot analysis revealed no change in protein expression of the LTCC α1C subunit or IP3 receptor in TPC KO aorta, but α1-adrenergic receptor expression was reduced compared to WT.

Discussion / Conclusion

These data suggest a functional crosstalk between the α1-adrenoceptor and TPCs that regulates Ca^{2+} influx, under NO dependency, highlighting a specific contribution of TPCs to the vascular α1-adrenergic response.

00150
Quercetin delivery system using molecular imprinting polymers based on biocompatible chitosan increase it bioavailability and long term antioxydant effect

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Polyphenols are a promising therapeutic treatment due to their antioxidant properties, but they have reduced stability and absorption in humans, needing use of high-dose treatments[1,2]. Given that molecularly imprinted polymers (MIP) gained interest as innovative drug delivery system allowing increased drug stability and extended release, we developed chitosan-based MIP (MIP-CS) as biocompatible nanocarrier of quercetin.

Materials and methods

After quercetin-MIP-CS polymerisation procedure optimization, the antioxidant effect of our lead formulation was evaluated using H2O2-induced toxicity in neuronal cell lines. Bioavailability and distribution were assessed using fluorescent polymers (fluorescein-chitosan and rhodamine-quercetin): first *in vitro* through internalization studies in SH-SY5Y cells using immunocytochemistry and correlative light electron

microscopy method (CLEM) detection; then, using *in vivo* imaging systems (IVIS) detection in mice (longitudinal study from 1 to 24h after gavage in mice). We used native quercetin as positive control and non-imprinting polymer (NIP, same polymerisation method, without quercetin) as negative control.

Results

Quercetin-MIP-CS showed a stronger antioxidant effect than NIP and native quercetin on SH-SY5Y cells in 24h co-treatment with H2O2 while preventive effect using quercetin treatment before H2O2-toxicity is under evaluation. *In vitro* bioavailability and distribution studies showed 60nm-nanoparticles colocalised in endosome while CLEM experiment allowed subcellular localization of both MIP-CS and released quercetin after 24h-treatment (persistence of these particles in cell compartment is currently evaluated). Finally, *in vivo* results showed presence of fluorescent Quercetin-MIP-CS and rhodamine-quercetin in bladder and an accumulation in digestive tract after 2h persisting up to 24h for fluorescent Quercetin-MIP-CS but only 8h for rhodamine-quercetin.

Discussion / Conclusion

Our results suggest nanoparticles internalisation into cells via energy-dependant endocytosis[3] allowing prolonged release of quercetin from internalised MIP. Confirmation by additional experiments is required including detailed *in vivo* tissue distribution and efficacy evaluation in animal models of oxidative stress related disease. However, they already support the high potential of MIP-CS for polyphenols effective delivery.

Reference(s)

[1]Dos Santos MG, Arbo BD, Hort MA. Effects of quercetin and its derivatives in vivo models of neuroinflammation: A systematic review and meta-analysis. Neural Regen Res. 2026 May 1;21(5):1783-1792.

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Keywords

Drug delivery

Molecularly imprintinf polymer

Quercetin

Anti-oxydant effect

Bioavailability

00174
Nefopam induces an additive analgesic effect for paracetamol and protects against paracetamol-induced acute liver injury in mice

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Osteoarthritic (OA) pain is a common public health problem and remains as an unmet medical need. Currently available analgesics usually have limited efficacy or are accompanied by many adverse side effects. To achieve satisfactory pain relief by multimodal analgesia, nefopam was evaluated in paracetamol-induced analgesia in OA pain murine models and in a paracetamol-induced hepatotoxicity murine model.

Materials and methods

The mechanical antinociceptive effect of paracetamol, nefopam or their combination was performed by the von Frey test in the destabilization of medial meniscus murine model of OA and studied by isobolographic analysis. Hepatotoxicity was assessed in a mouse model of paracetamol-induced liver injury co-treated with nefopam by measuring plasma levels of alanine aminotransferase and aspartate aminotransferase and by examining histology of hematoxylin and eosin-stained tissues sections.

Results

Nefopam and paracetamol induced a dose-dependent antinociceptive effect in mechanical hypersensitivity in an OA model. Isobolographic analysis showed that nefopam interacts additively with paracetamol to reduce OA pain. The combined treatment showed hepatoprotective activity against paracetamol-induced liver damage.

Discussion / Conclusion

The administration of the combination of paracetamol and nefopam to mice gave rise to an additive relieve of mechanic hypersensitivity in OA. The co-administration of the two drugs protected against paracetamol-induced hepatotoxic damage. Hence, the additive anti-nociceptive effect of combining paracetamol with nefopam could be advantageous for the management of OA pain, and the hepatoprotective activity should help to prevent the hepatotoxicity of paracetamol.

Keywords

Acetaminophen, Nefopam, Pain, Osteoarthritis, Isobolographic analysis, Additive effect

00180
Impact of acute and chronic consumption of psychoactive drugs on cognitive functions: behavioral and pharmacokinetic study in rats

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Older adults are particularly vulnerable to drug overexposure due to chronic polypharmacy and age-related pharmacokinetic and pharmacodynamic changes, which may lead to higher plasma concentrations compared to younger adults at equivalent doses. Opioid analgesics such as tramadol and selective serotonin reuptake inhibitors such as paroxetine are widely prescribed for long-term use in this population. Their use has been associated with acute and chronic neurocognitive disorders, although causality remains uncertain because of multiple confounding factors in studies involving polymedicated older patients. Animal models provide a valuable approach to isolate drug-specific effects and investigate exposure–outcome relationships. This study therefore evaluated the impact of chronic tramadol or paroxetine treatment on cognitive processes, both after treatment initiation and following prolonged exposure in rats.

Materials and methods

To model the drug overexposure commonly observed in older adults, rats (n=8/group) received a daily oral supratherapeutic dose of each psychoactive drug for six weeks. During this period, locomotor activity and memory performance were assessed. Plasma drug concentrations were also measured.

Results

After a single administration of each drug, locomotor hyperactivity and stereotyped behaviors were observed, suggesting a delirium-like effect. Following chronic administration, paroxetine impaired the acquisition of a new rule (cognitive flexibility), whereas tramadol induced short-term memory deficits that persisted after treatment discontinuation. The effects observed after repeated administration were associated with systemic accumulation of tramadol and paroxetine. Further investigations of brain concentrations are ongoing to determine whether cerebral accumulation occurs.

Discussion / Conclusion

These findings in rats underscore the need for caution when prescribing psychoactive medications to older adults, particularly those at risk of cognitive impairment. Advancing toward personalized medicine in geriatric populations is essential. In this context, therapeutic drug monitoring may help predict and prevent cognitive adverse effects associated with chronic psychoactive drug exposure.

Reference(s)

Bertin, Ph., Becquemont, L., Corruble, E., Derumeaux, G., Falissard, B., Hanon, O., Pinget, M., & Forette, F. (2013). The therapeutic management of chronic pain in ambulatory care patients aged 65 and over in France: The S.AGES cohort. Baseline data. The Journal of Nutrition, Health and Aging, 17(8), 681–686. https://doi.org/10.1007/s12603-013-0338-7

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Qiu Y, Huang X, Huang L, Tang L, Jiang J, Chen L, et al. 5-HT(1A) receptor antagonist improves behavior performance of delirium rats through inhibiting PI3K/Akt/mTOR activation-induced NLRP3 activity. IUBMB Life. avr 2016;68(4):311-9.

Keywords

paroxetine, sertraline, pharmacokinetics, animal behavior, delirium, cognition

00304
Soft to stiff hydrogels to allow in vitro pharmacological investigations of cardiac valve remodeling

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Drug-induced valvulopathy is due to the activation of the valvular interstitial cells (VIC) from a quiescent (VICq) to a myofibroblast phenotype (VICa). Although these fibroblast-like cells are known to be sensitive to mechanical stimuli, they are routinely cultivated on rigid substrates, such as glass or polystyrene cell culture dishes. This mechanical stress activates mechanosensitive transducers, such as the the Hippo pathway. When the Hippo pathway is OFF, its effector protein YAP translocates from the cytoplasm to the nucleus where it induces the transcription of extracellular matrix-related genes. The spontaneous VIC activation in vitro on rigid substrates makes it difficult to conduct pharmacological studies aimed at analyzing VIC activation. We made the hypothesis that we could observe a quiescent VIC phenotype when culturing cells on a soft substrate.

Materials and methods

The murine fibroblast cell line NIH-3T3 was used as a model, and cultured on polyacrylamide hydrogels of varying stiffness. We measured gel stiffnesses by nanoindentation (Chiaro Nanoindenter, Optics11life), assessed cell viability on those gels via an Alamar Blue assay, analyzed YAP trafficking and RNApolII activation by immunofluorescent labelling, and finally followed YAP-target promoter activation using a transfected luciferase reporter plasmid.

Results

Gels synthesized have measured Young's Moduli of 2 kPa and 12 kPa (compared to 7 GPa for glass), and cell viability was never impaired. We show YAP nuclear exclusion ($YAP_{nucleus}/YAP_{cytoplasm}<1$) when cells are cultivated on the 2 kPa hydrogel, as well as inactive RNApolII on the same gel. Finally, it was observed that YAP-induced luciferase expression diminished in parallel with the decrease in stiffness with a 70% reduction on 2 kPa compared to glass.

Discussion / Conclusion

Maintaining the NIH-3T3 in a quiescent phenotype is possible when culturing it on a 2 kPa substrate. Applying this effect to maintain the VICs in the VICq phenotype is a prerequisite to study their pharmacological modulation.

Keywords

Valvular interstitial cells

Mechanically-induced quiescence

Polyacrylamide hydrogels

Substrate's stiffness

Drug-induced valvulopathy

Cellular model

00406
Molecular-level characterization of the binding mode of the four stereoisomers of prasugrel active metabolite with its target, the P2Y12 receptor

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Prasugrel, an irreversible P2Y12 receptor antagonist, is used to prevent secondary cardiovascular events. It is a prodrug that is metabolized, forming four stereoisomers of the active metabolite of prasugrel (PAM), which do not all have the same potency of effect on P2Y12. This study aims to elucidate the binding mode of PAM to P2Y12 and to rationalize the difference in *in vitro* antagonism among these stereoisomers.

Materials and methods

Molecular dynamics simulated P2Y12 in its lipid environment in open and closed conformations and PAM covalently bound to cysteines 97 and 175 to characterize its binding pocket. The binding of PAM stereoisomers to the different conformations adopted by P2Y12 over time was determined by an ensemble docking approach.

Quantum chemistry assessed the energy required to form a covalent bond between PAM and a cysteine residue in P2Y12.

Results

First, PAM, regardless of the stereoisomer, preferentially binds to the closed conformation of P2Y12. Second, cysteine 175 is consistently closer to the sulfur atom of PAM than cysteine 97, making disulfide-bridge formation more likely with the former. Third, the four stereoisomers have similar physical affinity for this conformation. However, these same affinities correspond to different binding modes. Thus, the RS stereoisomer is located less deeply than other stereoisomers positioning it more favorably for forming a disulfide bridge between cysteine 175 and its thiol function.

Discussion / Conclusion

This study is the first molecular-level characterization of the binding mode of the PAM with its target. The RS stereoisomer, which is the most effective *in vitro* for inhibiting platelet aggregation, binds to P2Y12 at a binding site which is shared with an intermediate metabolite of prasugrel and with cangrelor, another P2Y12 antagonist. This improved understanding of how PAM binds to P2Y12 could explain the differences in clinical effects between P2Y12 antagonists and contribute to improving drug design in the future.

Keywords

Prasugrel, Antiplatelet agents, P2Y12, GPCR, Molecular Modeling

00492
Preliminary pharmacokinetic investigation of two Discoidin Domain Receptors 2 (DDR2) inhibitors in murine plasma and brain using a LC-MS/MS analysis

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Owing to its key role in extracellular matrix-cell interactions, Discoidin Domain Receptor 2 (DDR2) has emerged as a promising pharmacological target in several pathologies including neurodegenerative diseases and cancers. Two selective DDR2 inhibitors currently under investigation, WRG-28 and DDR2-IN-1 represent attractive candidates. However, their pharmacokinetic properties and blood–brain barrier (BBB) penetration remain poorly characterized.

Materials and methods

This study aimed to integrate in silico prediction and in vivo pharmacokinetic assessment to characterize the BBB permeability of these compounds. First, five independent prediction softwares were interrogated to estimate physicochemical and pharmacokinetic parameters related to central nervous system (CNS) exposure. To experimentally validate these predictions, a robust LC–MS/MS method was developed and validated according to EMA/ICH guidelines for the simultaneous quantification of WRG-28 and DDR2-IN-1 in plasma and mouse brain. This method was subsequently applied to preclinical pharmacokinetic studies. Brain and plasma exposure were quantified under baseline conditions and after co-administration of elacridar, a dual P-gp/BCRP inhibitor, to explore the contribution of efflux transporters to BBB penetration.

Results

Computational analyses suggested limited BBB penetration, with predicted brain-to-plasma log-ratios values of -1.41 ± 0.44 for WRG-28 and -0.30 ± 0.88 for DDR2-IN-1, and a high probability of efflux transporter interaction for DDR2-IN-1. Extraction method relied on protein precipitation followed by lipid removal, ensuring robust recovery and minimal matrix effects. In vivo pharmacokinetic studies in mice revealed low log-ratios under baseline conditions (-1.70 for WRG-28; -0.47 for DDR2-IN-1), consistent with predicted limited BBB penetration. Co-administration of elacridar, significantly increased brain exposure of DDR2-IN-1 (40-fold increase), whereas WRG-28 exposure remained unchanged. These results support a transporter-mediated restriction of brain distribution for DDR2-IN-1.

Discussion / Conclusion

This integrated predictive–experimental approach confirms limited baseline BBB penetration of DDR2 inhibitors and highlights the role of efflux transporters in modulating CNS exposure, providing a framework for future optimization strategies to enhance CNS delivery.

Reference(s)

Shaker, B. et al. A machine learning-based quantitative model (LogBB_Pred) to predict the blood-brain barrier permeability (logBB value) of drug compounds. Bioinformatics 39 (2023). https://doi.org/10.1093/bioinformatics/btad577

EMA. ICH guideline M10 on bioanalytical method validation, <https://www.ema.europa.eu/en/ich-m10-bioanalytical-method-validation-scientific-guideline> (2023).

Keywords

Brain, Discoidin Domain Receptor 2 (DDR2), Elacridar, LC-MS/MS, Pharmacokinetic, Tyrosine Kinase Inhibitor (TKI)

00520
Impact of intermittent hypoxia on clopidogrel and cytochromes in rats

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Obstructive sleep apnea syndrome (OSA) characterized by intermittent hypoxia (IH) and inflammation is frequently associated with comorbidities requiring drugs. However, drug response is often altered in OSA patients, with especially a reduced antiplatelet effect of clopidogrel[1]. As inflammation down-regulates cytochromes P450 (CYPs)[2], IH-induced inflammation could inhibit CYP2C and 3A involved in the metabolism of the prodrug clopidogrel and so reduce its antiplatelet effect. This study aimed to investigate the impact of IH on the antiplatelet effect of clopidogrel, hepatic CYPs and inflammation.

Materials and methods

Sprague-Dawley rats exposed to 4-weeks IH or normoxia (N) were orally treated by clopidogrel (6mg/kg/d) during the last week of exposure (n=8 in each group with 4 animals of each sex). Platelet reactivity index (PRI) was determined with VASP assay by flow cytometry. CYP2C and CYP3A gene expression (RT-qPCR), their

activities (luminescent assay P450-Glo, Promega performed in microsomes), as well as IL-6, IL-1β and TNF-α levels (ELISA) were measured in the liver.

Results

Clopidogrel reduces PRI compared to non-treated rats, but IH exposure did not further modify PRI (median PRI [min-max]: 22 [14-35]% for IH+clopidogrel vs 26 [10-41]% for N+clopidogrel; ns). Hepatic expression of CYP2C and 3A were not modified by IH, neither were CYP2C and CYP3A activities. IL1β and IL6 levels were increased after IH in male rats ($p<0.05$), which was not the case in female, while TNFα levels did not change.

Discussion / Conclusion

IH did not affect the antiplatelet effect of clopidogrel in ou model. Even if an hepatic inflammation was shown in male IH rats, expression and activities of CYP were unaffected by IH. Such findings do not explain the reduced antiplatelet effect of clopidogrel observed in OSA patients. Additional researches are needed to investigate the impact of IH on both pharmacodynamic and pharmacokinetic of clopidogrel, considering each sex separately.

Reference(s)

1, Gong et al, J Am Heart Assoc 2016.

2, Stanke-Labesque et al, Pharmacol Ther 2020.

Keywords

Intermittent hypoxia, clopidogrel, cytochrome, inflammation, obstructive sleep apnea.

2- Pharmacologie clinique et thérapeutique

00024
Secondary publications from biologic or small-molecule trials in psoriasis: A methodological review

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The legitimacy and contribution of secondary publications are controversial. Over 100 randomized controlled trials (RCTs) evaluating biologics and small-molecules for moderate-to-severe chronic plaque psoriasis (PsO) have been conducted over the past twenty years. This methodological review examined the prevalence, characteristics and trial-level factors associated with the number of secondary publications from PsO RCTs assessing biologics and small-molecules.

Materials and methods

We identified PsO RCTs of biologics and small-molecules that were published at least two years before the final search date based on the most recent Cochrane review. We searched for included RCTs' secondary publications on CENTRAL and MEDLINE, then categorized them into 10 patterns based on characteristics of

reported results. Complex results were defined as having ≥2 characteristics among Subset/Pooled/Extension. The temporal trend in secondary publications was studied using the yearly ratio of secondary publications to trials. Trial-level factors associated with the number of secondary publications per trial were examined using negative binomial regression.

Results

From 130 RCTs, we identified a large number (n=432) of secondary publications, with 68.5% (296/432) reporting complex results and 70% (125/413) lacking registration number in the abstract. Overall, 95/130 (73.1%) trials had at least one secondary publication. Ixekizumab had the most secondary publications (84), while tildrakizumab had the highest median number of secondary publications per trial (26 [IQR, 17-28.5]). The yearly ratio of secondary publications over trials did not increase over time, but this ratio increased for secondary publications reporting complex results. Increased number of secondary publications per trial within 5-year was associated with pivotality, multi-arm status, large number of sites (≥50) and increased number of primary publications' authors.

Discussion / Conclusion

Findings highlight the predominant status of secondary publications among all publications from PsO RCTs of systemic treatments over time, particularly those reporting complex and questionable results from pooled datasets and extended follow-up in participant subsets.

Reference(s)

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3. Nicholls SG, McDonald S, McKenzie JE, Carroll K, Taljaard M. 'A review identified challenges distinguishing primary reports of randomized trials for meta-research: A proposal for improved reporting'. J Clin Epidemiol. 2022;145:121-125.

4. Ebrahim S, Montoya L, Kamal El Din M, Sohani ZN, Agarwal A, Bance S, et al. 'Randomized trials are frequently fragmented in multiple secondary publications'. J Clin Epidemiol. 2016;79:130-139.

Keywords

randomized controlled trial; selective outcome reporting; secondary publication.

00033
Diagnostic Model Construction Based on Central-Peripheral anomalies: A Multimodal Biomarker Study in Treatment-Naïve Bipolar Disorder Patients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Bipolar disorder (BD) is characterized by complex central–peripheral system dysregulation, yet objective and clinically applicable diagnostic biomarkers remain lacking. This study aimed to construct a multidimensional diagnostic model integrating peripheral neurotransmitter metabolism, brain functional connectivity, and cognitive performance to assist clinical diagnosis of treatment-naïve BD.

Materials and methods

Fifty-two drug-naïve BD patients and forty-two matched healthy controls (HCs) were enrolled, with an independent validation cohort (BD=17, HC=11). Cognitive function was assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and the Stroop Color-Word Test. Resting-state functional MRI was used to evaluate brain activity via regional homogeneity (ReHo) and degree centrality (DC). Plasma levels of 14 key neurotransmitters and metabolites were quantified using ultra-performance liquid chromatography–tandem mass spectrometry. Neuroimaging transcriptomics was conducted using the Allen Human Brain Atlas to explore molecular substrates of functional abnormalities. Multimodal features were integrated using LASSO for feature selection and a K-nearest neighbor (KNN) algorithm to construct and validate the diagnostic model.

Results

BD patients exhibited increased ReHo and DC in the right hippocampus and parahippocampal gyrus, alongside decreased connectivity in the left middle frontal gyrus. Neuroimaging transcriptomics revealed enrichment of genes involved in dopaminergic, serotonergic, glutamatergic, GABAergic, and cholinergic synapses. Accordingly, peripheral neurotransmitter profiles and metabolic ratios differed significantly between BD and HCs and were strongly associated with altered brain connectivity and cognitive impairment. A multimodal model integrating neuroimaging, metabolomic, and cognitive features achieved high diagnostic accuracy (Accuracy=0.819, AUC=0.939) and demonstrated robust generalizability in a separate validation cohort (Accuracy=0.857).

Discussion / Conclusion

This study demonstrates that cognitive impairment in BD arises from coordinated central–peripheral neurotransmission abnormalities, particularly involving dysregulation of the right temporo-limbic system. The proposed multidimensional biomarker model provides a feasible and objective tool for early diagnosis and precision-oriented clinical intervention in BD.

Keywords

Bipolar disorder (BD), Diagnostic model, Multimodal biomarkers, Central-peripheral axis abnormalities, Neurotransmitter metabolism, Cognitive function

00034
Updated Adjunctive Minocycline for Schizophrenia: A Systematic Review and Meta-Analysis of Clinical and Cognitive Outcomes

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Negative symptoms and cognitive deficits in schizophrenia are major contributors to functional impairment and remain inadequately managed by standard antipsychotics. Minocycline, a tetracycline antibiotic with anti-inflammatory and neuroprotective properties, has been proposed as an adjunctive therapy. This study systematically evaluates its efficacy and safety, focusing on core symptom domains and cognitive function.

Materials and methods

A systematic review and meta-analysis of double-blind randomized controlled trials (RCTs) was conducted following PRISMA guidelines. PubMed, Web of Science, Embase, Ovid MEDLINE, and the Cochrane Library were searched from January 2000 to August 2025. Eligible studies with minocycline added to stable antipsychotic regimens and reported outcomes on psychotic and cognitive symptoms were examined. The primary outcomes included PANSS total and subscale scores and overall cognitive performance. Secondary outcomes encompassed SANS, CDS, CGI, GAF, and eight cognitive domains. Standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated. Heterogeneity, sensitivity, subgroup, and meta-regression analyses were performed.

Results

Ten RCTs (n = 895) met inclusion criteria. Adjunctive minocycline significantly improved negative symptoms (PANSS negative: SMD = −0.55, 95% CI: −0.96 to −0.13; SANS: SMD = −0.75, 95% CI: −1.00 to −0.49) and overall psychopathology (PANSS total: SMD = −0.49, 95% CI: −0.80 to −0.18). Benefits on cognition was observed in working memory (SMD = 0.24, 95% CI: 0.08 to 0.39), whereas other cognitive domains showed no significant effects. Subgroup analyses indicated that antipsychotic type, treatment duration, sample size, and region influenced outcomes. Adverse events were comparable between groups.

Discussion / Conclusion

Minocycline provides domain-specific benefits in schizophrenia, with consistent improvement in negative symptoms and modest but statistically significant enhancement of working memory. It is generally well tolerated. These findings suggest that minocycline may serve as an adjunctive treatment option in schizophrenia and highlight the importance of further confirmatory RCTs.

Keywords

Schizophrenia; Minocycline; Adjunctive therapy; Negative symptoms; Cognitive function; Meta-analysis

00043
Effectiveness of use of Proton pump Inhibitors in patients under Corticosteroids (EPIC study)

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Corticosteroids (CS) are the first-line treatment for many autoimmune diseases with a supposed increased risk of gastroduodenal bleeding without formal evidence. Nevertheless, CS are frequently combined with proton pump inhibitors (PPIs) to prevent this potential risk. Long-term adverse effects of PPIs are increasingly reported.

It is therefore important to evaluate whether PPI use is beneficial in patients receiving CS to prevent gastroduodenal complications.

Materials and methods

We conducted a retrospective study based on medical records of patients discharged on CS therapy for at least 28 days, comparing those who received PPIs with those who did not. Patients in both groups were matched using propensity score weighting (IPTW).

The primary composite endpoint was the occurrence of upper gastrointestinal events during CS therapy within the first three months after CS initiation, defined as overt bleeding, occult bleeding, gastroduodenal ulcer, upper gastrointestinal obstruction, or perforation.

Secondary endpoints included the need for transfusion, duration of CS therapy, and use of steroid-sparing treatments.

Results

A total of 200 patients were included between 01/09/2022 and 31/12/2024. Mean age was 55 ± 20 years, and 60% were female. One hundred and four patients (52%) received PPIs at the time of CS initiation.

The primary endpoint at 3 months occurred in two patients (2.1%) in the non-PPI group versus none in the PPI group (p=0.23). After propensity score matching, no significant difference was observed in the occurrence of the primary endpoint at 3 or 6 months. Similarly, there was no significant difference between groups regarding transfusion rates or all-cause mortality at 6 months.

Discussion / Conclusion

This retrospective study does not demonstrate a clear benefit of PPI use in patients receiving CS therapy. These findings need to be confirmed in larger cohorts but support careful consideration of the benefit–risk balance when prescribing PPIs in patients treated with CS.

Keywords

Corticosteroids ; proton pump inhibitors ; peptic ulcer disease ; gastrointestinal bleeding.

00061
Benefit-risk balance assessment based on single-arm clinical trials in the context of Accelerated Approvals and Conditional Marketing Authorizations in oncology and malignant hematology: A Systematic Review

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have introduced accelerated pathways (accelerated approvals, AA, and conditional marketing authorization, CMA, respectively), to enhance early access to treatments for serious conditions. In cancer, AAs and CMAs are frequently based on single-arm trials (SATs), with confirmatory randomized controlled trial (RCTs) often required. While meta-research on SATs has focused on their efficacy assessment, limited attention has been paid to safety assessment. The primary objective of our study is to describe how safety has been reported in SATs that led to AA or CMA, and to compare the safety profile between SATs and subsequent RCTs.

Materials and methods

We conducted a systematic review of indications granted AA or CMA by the FDA or EMA up to December 31, 2024. Eligible indications received AA or CMA based on a SAT and were converted to standard authorization or withdrawn after a confirmatory RCT. Indications were identified using drug labels from FDA's @DrugsFDA database and EMA database. Publications supporting the initial AA or CMA and corresponding confirmatory RCTs were identified. The consistency between adverse events rates between SATs and RCTs was assessed with intraclass correlation coefficients (ICC).

Results

A total of 66 indications met our inclusion criteria out of 386 identified. Differences in population or intervention were observed in 68.6% and 32.8% of situations, respectively. The ICCs for treatment-related adverse events grades ≥3 and for adverse events grades 3 and/or 4 were 0.831 [0.154; 0.981] and 0.664 [-0.076; 0.943], respectively. For efficacy primary endpoints assessed in SATs and their equivalents in confirmatory RCTs, the ICC was 0.413 [0.121; 0.620].

Discussion / Conclusion

This systematic review highlights heterogeneity in adverse event reporting across SATs. Despite wide confidence intervals, safety outcomes were more consistent than efficacy between SATs and RCTs. Population or intervention differences may contribute to these findings.

Keywords

Accelerated approvals; Conditional marketing authorizations; Confirmatory randomized controlled trials; Single-arm trials; Benefit-risk balance.

00083
Real-time improvement in the relevance of prescriptions for elderly patients: impact of the Vidal Focus automated system.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Optimizing the relevance of prescriptions is key to improving healthcare efficiency. The Vidal Focus system continuously analyzes prescription data and applies rules to identify risky situations for patients over 65 years of age. The prescriber then receives a notification, allowing them to correct the prescription in real time.

Materials and methods

Evaluating the feasibility, acceptability, and impact in real-world conditions within the WEDA software of the Vidal Focus system, which detects and flags potentially inappropriate prescriptions. The study was conducted based on prescriptions issued between February and October 2025 by 8,000 general practitioners.

Results

Of the 1,163,857 anonymized prescriptions analyzed, 37.3% triggered a notification, representing 434,212 identified risky prescriptions. The system triggered a significant number of corrections: 30,968 prescriptions were corrected in real-time, representing 7.1%. The most frequent notifications involved PPIs (159,684), NSAIDs (134,693),

benzodiazepines (110,572), and statins (93,611). Other situations were associated with high correction rates: statins+fibrates (15.8%) and domperidone (12.0%). The disconnection rate of <1% indicates an excellent integration into usage patterns.

Discussion / Conclusion

This study demonstrated the feasibility of the automated system on a sample of 8,000 physicians, its technical robustness, and its immediate impact on the appropriateness of prescriptions. Its high level of acceptability and its ability to process a large volume of prescriptions demonstrate measurable improvements in patient care. These results suggest that an enhanced version of the system, incorporating recommendations for action, a prioritization of rules, and reinforced learning mechanisms, could make a major contribution to national challenges in terms of relevance, harmonization of practices, and efficiency of care.

Keywords

Realworld evidence, Clinical Decision Support System, Medical intelligence, Expert system and artificial intelligence, Evidence based medecine

00087
Non-inferiority of lower doses of activated charcoal for rivaroxaban antagonization: a phase 1, randomized, cross-over study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Patients treated by rivaroxaban are often elderly, with multiple fall risk factors. When urgent surgery is needed, anticoagulant activity must be promptly reversed. Activated charcoal, by disrupting rivaroxaban entero-hepatic recirculation, is a safe and effective alternative to andexanet-alfa, but oral administration may be challenging in the elderly or in emergency situations.

This study aimed to evaluate the non-inferiority of lower doses (24g, 12g, and 6g) toward the full dose (50g) of activated charcoal administration to antagonize rivaroxaban.

Materials and methods

A randomized, cross-over study was conducted on 12 healthy volunteers (NCT04767776). Activated charcoal was administered 2h after 40mg of rivaroxaban, and three separate charcoal doses were studied for each patient (incomplete cross-over). Pharmacokinetics parameters of interest were rivaroxaban plasma concentration observed 24h after the administration (C_{24}), the $AUC_{2\text{-}24}$ estimated via non-compartmental analysis, and the first-order elimination constant estimated via a log-linear model (k_{el}). Inter-individual and inter-occasion variabilities of observations were modelled using random effects. For each dose, non-inferiority was tested against the typical bioequivalence ratio limit (0.8 or 1.2).

Results

After charcoal full dose administration, mean rivaroxaban C_{24} was 9.9 µg/L ($CI_{95\%}$ 9.37 – 10.5), mean $AUC_{2\text{-}24}$ was 996 $\mu g \cdot (L \cdot h)^{-1}$ ($CI_{95\%}$ 835 – 1187), and estimated k_{el} was 0.26 h^{-1} ($CI_{95\%}$ 0.23 – 0.29). All lower charcoal doses were non-inferior to the full dose in terms of C_{24}, being the ratio between the 6g and the full dose 1.06 ($CI_{95\%}$ 0.99 – 1.13). The 24g dose was inferior to the full dose in terms of $AUC_{2\text{-}24}$ and k_{el}, the ratios being 1.15 ($CI_{95\%}$ 0.93 – 1.42) and 0.83 ($CI_{95\%}$ 0.73 – 0.93), respectively. Doses lower than 24g were not tested.

Discussion / Conclusion

6g of activated charcoal are as effective as 50g in suppressing rivaroxaban plasma concentration observed 24h after last dosing. Further interventional studies are needed to compare the clinical efficacy of anti-Xa activity reversal strategies.

Reference(s)

Ollier, E., Hodin, S., Lanoiselée, J. et al. Effect of Activated Charcoal on Rivaroxaban Complex Absorption. Clin Pharmacokinet 56, 793–801 (2017). https://doi.org/10.1007/s40262-016-0485-1

Keywords

rivaroxaban, activated charcoal, pharmacokinetics

00094
Anatomy of 237 zombie randomized controlled trials threatening evidence-based medicine: 94% significant results from 100% fraud

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Clinical decisions and guidelines rely on evidence derived from randomized controlled trials (RCTs). However, scientific literature is increasingly contaminated by 'zombie trials' containing fabricated data, which compromise evidence syntheses1 and mislead conclusions about treatment efficacy. Identifying 'zombie trials' is a step in preventing their dissemination, and understanding their characteristics informs prevention strategies while safeguarding the integrity of evidence-based medicine.

Materials and methods

Based on the cohort of retracted human RCTs from the Retraction Watch database identified by Xu et al.2, we updated and extended the dataset to include all retracted ‘zombie trials’ from inception through December 11, 2025. ‘Zombie trials’ were defined as those with fabricated, fictive, or imaginary data. Retraction reasons were analyzed across PubMed, Retraction Watch Database, and PubPeer using an R-based text-mining procedure to match retraction reasons with the ‘zombie’ definition. We performed both automated and manual extraction of variables to characterize these trials.

Results

We identified 236 retracted ‘zombie trials’. The analysis reveals a retraction latency of 12.5 years (5.4-15.0). Geographical clusters in Japan (n=125, 52.9%) and Germany (n=23, 9.7%) were mainly driven by 2 authors, who accounted for 52.1% (n=123/236) of ‘zombies’. Anesthesiology (n=137, 58.1%) and cardiology (n=46, 19.5%) were the most affected fields, reflecting the respective disciplines of these authors. Trials predominantly involved pharmacological interventions (n= 196, 83.1%). Primary pharmacological targets were antiemetics (n=74, 31.4%) and anesthetics (n=22, 9.3%). Notably, 94.9% (n=224) of these fabricated trials reported a statistically significant primary outcome. These 237 retracted zombies involved 66 first authors: ‘recidivists’ (n=12, 18.2%,179 ‘zombies’) and ‘non-recidivists’ (n=54, 81.8%, 57 ‘zombies’).

Discussion / Conclusion

Retracted ‘zombie trials’ are disproportionately published by authors with a history of similar studies. This pattern may reflect the intensive scrutiny authors attract. Still, it suggests that reviewing an author’s publication record is crucial for detecting potential fraud and preventing contamination of the evidence base.

Reference(s)

1. Graña Possamai C, Cabanac G, et al. Inclusion of retracted studies in systematic reviews and meta-analyses of interventions: A systematic review and meta-analysis. JAMA Intern Med. 2025 Jun 1;185(6):702-709. DOI: 10.1001/jamainternmed.2025.0256

2. Xu C, Fan S, Tian Y, et al.; VITALITY Collaborative Research Network. Investigating the impact of trial retractions on the healthcare evidence ecosystem (VITALITY Study I): retrospective cohort study. BMJ. 2025;389:e082068. doi: 10.1136/bmj-2024-082068.

Funding: The French National Research Agency (ANR; grant number ANR-23-CE36-0006)

Keywords

zombie trials; data fabrication; retraction; research integrity; scientific misconduct; evidence-based medicine.

00106
Scientific expertise, public debate and health safety decisions

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Health safety decisions are based on scientific expertise designed to support public action, but their legitimacy also depends on their social acceptability, i.e. how they are understood and appropriated by citizens. Recent crises, including COVID-19, have highlighted tensions between knowledge production, political requirements, media dynamics and social expectations, in a context marked by mistrust and misinformation. This work, conducted by the Scientific Council of the French National Agency for Medicines and Health Products Safety (ANSM), aims to identify conditions that can strengthen public trust in health safety decisions.

Materials and methods

We conducted a multidisciplinary reflection based on inputs from experts in public health, social sciences, ethics, regulatory agencies, and stakeholder organizations. These insights were complemented by a narrative review of both French and international literature on scientific expertise, health democracy, communication under uncertainty, vaccine hesitancy, and online misinformation.

Results

Several key points emerged. First, the credibility of expertise depends both on scientific rigour and on the quality of procedures (selection of experts, management of conflicts of interest, integration of divergent views), particularly under crisis conditions. Second, transparency alone is not sufficient: it must be accompanied by clear and accessible communication on inherent scientific uncertainties, to avoid confusion between evolving knowledge and inconsistency. Third, the limited visibility of collectively mandated scientific voices (agencies, learned societies) in the public space and on social networks favours the dissemination of fragmented or unfounded messages. Fourth, citizens' and patients' perceptions are shaped by social, historical and institutional factors that require greater mobilisation of social sciences.

Discussion / Conclusion

Two complementary orientations are proposed: strengthening a reference scientific voice in the public space, particularly through agencies and learned societies, and more systematically mobilising social sciences to better understand perceptions and support dialogue between expertise, politics and society.

Reference(s)

Oualikene-Gonin W, Castel P, Paccaud F, Maison P, Ankri J, on behalf of the Scientific Advisory Board of the ANSM.
Scientific expertise, public debate, and health safety decision-making.
Bulletin de l'Académie Nationale de Médecine. 2026;Volume 210, Issue 1, January 2026, Pages 70-77

Keywords

Science
Expertise
Decision Making
Health Policy
Transparency
Trust
Social Perception
Health Democracy
Community Participation
Learned Societies

00145
French public views on financial compensation for participants

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Clinical trial participants should be fairly compensated for inconvenience while avoiding undue inducement. However, European regulations provide limited operational guidance on when compensation should be offered and how it should be determined. The INDEM3 project aims to develop a decision-support tool for sponsors and ethics committees, beginning with an assessment of community perspectives in France.

Materials and methods

An exploratory population-based survey was conducted using a self-administered questionnaire with an estimated completion time of approximately seven minutes. A minimum of 60 individuals was targeted, with at least one-third living with chronic disease. The questionnaire assessed general views on financial compensation and responses to three fictional clinical trial scenarios varying in risk, burden, and direct benefit. Distribution occurred through hospital departments, a community pharmacy, and online via social media.

Results

Between June 2024 and January 2025, 65 responses were collected. Most respondents (93%) supported financial compensation for participation in clinical trials. The most frequently cited justifications were exposure to a new investigational drug (65%), invasive procedures (63%), loss of income (63%), and absence of direct personal benefit (28%). For the scenarios, the proportion of respondents supporting compensation and the median proposed amounts were as follows:

Scenario 1 (no direct benefit, high burden, low risk): 81%; €300 [€140–300].

Scenario 2 (some direct benefit, low burden, risk): 53%; €150 [€100–200].

Scenario 3 (some direct benefit, high burden and risk): 68%; €500 [€200–1,000].

Discussion / Conclusion

French public opinion largely supports compensating patients participating in clinical trials. Compensation is perceived as a proportionate ethical and social recognition of risk, burden, time commitment, and lack of direct benefit. These findings provide an empirical basis for developing transparent tools to guide compensation decisions.

Keywords

Clinical trials; Financial compensation; Ethics; Community perspectives; Patient empowerment; Survey

00184
Prescribing Practices of Long-Acting Injectable Antipsychotics in Bipolar Disorder Type I: A Cross-Sectional Real-World Study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Long-acting injectable antipsychotics (LAIs) are increasingly prescribed in bipolar disorder type I (BD-I) despite limited comparative evidence and the absence of marketing authorization for this indication in France [1,2]. Understanding real-world prescribing practices and determinants is essential to optimize evidence-based treatment strategies and align clinical practice with regulatory frameworks.

Materials and methods

We conducted a cross-sectional descriptive study using an online questionnaire distributed to psychiatrists and psychiatry residents in Loire-Atlantique and Vendée (France) between May and July 2025 [3]. The primary objective was to describe LAI prescribing practices in BD-I. Secondary objectives included assessing physicians' knowledge of approved marketing authorizations, motivations for prescribing LAIs, perceived benefits and risks compared with oral antipsychotics, lithium, and antiepileptics, and the frequency of off-label prescribing.

Results

More than half of respondents (57%) reported prescribing LAIs in BD-I, mainly aripiprazole, olanzapine, and paliperidone. Knowledge of official marketing

authorizations was extremely limited, with only 5% of physicians correctly identifying approved indications. Prescriptions were primarily driven by clinical experience, scientific literature, and international guidelines. LAIs were perceived as improving treatment adherence and reducing relapse risk compared with oral antipsychotics and antiepileptics, whereas lithium remained considered the reference mood stabilizer. Off-label prescribing was widely reported, highlighting a substantial discrepancy between approved indications and clinical practice.

Discussion / Conclusion

This study demonstrates a significant gap between regulatory indications and real-world prescribing practices. These findings underscore the need for improved dissemination of regulatory information, targeted educational interventions, and robust comparative clinical studies to better define the role of LAIs in BD-I treatment strategies. Understanding prescribers' decision-making processes may contribute to more rational and guideline-concordant therapeutic approaches.

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Keywords

Long-acting antipsychotics ; bipolar I disorder ; prescribing practices ; off-label use

00190
Unusual rheumatologic manifestations of MGCS: a case of morphea with fasciitis and refractory polyarthritis

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Monoclonal gammopathies of clinical significance (MGCS) are characterized by monoclonal immunoglobulin production by a plasma cell clone without criteria for multiple myeloma, but causing organ damage.

Materials and methods

We report a rare manifestation: diffuse morphea associated with fasciitis and polyarthritis, forming a complex clinical presentation requiring targeted management.

Results

Case report
A 62-year-old woman has been followed since 2020 for polyarthritis involving small and large joints, inflammatory syndrome (C-Reactive Protein up to 150 mg/L), and progressive cutaneous fibrosis (thighs, forearms, abdomen) causing pain, contractures, and functional impairment. Painful palmar-plantar erythema and moderate sclerodactyly with tendon retractions suggested palmar fasciitis. Skin biopsies (2020–2023) excluded vasculitis, cutaneous lymphoma, and interstitial granuloma, then confirmed morphea. Immunological tests (ANCA, ANA, myositis/scleroderma panels, RF, anti-CCP) were negative. Imaging showed non-erosive synovitis; PET-CT revealed isolated articular hypermetabolism; upper limb

MRI demonstrated muscle and superficial fascia inflammation. Neoplastic workup was negative. An IgG lambda MGUS was identified in 2020. In 2025, two monoclonal peaks (4.1 and 2.7 g/L) were detected, with excess free lambda light chains (kappa 9.67 mg/L; lambda 16.68 mg/L) and decreased kappa/lambda ratio (0.58). Bone marrow biopsy (2021) excluded lymphoma. Cytogenetics (2025) showed t(11;14) in 89% of cells without major abnormalities; TP53, FGFR3, and UBA1 were negative. High-dose corticosteroids (>30 mg/day) were effective, but colchicine, methotrexate, hydroxychloroquine, sulfasalazine, tocilizumab, etanercept, baricitinib, tocilizumab plus ciclosporin, cyclophosphamide, anakinra, IVIG, and rituximab failed.

Discussion / Conclusion

MGCS was retained as the cause of morphea, fasciitis, and severe inflammatory polyarthritis. After national multidisciplinary review (“cutaneous MGCS”), daratumumab, lenalidomide, and dexamethasone were started (July 2025), resulting in cutaneous stabilization, partial pain control, and CRP reduction. Multidisciplinary rehabilitation was implemented. This case highlights the diagnostic complexity of MGCS with extra-hematological involvement and the need for specialized multidisciplinary management in refractory cases.

00191
Tocilizumab and Rheumatoid Arthritis: Which Predictive Factors for Long-Term Treatment Persistence ?

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Tocilizumab (TCZ), an anti–interleukin-6 receptor monoclonal antibody, controls rheumatoid arthritis (RA) activity. However, long-term persistence and its predictive factors remain poorly documented. This study aimed to evaluate 10-year TCZ survival, to analyze the reasons and factors for persistence or discontinuation.

Materials and methods

We conducted a prospective observational study including RA patients treated with TCZ between 2012 and 2013 in a University Hospital. Sociodemographic, clinical, biological, and therapeutic data were collected. Ten-year follow-up assessed treatment persistence and reasons for discontinuation. Multivariate analysis evaluated factors associated with prolonged TCZ maintenance, including age, sex, cardiovascular history, disease duration, erosive and seropositive status and remission at 6 months.

Results

The study included 110 patients (83.6% women), mean age 55 ± 15.7 years, with longstanding RA (17.8 ± 11.2 years). Cardiovascular comorbidity was present in 23.6%. Most were seropositive (RF 66.4%, ACPA 56.4%), with a mean DAS28 of 5.1

± 1.4. Nearly half had received ≥3 biologics therapies. After 10 years, 85.5% discontinued TCZ. The main reason was loss of efficacy (52.1%). Adverse events accounted for 21.3% of discontinuations — infections and intolerance (7.4% each), hematological events (3.2%), allergic reactions (2.1%), diverticulitis (1.06%), and recurrent lithiasis (1.1%)—occurring predominantly within the first year (40%). Other causes (26.6%) included cancer (6.4%), death (5.3%), remission (3.2%) and surgery (2.1%). Among the 16 patients remaining on TCZ, 81.3% had erosive RA (RF 50%, ACPA 37.5%) ; 50% received monotherapy. Prolonged persistence was independently associated with younger age (OR 0.961), cardiovascular comorbidity (OR 6.693), and remission at 6 months (OR 6.233).

Discussion / Conclusion

Ten-year TCZ persistence was low. Younger age, cardiovascular history, and early remission predicted sustained treatment, while discontinuation was mainly driven by inefficacy and adverse events.

00196
Safety and efficacy of cangrelor use in intracranial aneurysms: A Single-arm Meta-analysis and Systematic Review

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Dual antiplatelet drugs are important for the treatment of intracranial aneurysms(IAs). However, postoperative complications(mainly Cerebral infarction and Cerebral hemorrhage) continued plaguing doctors and patients. Cangrelor was a newly developed intravenous P2Y12 receptor inhibitor in 2015. Its pharmacological action showed that it may be safer and more effective in the treatment of IAs. Therefore, we conducted a single arm meta-analysis and aystematic review to assess the feasibility of cangrelor in IAs.Dual antiplatelet drugs are important for the treatment of intracranial aneurysms(IAs). However, postoperative complications(mainly Cerebral infarction and Cerebral hemorrhage) continued plaguing doctors and patients. Cangrelor was a newly developed intravenous P2Y12 receptor inhibitor in 2015. Its pharmacological action showed that it may be safer and more effective in the treatment of IAs. Therefore, we conducted a single arm meta-analysis and aystematic review to assess the feasibility of cangrelor in IAs.

Materials and methods

We searched PubMed, Cochrane, Web of Science and Embase and Embase for randomized clinical trials and nonrandomized studies of intervention including IAs patients who received cangrelor during operation. Statistical analysis was carried out using R software.

Results

We included 6 studies comprising 115 patients. Median age ranged 56-61 from 41 to 86 years. In a pooled analysis, the preventing infarction effective rate of 98% (95% CI 0.93 to 1.00; I2=0%) and cerebral hemorrhage rate of 2% (95% CI 0.00 to 0.07; I2=25%).

Discussion / Conclusion

In the limited studies published so far, we tentatively believe that cangrelor is safe and effective in IAs. However, we still look forward to more relevant studies to help us further confirm, and the optimal treatment plan can be obtained.

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Keywords

cangrelor; intracranial aneurysms; antiplatelet

00223
Barriers to prescribing methylphenidate for adults with ADHD: A qualitative study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Attention Deficit/Hyperactivity Disorder (ADHD) affects approximately 2.5% of the adult population. In France, the pharmacological management of adults with ADHD is based on methylphenidate, a medication for which the initial prescription and annual renewal must be carried out by a specialist such as a psychiatrist or a neurologist. Despite the high prevalence of this disorder, the prescription of methylphenidate by psychiatrists remains limited. We therefore aimed to explore the barriers to prescribing methylphenidate by psychiatrists for adults with ADHD.

Materials and methods

A qualitative study using semistructured individual interviews was conducted with French psychiatrists practicing in the public healthcare system between June and July 2025. An initial coding phase was conducted by identifying significant passages in each participant's discourse and assigning codes to each transcript using QualCoder software. Codes were grouped around main ideas to generate distinct themes, and relevant quotations were selected to illustrate participants' responses. Participant inclusion was continued until data saturation was achieved, corresponding to the point where no new codes were being generated while analyzing participants' discourse.

Results

Ten psychiatrists were interviewed, with a diversity of profiles in terms of age and type of practice. Three main themes emerged as barriers to prescribing. First, participants reported a lack of knowledge about the disorder and its management. Second, they described uncertainty regarding possible differential diagnoses, as well as therapeutic constraints in the presence of psychiatric or substance use comorbidities. Finally, they highlighted the time-consuming nature of the diagnosis and management of this disorder. Other aspects were also mentioned including delays in accessing cardiology consultations, some patients' reluctance regarding drug treatment, the occurrence of adverse drug reactions, and medication shortages

Discussion / Conclusion

In light of the identified barriers, strengthening professional training, providing adult-specific prescribing guidelines, and structuring the care pathway appear to be key levers to improve access to care.

Keywords

Attention Deficit/Hyperactivity Disorder, Methylphenidate, Psychostimulant, Psychiatrist, Qualitative Research

00232
Prior probability of treatment efficacy and reliability of clinical trial results: lessons from the COVID-19 pandemic

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The probability of the true efficacy of a clinical trial (i.e. the post-trial probability) depends on the pre-trial probability. The rapid search for treatments during the first wave of the COVID-19 bypassed typical phase 2 trials. Whether this accelerated process has influenced the ability of phase 3 trials to reliably identify effective treatments remains unknown.

Materials and methods

The overall pre-trial probability was derived from the ratio of trials documenting effective treatments to the total number of COVID-19 first-wave trials. For each trial, post hoc statistical power was estimated using the reported sample size and the number of events. Bayes' theorem was used to calculate the post-trial probability of efficacy, based on sensitivity (i.e. trial power), specificity (i.e. 1 minus 0.025), and pre-trial probability. We then compared the positive predictive values of COVID-19 and non-COVID19 trials.

Results

Of the 463 first-wave trials evaluating 150 molecules, 51 confirmed effective treatments, giving an overall pre-trial probability of 11%. The median power of COVID-19 trials was 9% (min-max: 5-100%). Accordingly, the probability of true efficacy after a positive study was 31% (20%-83%), compared to 94% for non-COVID19 trials that were characterized by a pre-trial probability of 50%. With a pre-trial probability of 11%, a replication framework consisting of two independent, 80%-powered trials yielded a positive predictive value of 99.2%. This contrasts with a single 90%-95%-powered trial, which yielded a positive predictive value of 81%-82%.

Discussion / Conclusion

Clinical trials during the first wave of the pandemic were frequently underpowered and more likely to produce negative results. Accelerated drug development for the treatment of COVID–19 thus led to a lower pre-trial probability of efficacy, and consequently a lower post-trial probability of true efficacy compared to traditional pathways. These findings highlight the need for stronger pre-trial evidence to enhance the reliability of clinical trial outcomes in future pandemic responses.

Keywords

Bayesian analysis, COVID–19, drug development, randomized controlled trial, pre–trial probability, post–trial probability

00238
Personalized Rituximab Treatment Preserves Renal Function in Membranous Nephropathy

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Membranous nephropathy (MN) is an autoimmune kidney disease most commonly associated with autoantibodies against the phospholipase A2 receptor (PLA2R1)[1]. Its clinical course is heterogeneous, with one-third of patients progressing to kidney failure[2]. Epitope spreading to multiple PLA2R1 domains reflects increased immunological activity and is associated with poorer prognosis and lower remission rates[3,4]. Current international guidelines recommend immediate immunosuppressive therapy only for patients with life-threatening nephrotic syndrome or rapidly declining kidney function[5].

We previously demonstrated that a personalized rituximab strategy, guided by PLA2R1 epitope spreading with earlier administration and higher dosing in patients with spreading, was superior to the standard protocol in achieving clinical remission and preserving estimated glomerular filtration rate (eGFR) at month-12[6]. Here, we report the 24-month outcomes.

Materials and methods

In a randomized, prospective trial (12 French hospitals), 64 MN patients were assigned to either standard GEMRITUX (six months of symptomatic treatment followed by two rituximab 375 mg/m² infusions at month-6 if nephrotic syndrome persisted) or a personalized rituximab protocol. In the personalized arm, patients

without epitope spreading followed GEMRITUX, whereas those with spreading at baseline or month-6 received two immediate 1,000 mg rituximab infusions.

Results

At month-24, renal function was significantly better preserved in the personalized arm, with a relative change in eGFR from baseline of −2.7% compared with −14.5% in the standard arm ($p = 0.009$). Analysis of the eGFR slope confirmed a significantly more favorable trajectory of renal function in the personalized group ($p = 0.02$). In multivariable analysis, treatment delay was independently associated with eGFR decline. Clinical remission rates and symptomatic therapy were comparable between groups.

Discussion / Conclusion

This is the first prospective study showing that early rituximab treatment guided by PLA2R1 spreading preserves long-term renal function. These results emphasize the importance of timely, personalized therapy based on immunological biomarkers to prevent progressive renal decline, especially in immunologically aggressive MN.

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Keywords

Clinical trial; Epitope spreading; Membranous nephropathy; Personalized treatment; Rituximab.

00259
Estimating the environmental impact of clinical research : carbon footprint and major hotspots of two academic clinical trials

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The healthcare sector accounts for around 8% of global greenhouse gas emissions, with clinical research contributing to this footprint. Integrating eco-design principles into clinical trials requires pragmatic tools to estimate their carbon impact. While life cycle assessment (LCA) provides detailed results, its complexity limits routine use. A simplified carbon estimation method has recently been proposed [1, 2]. This study aimed to estimate the carbon footprint of two academic clinical trials and, for one of them, to compare results obtained using this simplified method with those from a full LCA.

Materials and methods

Two randomized academic clinical trials sponsored by Rennes University Hospital were included. Trial A (multicentric therapeutic trial, 202 patients, NCT02650609) had previously undergone a full LCA. Trial B (monocentric trial, 66 patients, NCT03805997) differed in design and scope. Trial activity data were retrospectively collected using an Excel-based carbon calculator covering the clinical trial activity from setup to closure in 10 modules. Activity data were combined with emission factors from public databases or literature to estimate overall carbon footprints. Carbon hotspots were defined as activities contributing the largest share of emissions.

Results

Trial A emissions were estimated at 38.3 tCO_2e (190 $kgCO_2e$ per participant), with main hotspots being clinical trial unit emissions, meetings and travel, and patient assessments. Using LCA, emissions were estimated at 31.6 tCO_2e (156 $kgCO_2e$ per participant), with patient transport and staff travel as primary contributors. Trial B emissions were estimated at 20.5 tCO_2e (311 $kgCO_2e$ per participant), with clinical trial unit emissions, trial close-out including biological sample storage, and meetings and travel identified as key contributors.

Discussion / Conclusion

Carbon emissions and hotspots varied according to trial design and activity profiles. Although estimates were of similar magnitude, results differed between LCA and simplified approaches. These findings highlight the need for standardized tools to support eco-design and targeted mitigation strategies in clinical research.

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CO3.4 - Estimating the carbon footprint of academic clinical trials: a feasibility study with adaptation of a British tool to the French setting,Journal of Epidemiology and Population Health,Volume 73, Supplement 2,2025.
doi.org/10.1016/j.jeph.2025.203002.

Keywords

carbon footprint

clinical trials

hotspots

00285
Safety Issues During a First-in-Human Clinical Investigation of a Novel Hemodialysis Medical Device

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Tunneled cuffed central venous catheters used for maintenance hemodialysis are associated with a significant risk of infection and mechanical dysfunction, largely due to the repeated manipulations required for connection and disconnection procedures. An innovative connection device was developed to minimize catheter hub openings and potentially reduce these complications. The device obtained CE marking by equivalence in 2021, prior to implementation of the European Medical Device Regulation (MDR). The objective of this first-in-human study was to evaluate the feasibility and safety of repeated use of this investigational device during routine hemodialysis sessions in real-world clinical practice.

Materials and methods

This was a single-center interventional study (ClinicalTrials.gov identifier: NCT05670964) conducted in a university hospital setting. Fifteen participants undergoing chronic hemodialysis were enrolled and followed for six weeks, including four weeks of exposure to the investigational device. Feasibility and safety outcomes were prospectively collected and analyzed.

Results

Two consecutive study suspensions were mandated for safety concerns, including leakage and connection difficulties. Following enrollment of four participants using version A of the device, the Data Safety Monitoring Board recommended additional preclinical investigations. Subsequent animal testing of version B yielded satisfactory results, allowing study resumption. However, a manufacturing defect affecting the Luer-lock component led to a second suspension after eight total inclusions. One participant was exposed to a potentially serious risk and required antibiotic prophylaxis. After a change in manufacturer and reinforcement of the production process, no major device-related failures were observed among the final 13 participants treated with version C.

Discussion / Conclusion

CE marking obtained prior to MDR implementation did not provide sufficient assurance of safety for first-in-human use. A more stringent regulatory framework and comprehensive preclinical evaluation would likely have identified these shortcomings earlier. The current iteration (version C) appears sufficiently mature to justify further feasibility studies before assessing its clinical impact on complication reduction.

Reference(s)

Trial registration: Registered at ClinicalTrials.gov with study number 05670964.

Keywords

Hemodialysis; Tunneled central venous catheter; Medical device; First-in-human study; Device safety; CE marking; Medical Device Regulation (MDR); Luer-lock defect; Preclinical evaluation; Feasibility study

00296
Patterns of AI tool adoption among researchers: a cross-sectional survey in very-high-impact journals

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Artificial intelligence (AI) tools have rapidly entered the scientific workflow, yet systematic data on adoption patterns among researchers remain scarce. We aimed to characterise the prevalence, tools used, tasks performed, and perceived benefits of AI across the research community of very-high-impact journals.

Materials and methods

A cross-sectional online survey was distributed in December 2025 to researchers with recent publications in very-high-impact A+ journals (NEJM, Lancet, Nature, JAMA, BMJ). Descriptive analyses were performed on tool usage, task categories, and perceived benefit ratings (0–10 Likert scale).

Results

Respondents included faculty members (69.7%), clinician-researchers (25.9%), and scientists, predominantly from the UK, USA, France, and Germany. Most respondents (91.6%) had used at least one AI tool. ChatGPT dominated general adoption (85.4%), followed by Gemini (43.1%), Grammarly (20.8%), and DeepL (19.0%). However, uptake for scientific publications was markedly lower: only 38.7% had used ChatGPT for a publication, and 48.9% reported no AI use in their scholarly work. The most frequent research-related tasks were literature searching and reviewing (36.1%), manuscript writing or editing (34.3%), and administrative tasks such as drafting emails (42.7%). Regarding perceived benefits, respondents rated language accessibility (mean 6.59/10), literature search support (6.42/10), and article synthesis (6.27/10) most highly, while AI assistance for data interpretation (4.14/10) and error reduction in analysis (4.39/10) received the lowest scores. AI literacy was self-reported as average or below by 65% of respondents, and only 52.6% could distinguish between AI, machine learning, and deep learning.

Discussion / Conclusion

AI tools are widely used among active biomedical researchers, primarily for peripheral tasks such as writing assistance and literature searching. Their integration into core analytical processes remains limited, reflecting both cautious adoption and a genuine gap in AI literacy. Training initiatives appear warranted to optimise and standardise AI use in the research process while fostering a research culture that values ethics and transparency.

00297
AI transparency in scientific publishing: a cross-sectional survey in very-high-impact journals

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The integration of AI into scientific publishing raises pressing ethical questions around transparency, reproducibility, and accountability. Pharmacology, as a discipline highly sensitive to research integrity, stands at the intersection of these debates. We examined how researchers perceive the risks of AI, practise disclosure, and envision adequate governance frameworks.

Materials and methods

In December 2025, an international cross-sectional survey was administered to researchers with recent publications in very-high-impact A+ journals (NEJM, Lancet, Nature, JAMA, BMJ).

Results

A total of 274 complete responses were analysed. Perceived risks were rated substantially higher than perceived benefits across all dimensions. The most highly scored concerns were the risk of biased or skewed results (8.27/10), lack of transparency in AI decision-making (8.12/10), difficulty handling context-specific or rare cases (8.05/10), and the inability to replicate human reasoning and nuance (8.01/10). Despite 85% of respondents considering AI important or very important for the future of science, 27% anticipated a negative impact on research quality. Regarding disclosure, only 35.4% reported always declaring AI use when submitting manuscripts, while 10% admitted selectively disclosing or never doing so. Crucially, 71.2% feared that disclosure would negatively affect their work's reception by peer reviewers, and 64.2% by editors. Journal policies were seen as unclear or absent by over 30% of respondents. On best practices, 54% endorsed mandatory detailed disclosure for any AI use, 41.6% restricted it to substantial contributions, and 4.4% saw no need for disclosure. Workshops and seminars (61.7%), university-integrated teaching (56.6%), and online courses (53.3%) were the preferred training formats; only 12.8% were uninterested in AI education.

Discussion / Conclusion

Science researchers exhibit a clear awareness of AI's ethical risks, yet disclosure practices lag behind stated values, partly driven by fear of professional stigma. The field urgently needs both standardised, enforceable disclosure policies and structured training programmes embedding ethical reasoning alongside technical skills.

00352
Constructing an external control arm using the French REALYSA cohort to replicate outcomes of a randomized trial arm in advanced Hodgkin lymphoma.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

External control (EC) arms using routine care data can be used as comparators in clinical trials under certain conditions. The objective of this study was to assess the ability of an EC arm to replicate outcomes of a randomized controlled trial (RCT) arm receiving the same treatment strategy in advanced stage classical Hodgkin lymphoma, and serve as comparator in future trials.

Materials and methods

Using the prospective real-world data in lymphoma and survival in adults (REALYSA) cohort, we constructed an EC arm by applying eligibility criteria of the AHL2011 phase III RCT. Inverse probability weighting (IPW) was used to balance baseline characteristics between the EC arm and the RCT arm that received the same treatment. First, we estimated the propensity score (PS) that corresponded to the probability of a patient being in the RCT arm given the baseline predetermined covariates. Second, weights based on PS were calculated for estimating the average treatment effect on the treated (ATT). Progression-free survival (PFS) and overall response rate (ORR) at the end of first-line treatment were estimated in both arms. Hazard ratio (HR) for PFS and odds ratio (OR) for ORR were estimated using EC arm as reference. A sensitivity analysis evaluated PS matching.

Results

Three hundred ninety RCT patients and 191 EC patients were analysed. After PS weighting, patient's characteristics were well-balanced between arms. PFS estimates were similar in RCT and EC arms with an HR close to 1 (HR, 0.96; 95%CI, 0.57 to 1.76). ORR estimates were comparable in both arms; however, CI of OR was large. Weighting performed better than matching.

Discussion / Conclusion

Using PS weighting gave similar outcomes in the EC arm compared to the RCT arm. Our results suggest that EC studies using routine care data could be considered in the development of strategies for advanced Hodgkin lymphoma.

00369
Complications associated with psilocybin use outside a medical setting

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Psilocybin, a psychedelic compound found in mushrooms, is gaining interest for therapeutic use in psychiatry. Clinical trials conducted in controlled settings suggest a favorable safety profile, however, real-world data remain limited. The objective was to describe adverse events (AEs) reported at the national level in order to better characterize the safety profile of psilocybin in the real-life context.

Materials and methods

Data were extracted from the French National Pharmacovigilance Database from 2019 to 31/12/2025 using the terms “psilocybin,” “psilocin,” “psilocybe,” and “hallucinogenic mushroom.” A descriptive analysis was performed on all cases, excluding therapeutic use in clinical trials, then restricted to cases without co-reported substances, and supplemented by a qualitative analysis of case narratives.

Results

A total of 162 reports were identified, of which 54% involved at least one additional substance (mean: 4, range: [1–15]). The median age was 27 years (range: [2–61]),

81% were male, and 52% of cases were classified as serious. Among isolated psilocybin exposures (n=75), a total of 204 AEs were reported, 56% of which were psychiatric disorders (hallucinations, anxiety, agitation) and 10% gastrointestinal disorders (nausea, vomiting, abdominal pain), consistent with a pattern of typical AEs following psilocybin exposure.

Less frequent but clinically significant AEs were also reported: accidental intoxications (n=5), psychotic decompensation in predisposed individuals (n=2), deaths following a fall (n=2), worsening of anxious-depressive symptoms (n=1), and one myocardial infarction in a patient with cardiovascular risk factors.

Discussion / Conclusion

These national data confirm the predominance of acute psychiatric and gastrointestinal AEs, while highlighting the existence of rare yet serious complications. Despite the inherent limitations of spontaneous reporting, these findings underscore the importance of identifying psychiatric and cardiovascular vulnerability factors and ensuring appropriate supervision when administering psilocybin.

Keywords

psychedelics, psilocybin, adverse events, psychiatry

00380
Quality of Data : a Cornerstone for AI in HIV treatment optimization - the Octavia Project example

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Artificial Intelligence requires clean, structured, and standardized data to convert large-scale health records into reliable predictive tools. The NADIS database, encompassing over 93,000 HIV patients, offers a rich real-world resource, yet its raw form is heterogeneous, incomplete, and unsuitable for direct machine learning. The Octavia Project, addresses this by transforming these complex records into a high-quality clinical dataset, forming the essential first phase toward AI-driven optimization of HIV treatment.

Materials and methods

The database is structured into 32 distinct modules, including demographics, therapeutic history, safety data,comorbidities, prescriptions (over 6 million records), and biological examinations (hematology, lymphocyte subsets, creatinine, viral load, hepatic markers, etc.).

Data preparation followed three major steps:

1. Standardization: Automated harmonization of measurement units (e.g., mg/L to g/L) and correction of invalid or inconsistent units (including erroneous “%” entries). Missing or non-reported values (NA) were systematically identified and structured.

2. Statistical Cleaning: Duplicate entries were removed by prioritizing the most complete and most recent records. Outliers and probable data-entry errors (e.g., extreme weight values) were detected using a Modified Z-Score based on the median, ensuring robustness against extreme values.

3.Pharmaceutical Unification: Drug names, abbreviations, and combinations were mapped to their active molecules and alphabetically reordered to ensure therapeutic equivalence (e.g., A+B equivalent to B+A).

Results

This pipeline consolidated fragmented records into a coherent longitudinal dataset. By harmonizing 32 interconnected modules and eliminating inconsistencies, we reduced analytical bias and ensured each medical event was unique, traceable, and clinically credible. Thus, We obtained more than 90% of usable data for the predictive machine learning model to optimize HIV treatment.

Discussion / Conclusion

In medical application of AI, the reliability of predictions depends primarily on data quality rather than algorithmic complexity. Combining advanced data engineering with clinical expertise transforms real-world databases into safe, interpretable tools ready to support bedside decision-making.

Keywords

NADIS Database, Data Quality, AI in Healthcare, Data Cleaning, data engineering, Octavia Project, Pharmacovigilance

00381
Safety Data from Clinical Trials in the Context of Open Science in France: Challenges and Perspectives

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

A clearer distinction is emerging between scientific publication by the investigator and the regulatory submission of statistical and safety results by the sponsor (posting within an open science framework). These two approaches pursue distinct objectives: academic dissemination to enable peer review versus regulatory and public transparency. Posting places sponsors before major technical and political challenges. The first difficulty lies in identifying the appropriate posting platform.

Materials and methods

For clinical trials on medicinal products, the deployment of the Clinical Trials Information System (CTIS), established by European Regulation No. 536/2014, represents a structuring opportunity.

For clinical investigations involving medical devices, the EUDAMED database is expected, in the long term, to become the reference platform; in the meantime, the use of ClinicalTrials.gov remains necessary.

For Interventional Research Involving the Human Person (RIPH) excluding health products (Category 1) and for RIPH Category 2 studies, the absence of a fully operational dedicated European registry also leads to reliance on ClinicalTrials.gov.

Results

Producing a final safety report that can be readily posted requires anticipation of the specific formats and requirements of each database. Safety data cannot be published at the individual level (patient or event) without posing risks under the GDPR; they must therefore be aggregated and anonymized. While, for medicinal product trials, Annex IV of the European Regulation partially frames the reporting of results, Regulation (EU) 2017/745 on medical devices is far less prescriptive.

Discussion / Conclusion

The continued dependence on ClinicalTrials.gov - with access difficulties reported in 2025 - highlights the need for an operational European alternative. The concurrent use of distinct registries exposes stakeholders to risks of inconsistency and duplicate data entry. Within the framework of the National Plan for Open Science, the growing requirement for transparency will increase sponsors' vigilance, as they await clearer guidance from authorities in order to harmonize practices and secure the posting process.

Keywords

Clinical trial safety data

Open science

Europe

Scientific publication

Sponsor responsibilities

Regulatory transparency

Public transparency

Posting of results

00388
From emails to structured data: digital transformation of special situation reporting (medication errors) to enable future analyses

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Under-reporting and heterogeneous reporting of special situations, particularly medication errors, limit safety monitoring in clinical trials. A national REVISE study showed variability in practices and the need to strengthen reporting culture (1). Medication errors related to investigational drug complexity may compromise participant safety and data integrity (2,3) and are considered reportable safety information by the French competent authority (ANSM). At Angers University Hospital, reporting was fragmented. The objective was to standardize special situation reporting to enable real-time surveillance and future analyses.

Materials and methods

A fully digital workflow was implemented. At study initiation, clinical research associates promote reporting by presenting investigators with a predefined list of potential special situations established by the vigilance. Sites report directly in the study eCRF (Ennov Clinical®), generating automatic notifications to vigilance and monitoring teams and enabling real-time surveillance. Cases are then documented by the vigilance in BlueKango®, an institutional web-based quality and risk-management platform for adverse event reporting and risk analysis, ensuring standardized data capture and traceability.

Predefined variables included error type and stage, confirmed/potential status, treatment involved, qualitative context, occurrence and reporting dates, linkage with adverse events and seriousness, identification of serious breaches, and corrective and preventive actions with effectiveness assessment. Each case was medically reviewed and closed by the vigilance officer to ensure data quality and regulatory consistency.

Results

Before implementation, reporting was rare (2 notifications in 2024 across 5 medicinal trials) and non-standardized. The digital workflow enables systematic capture, centralized storage, and consistent follow-up, creating an analysis-ready sponsor database. It also facilitates detection of serious breaches and contributing factors related to protocol design or investigational product management.

Discussion / Conclusion

Digitalization transforms fragmented declarations into structured safety data, supporting reporting culture, regulatory compliance, and proactive risk management. Ongoing evaluation will assess adoption, completeness, and timeliness and support future observational analyses of medication error patterns.

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Keywords

medication error; special situations; clinical trials; digitalization; data quality.

00428
A Mechanistic PK/PD Model to Predict VWF and FVIII Response to Desmopressin in Mild Hemophilia A and Female Carriers

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Desmopressin (DDAVP) is commonly used to increase hemostatic factors in patients with mild bleeding disorders such as mild hemophilia A. However, marked inter-individual variability in response limits prediction of treatment efficacy.

Objectives : To develop a mechanistic pharmacokinetic/pharmacodynamic (PK/PD) model of DDAVP to describe the time course of von Willebrand factor (VWF) and factor VIII (FVIII), using a quantitative systems pharmacology (QSP) approach to account for inter-individual variability and identify patient characteristics influencing response.

Materials and methods

Data from 72 subjects with mild or moderate hemophilia A or female carriers were analyzed. Each received an intravenous infusion of approximately 0.3 µg/kg DDAVP

over 30 minutes. Plasma DDAVP, FVIII and VWF concentrations were measured at multiple points, yielding 631 observations. A nonlinear mixed-effects modeling approach, based on a quantitative systems pharmacology (QSP) framework, was used to describe DDAVP pharmacokinetics and its effects on VWF and FVIII.

Results

DDAVP pharmacokinetics were best described by a two-compartment model (Cl = 8.4 L/h, V1 = 17.1 L, V2 = 10.1 L, Q =7.0 L/h). VWF and FVIII responses were well captured by mechanistic indirect response models within a quantitative systems pharmacology (QSP) framework. FVIII levels increased concurrently with VWF following DDAVP administration, supporting a stimulatory effect of DDAVP on FVIII release. Body weight and age markedly influenced DDAVP exposure and subsequent VWF/FVIII responses, with simulated pediatric profiles showing approximately 35-40% lower post-DDAVP exposure. Female sex was associated with higher FVIII responses.

Discussion / Conclusion

This study presents the first mechanistic integrated PK/PD model jointly describing DDAVP, VWF, and FVIII dynamics in patients with mild hemophilia A and female carriers. The model quantitatively characterizes inter-individual variability in response and provides a framework to support model-informed individualized dosing in clinical practice.

00437
Clinical Trials in Rare Diseases: A Global Observational Study Over 20 Years Using the Orphanet Database

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Rare diseases comprise more than 7,000 heterogeneous conditions, defined in Europe as affecting fewer than 1 in 2,000 individuals, and impacting approximately 350 million people worldwide. Fewer than 10% currently benefit from a disease-specific treatment[1,2].The aim of our study was to describe interventional clinical trials in rare diseases registered in the Orphanet database, their characteristics, and their evolution over time.

Materials and methods

We conducted a retrospective descriptive study including interventional trials recorded in the Orphanet database, primarily sourced from ClinicalTrials.gov, EudraCT/CTIS, and ICTRP. Data collection began in 2004 but includes some trials that started in the early 1990s. Extracted variables included trial start and end dates, studied diseases and molecules, geographic coverage, development phase, and sponsor type.

Results

A total of 7,910 trials were identified, including 4,907 multinational and 3,003 national studies. Annual trial initiation increased steadily until 2017 (608 trials initiated), followed by a decline to 147 trials in 2025. Trials were predominantly multinational (49.8%), followed by national (38.0%) and European-only studies (12.2%). Phase II (29%) and Phase III (30%) trials predominated. Overall, 1,427 distinct rare diseases were investigated, with onco-hematology predominating and multiple myeloma being the most studied disease (5.5%).Cystic fibrosis was the leading non-oncologic disease (1.9%). The 20 most frequently studied diseases accounted for 44% of all trials. A total of 2,094 distinct molecules were evaluated, largely anticancer therapies. Multinational trials were predominantly industry-sponsored, while the National Cancer Institute represented the leading academic sponsor.

Discussion / Conclusion

Drawing on a structured international database spanning more than 20 years, this study represents one of the most extensive descriptive analyses of rare disease clinical trials to date. Trial initiation increased steadily until 2017, followed by a marked decline in recent years. Clinical trial activity was predominantly industry-sponsored and largely concentrated in oncologic indications. However, a large proportion of rare diseases remain largely unstudied.

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We gratefully acknowledge Orphanet for providing access to the clinical trials database used in this study.

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Keywords

Rare diseases

Clinical trials

Orphanet

00500
Impact of salt intake on blood pressure during treatment with bevacizumab

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Bevacizumab is an anti-angiogenic monoclonal antibody used in cancer treatment. Elevated systolic blood pressure (SBP) is a frequent adverse effect of anti-angiogenic drugs, and no biomarker currently predicts its onset. This study evaluated sodium intake, estimated by 24-hour natriuresis, as a potential biomarker associated with SBP elevation during bevacizumab therapy.

Materials and methods

Prospective, single-center cohort of adults starting bevacizumab for cancer. Self-measurements of SBP were taken before the first three courses (C1 to C3) of bevacizumab. 24-hour natriuresis (Na24), blood bevacizumab concentration (Cbev), NTproBNP, plasma methoxylated derivatives, aldosterone, and urinary cortisol were analyzed. The statistical analysis compared SBP between patients with high versus low Na24 (> or < median) before and after adjustment for other biomarkers.

Results

28 patients with cancer (88% colon cancer) were included. Patients in the high natriuresis group vs. low had higher SBP before C1 (134 vs. 122 mmHg) and before C3 (136 vs. 125 mmHg). The increase in SBP between C1 and C3 was + 4.2 ± 9.6 mmHg ($p<0.05$) in the overall cohort, and was greater in the high natriuresis group than in the low one (+ 5.7 vs. + 3.0 mmHg, NS). Na24 evolved in the opposite direction between C1 and C3, increasing in the low natriuresis group and decreasing

in the high natriuresis group. No other biomarkers changed significantly between C1 and C3, except for Cbev, nor between the two groups. Factors most strongly associated with SBP during treatment were pre-existing hypertension, male sex, and natriuresis, but not Cbev.

Discussion / Conclusion

High natriuresis is associated with higher SBP and appears to be a moderate predictor of blood pressure elevation in patients treated with bevacizumab.

00545
BleedRisk: a Bayesian online application for predicting Apixaban washout time

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Managing patients treated with apixaban who require urgent surgery remains a clinical dilemma: should clinicians wait for spontaneous drug clearance or administer reversal agents? Current guidelines recommend a safety threshold of apixaban <30 ng/mL before invasive procedures (1). However, rapid drug monitoring is not consistently available in routine practice. To improve perioperative management, we developed BleedRisk (2), a Bayesian-based online tool designed to predict individual time-to-threshold based on patient characteristics and drug concentrations. This study aimed to validate the application and determine whether a single plasma concentration is sufficient, compared with a three-sample kinetic profile, to accurately estimate the required washout time.

Materials and methods

A retrospective pharmacokinetic study was conducted using data collected between January 2015 and January 2025. Eligible patients were undergoing apixaban discontinuation and had at least two plasma concentrations measured within a 72-hour interval. Covariates included age, sex, total body weight, dosing regimen, and creatinine clearance. Model performance was assessed by evaluating the robustness of posterior Bayesian estimates and informational gain, specifically quantifying refinement of the individual elimination half-life when integrating one, three, or more observed concentrations as priors.

Results

The initial concentration-based database included 6,899 plasma measurements from 2,000 patients (mean 3.4 samples per patient). After verification of covariate availability and confirmation of clinically appropriate concentration decay profiles, approximately 1,000 patients remained in the database. Preliminary validation was conducted in 43 patients. Predictive performance was satisfactory. Bland–Altman analysis comparing single-sample and three-sample estimations demonstrated a low mean bias of –2.17 hours. Although multiple measurements reduced the width of confidence intervals, integration of a single concentration into the Bayesian framework yielded clinically comparable washout time predictions in the majority of cases.

Discussion / Conclusion

BleedRisk is a robust, data-driven tool for estimating individualized apixaban washout times. Further validation using the full 1,000-patient dataset is ongoing to confirm these findings.

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Keywords

Apixaban; Pharmacokinetics; Preoperative management

00555
Does citalopram prescription still justified in 2026 ?

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Since French marketing of escitalopram (SEROPLEX®) in 2002, all healthcare professionals know that 20 mg of racemic citalopram (R+S) is equivalent to 10 mg of escitalopram, as R-form has no efficacy on depression. However, R-citalopram has its own properties1 which can nuance this dogma and even ask questions of racemic citalopram prescription in 2026. The goal of this work was to precise the R-citalopram influence on racemic efficacy and tolerance and to consider citalopram prescription for depression.

Materials and methods

A litterature review has been realized on pubmed with the keywords «citalopram escitalopram pharmacodynamic pharmacokinetic efficacy toxicity». French Ambulatory deliveries on MedicAM and our laboratory therapeutic drug monitoring data have also been checked.

Results

A study from Sánchez et al.2 precised that R-citalopram decreases S-citalopram affinity on serotonin transporter (SERT) and consequently the efficacy on serotonin reuptake inhibition. The clinical effect appeared later with an equivalent dose of racemic compared with S-citalopram. About adverse events, electrocardiogram intervalQT prolongation was highest with racemic citalopram than with S-citalopram equivalent dose3. Half-life of R-citalopram is a bit higher than S-citalopram and at

steady-state, seric R-citalopram concentration is also higher, contradicting the (R+S/S) well-known 2/1 ratio ; as the fact than therapeutic reference ranges (µg/L) haven't a 2/1 ratio (citalopram : 50-110, escitalopram : 15-80)4. CYP2D6 metabolizes mainly R-citalopram and 2C19/3A4 S-citalopram, differentiating the pharmacogenetic recommendations for the 2 medications. MedicAM data showed a year citalopram boxes deliveries decreased, between 2012 to 2024, from 2.7 million to 1.2 whereas the escitalopram year number stayed around 9 million. The numbers of dosages in our laboratory, for citalopram and escitalopram respectively, decreased and increased since 2014.

Discussion / Conclusion

Action delay augmentation, decreasing of efficacy and increasing of cardiac risks don't give any arguments to prescribe citalopram instead of escitalopram ; justifying decreasing of citalopram prescriptions.

Reference(s)

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2. Sánchez C and al, Escitalopram versus citalopram: the surprising role of the R-enantiomer, 2004, doi:10.1007/s00213-004-1865-z.

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Keywords

Enantiomers, R-citalopram, S-citalopram, risk-benefit ratio

00570
Effectiveness of antihistamine eye drops in the treatment of allergic conjunctivitis in Abidjan

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Allergic conjunctivitis, common in young subjects in urban areas, is often associated with an atopic background. The aim of this study was to evaluate the effectiveness and tolerance of antihistamine eye drops, as well as their impact on quality of life.

Materials and methods

This descriptive prospective study was conducted over 6 months with seventy-seven patients suffering from allergic conjunctivitis at the ophthalmology department of the CHU of Cocody (Abidjan, Côte d'Ivoire). The data collected concerned sociodemographic characteristics, allergic history, clinical data, prescribed treatments, symptom progression, patient satisfaction, and the occurrence of adverse effects. The results were compared with data from the literature.

Results

The patients were female (80%), with an average age of 20.4 years, and were pupils or students. Personal (71.4%) and family (19.5%) allergic histories were present. Olopatadine eye drops were prescribed (62.3%), at a dosage of one drop twice a day

(88.3%). Rapid improvement (less than 15 minutes) was observed in 70% of patients, and satisfaction reached 90.9% when an eye wash was performed beforehand. No adverse effects or relapse were reported during follow-up.

Discussion / Conclusion

Antihistamine eye drops, particularly olopatadine, are remarkably effective and well tolerated, especially when combined with prior eye washing. Despite the atopic background, appropriate management and therapeutic education of patients are necessary to improve patients' quality of life. Longer-term studies will make it possible to assess the durability of the results.

Reference(s)

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Keywords

Allergic conjunctivitis - antihistamines - olopatadine eye drops – efficacy -tolerance – atopic

00590
Medical Nihilism or Medical Hubris? Assessing the accuracy of ChatGPT-4o's answers on the effectiveness of therapeutic interventions

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Generative AI chatbots are increasingly used for health information and may influence therapeutic decision-making. We evaluated the accuracy of ChatGPT-4o in appraising the effectiveness of therapeutic interventions compared with Cochrane systematic reviews. We assessed the model's ability to report GRADE certainty of evidence, effect direction and effect size.

Materials and methods

We conducted a cross-sectional diagnostic test-accuracy study (preregistered on OSF: https://osf.io/c6mdp). We asked 500 semi-standardized questions, each derived from one efficacy-related PICO (Patient, Intervention, Control, Outcome) randomly selected from the 500 most recent Cochrane reviews, to ChatGPT-4o in English and French. Queries were submitted via the standard ChatGPT web interface between June and August 2025. Agreement with Cochrane was quantified for GRADE and effect direction using weighted kappa and directional bias was assessed with Mean Signed Error (MSE). Agreement for point estimates (RR/OR/HR; log-transformed) was evaluated with intraclass correlation coefficients (ICC) and directional bias was assessed with mean relative effect-size ratio.

Results

For English prompts, agreement between ChatGPT-4o and Cochrane on GRADE certainty was moderate (linear-weighted kappa = 0.46, 95% CI 0.40–0.52) with a positive mean signed error indicating systematic overestimation (MSE = +0.20, 95% CI 0.12–0.30). Agreement on effect direction was also moderate (kappa = 0.57, 95% CI 0.46–0.67) with overestimation (MSE = +0.15, 95% CI 0.10–0.20). Point estimates of effect size were reproduced with good accuracy (aggregated RR/OR/HR ICC = 0.82, 95% CI 0.77–0.86) and showed no directional bias (mean relative effect-size ratio = 1.03, 95% CI 0.98–1.09).

Discussion / Conclusion

Across a large randomized sample of therapeutic questions, ChatGPT-4o showed moderate agreement with Cochrane for GRADE certainty and effect direction, with a consistent tendency to overestimate certainty and effectiveness (medical hubris), especially in French. Point estimates of effect size were reproduced with good agreement and no systematic bias. However, users should interpret therapeutic chatbot advice cautiously and verify against trusted evidence syntheses.

Reference(s)

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Keywords

Therapeutics ; Cochrane ; Clinical Epidemiology ; ChatGPT

00595
Temporal Erosion of Traditional Study Design Labels and the Rise of “Real–World” Framing (2010–2024) in Pharmacological Research

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The term “real–world” has increasingly emerged in the medical literature as a descriptor of non-randomized designs. However, unlike established labels, “real–world” does not unambiguously correspond to a specific epidemiological design. We aimed to quantify and compare the trends in the use of real-world terminology.

Materials and methods

A structured PubMed search identified studies published between 2010 and 2024, assessing therapeutic interventions and containing at least one of the following descriptors in the title or abstract: observational, cohort, case–control, cross-sectional, or “real-world” (or equivalent expressions). Extracted data included PMID, title, abstract, publication year, journal, and authors. Annual proportions of articles mentioning “real–world” were calculated. A binomial logistic univariate regression model assessed the association between publication year and the presence of the term “real-world”, with model fit evaluated using McFadden’s pseudo–R^2. The same model was used to assess traditional design descriptors.

Results

The search yielded 44,144 studies. 52% were distributed across ten medical domains, including onco-hematology (32.4%), infectiology (18.7%) and cardiology (10.9%). Of the 44,144 studies, 19,8% used “real-world” and 6.0% used “real-world” and a traditional descriptor. The proportion mentioning “real–world” increased from 8.5% (95%CI 6.9–10.2) in 2010 to 28.3% (95%CI 27.1–29.6) in 2024, corresponding to a 3.3–fold increase. Logistic regression showed an OR per calendar year of 1.120 (95%CI 1.110–1.130), indicating a consistent annual increase in the use of “real-world” terminology (pseudo-R^2 = 0.885). Traditional design descriptors such as cohort (OR 0.984, 95%CI 0.979–0.989), case-control (OR 0.954, 95%CI 0.943–0.965), and cross-sectional (OR 0.986, 95%CI 0.979–0.993) declined over time.

Discussion / Conclusion

Between 2010 and 2024, the use of “real-world” terminology increased exponentially while traditional epidemiological design labels declined suggesting a shift in authors and publishers’ editorial choices towards a more ambiguous label. The consequences regarding interpretability remain to be determined.

Keywords

Real-World, Real-World Evidence, cohort studies (MeSH), observational studies (MeSH), Abstracting and indexing Methods (MeSH), Semantics (MeSH)

00626
Decoding Methotrexate resistance in Rheumatoid Arthritis through integrative plasma proteomics

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Methotrexate (MTX) is the anchor therapy for rheumatoid arthritis (RA); however, 30–50% of patients show an inadequate response. Early identification of MTX non-response is crucial for optimizing treatment. We performed untargeted plasma proteomic analysis to identify molecular signatures discriminating responders from non-responders after six months of treatment.

Materials and methods

RA patients were classified as responders or non-responders based on the Disease Activity Score (DAS28). Plasma samples collected at month 6 underwent untargeted high-resolution mass spectrometry with label-free quantification. Differential expression was analyzed using Limma (Benjamini–Hochberg correction). Multivariate modeling included sparse Partial Least Squares Discriminant Analysis (sPLS-DA), Random Forest, and Elastic Net regression. A consensus panel was defined by proteins selected by at least three of these four methods. Functional insights were derived via KEGG/Reactome enrichment and Louvain-clustered correlation networks.

Results

Among 69 patients (25 responders, 44 non-responders), 524 proteins were identified. Eighty-four proteins were differentially expressed (adjusted $p < 0.05$), with 24 upregulated and 60 downregulated in responders. The sPLS-DA (AUC = 0.955),

Random Forest (AUC = 0.995), and Elastic Net (AUC = 0.962) models demonstrated high discriminative power, yielding a robust 23-protein consensus panel with Filamin A emerging as a top candidate for biomarker development. Responders exhibited reduced systemic inflammation (notably decreased C-reactive protein levels), modulated lipid metabolism, and cytoskeletal remodeling. Enrichment analysis highlighted complement and coagulation cascades, cholesterol metabolism, and neutrophil degranulation.

Discussion / Conclusion

This integrative proteomic approach identified a protein signature discriminating MTX responders with high accuracy. The identification of Filamin A as a top candidate is particularly significant, as it is a known RA-specific autoantigen linked to synovial cell invasion and the gut-joint inflammatory axis (2). While these month-6 markers reflect treatment efficacy, future analysis of pre-treatment samples will determine whether this signature can serve as a predictive biomarker, enabling earlier therapeutic stratification and advancing precision medicine in RA.

Reference(s)

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Keywords

Rheumatoid arthritis; Methotrexate resistance; Pharmacoproteomics; Treatment response

00648
Determinants of the first diarrhea episode in mycophenolic acid-treated renal transplant recipients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Mycophenolic acid (MPA) is a cornerstone of immunosuppressive therapy after renal transplantation but is frequently associated with diarrhea, leading to treatment modification and impaired quality of life. While MPA-related gastrointestinal toxicity is well documented, factors associated with the first diarrhea episode after transplantation remain poorly defined. Identifying early determinants is crucial for risk stratification and prevention.

Materials and methods

We analyzed data from the EPIGREN/EPHEGREN(1) retrospective cohort, including adult renal transplant recipients enrolled within 30 days after transplantation, all treated with MPA and followed for up to three years. Diarrhea was self-reported using standardized questionnaires administered at months 1, 3, 6, 12, 18, 24, and 36 post-transplantation. Patients reporting diarrhea during the first month were excluded to ensure accurate time-to-event analysis, and first diarrhea episodes were assessed from month 3 onward. Factors associated with the first diarrhea episode were screened using random survival forests and their pronostic value assessed by Cox regression.

Results

Among 323 eligible patients, 110 experienced a first episode of diarrhea during follow-up. Independent predictors included the type of calcineurin inhibitor, cytomegalovirus infection, antiviral therapy at inclusion, and antifungal treatment at inclusion. Exposure to antifungal therapy at inclusion was associated with a significantly reduced risk of first diarrhea (hazard ratio 0.43, 95% confidence interval 0.26–0.70).

Discussion / Conclusion

Diarrhea is common in MPA-treated renal transplant recipients and is influenced by early clinical and pharmacological factors. The protective association with antifungal therapy supports a role for microbial-related mechanisms in MPA-associated gastrointestinal toxicity and highlights potentially modifiable risk factors.

Reference(s)

(1) Villeneuve, C. et al. (2020) Patient Educ. Couns. 103, 189–198

Keywords

renal transplantation, mycophenolic acid, gastointestinal adverse effect, first diarrhea

00670
Optimal dalteparin dose in obese patients – (THE ODOP STUDY)

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Optimal dosing strategies for anticoagulants in obese population are necessary, as the risk of thromboembolism and atrial fibrillation in this population is increased. Although the volume of distribution (Vd) of dalteparin increases proportionally with increasing total bodyweight (TBW), the manufacturer recommends dose capping on 18.000 IU daily in patients >90 kg. Limited information is available regarding higher doses of therapeutic dalteparin. Our study aimed to evaluate this current practice.

Materials and methods

In this observational, multicentre cohort study, 3 years of data were retrospectively collected in our hospitals. Patients weighing >99 kg with a dalteparin dose ≥7500 IU/day were included. We evaluated anti-Xa levels at 3-5 hours post injection in steady state and differentiated between anti-Xa levels below upper threshold (BT) of <2.0 IU/ml for once daily dosing and <1.0 IU/ml for twice daily dosing and anti-Xa levels above this threshold (AT). Furthermore, we identified thrombotic and bleeding events (classified as minor of major). We used a repeated measures proportion-nal odds model to estimate the association between anti-Xa categories and dose categories.

Results

326 anti-Xa measurements were taken in 219 patients. 21 samples were from patients weighing >149kg, and 66 samples were from patients with class III obesity (BMI >40). Of all anti-Xa mea-surements, 89% were BT. Off the AT anti-Xa levels, 38.9 % were obtained in patients with class III obesity. 16 minor and 14 major bleeding events were reported, mostly in 100% dosed patients (88% and 79%, resp.) with BT anti-Xa levels (94% and 93%, resp.). 5 thrombotic events were reported, of which 3 (60%) in <85% dosed patients.

Discussion / Conclusion

Uncapped TBW dalteparin dose in patients >99 kg resulted in few AT anti-Xa levels with no increase in bleeding or thrombotic events. We recommend uncapped dosing of 200 IU/kg on TBW in all classes of obese patients, without the need for anti-Xa monitoring.

4- Pharmacovigilance

00027
Machine learning in pharmacovigilance : a proof-of-concept study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Machine learning (ML) applications in pharmacovigilance remain limited and underexplored. Using data from the French National pharmacovigilance database (FNPV), this proof-of-concept study aimed to assess the feasibility of using a ML algorithm—extreme gradient boosting (XGBoost)—combined with SHapley Additive exPlanations (SHAP) analysis, to classify a well-defined drug-adverse reaction pair (warfarin-associated gastrointestinal bleeding) and identify risk factors for reporting this adverse reaction.

Materials and methods

We extracted individual case safety reports (ICSRs) involving warfarine from the FNPV. Folowing data pre-processing, the dataset was randomly split into a training set (75%) and an independent test set (25%). The XGBoost algorithm was trained to classify reports as either gastrointestinal bleeding or non-gastrointestinal bleeding adverse reactions. Model performance was assessed on the test set using multiple metrics: accuracy, precision, recall, F1-score, and the area under the receiver operating characteristic curve (AUC-ROC). Feature importance and directional effects were interpreted using SHAP values.

Results

A total of 2,025 ICSRs involving warfarin were extracted from the FNPV. After preprocessing, 1,045 ICSRs were retained. On the test set, the XGBoost model demonstrated an accuracy of 0.67, recall of 0.81, precision of 0.67, F1-score of 0.74, and an AUC-ROC of 0.719. SHAP analysis revealed four most influential features in predicting gastrointestinal bleeding reporting: age, history of renal dysfunction, antiaggregant use, and gastrointestinal bleeding risk factors.

Discussion / Conclusion

We demonstrated the feasibility of using an XGBoost algorithm combined with SHAP analysis to pharmacovigilance data to classify adverse drug reactions and identify potential predictive features of reporting, after a post hoc model interpretation by pharmacologists.

00059
Are we just observers? The clinical activity of pharmacovigilance centers

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

One of the missions of the Regional Pharmacovigilance Centers (RPVCs) is to provide expert pharmacological advice regarding suspected adverse drug reactions (ADRs) and medication management, particularly within the university hospitals in which they are located. To date, the impact of these recommendations on the management of patients who experienced ADRs has not been clearly assessed. The aim of this study was to analyze the impact of responses provided by the Toulouse RPVC to requests for advice originating from Toulouse University Hospital.

Materials and methods

All requests for advice from Toulouse University Hospital (excluding pregnancy-related queries) recorded in 2024 were extracted from our database. Only requests submitted prior to any decision regarding the patient's drug management were included. The impact of RPVC responses was assessed according to: (1) the consistency between the advice provided and the clinical action undertaken, and (2) documentation of the RPVC responses in the hospital medical report. A predefined scale was developed to classify impact as "certain", "probable", or "uncertain". Each case was independently assessed by two reviewers; disagreements were resolved by a third reviewer. Inter-rater agreement was evaluated using Cohen's kappa coefficient.

Results

Among the 347 requests recorded in 2024, 136 were eligible for analysis, of which 92 were submitted before any patient management decision was made. Patient management decision was consistent with RPVC recommendations in 78% of cases (n=72), and the impact was considered "certain" in 62% of cases (n=57) and "probable" in 24% of cases (n=22). Inter-rater agreement was excellent (κ = 0.88).

Discussion / Conclusion

When the RPVC is consulted prior to clinical management of a patient who has experienced an ADR, its recommendations are largely taken into account, with a “certain” impact on medical decision in the majority of cases. This study highlights the importance of RPVC clinical activity within university hospitals.

00064
Development of a Structured Risk Management Plan-Based Tool for Signal Detection in Clinical Trials

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Signal detection is a core activity of pharmacovigilance and is essential for the continuous assessment of the benefit-risk balance of medicinal products. Within clinical trials, early identification and monitoring of safety concerns are particularly important. Risk Management Plans (RMPs) provide a structured framework describing important identified risks and potential risks. Therefore, it represents a relevant tool to orient safety surveillance activities of authorized medicines during clinical trials.

Materials and methods

Following dedicated training on signal detection principles, a comprehensive Excel-based table compiling safety concerns was created for investigational medicinal products monitored by our clinical trials vigilance unit. For centrally authorised products, versioned RMPs were retreived from publicly available European Medicines Agency (EMA). For non-centrally authorised products, safety were extracted from documentation issued by the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh). The table focused on important identified risks, defined by sufficient evidence of an association, and important potential risks, corresponding to signals not yet meeting the criteria for identification, in accordance with ICH E2E guidance.

Results

The resulting table provided a harmonised overview of safety concerns for 16 investigational medicinal products including 2 under additional monitoring. A total of 9 safety concerns were identified that were not listed in the available safety reference documents, including 3 classified as important identified risks. Drug interactions accounted for 4.8% of safety concerns, while risks related to specific populations also represented 4.8%. The table is intended to be reviewed and updated on a semi-annual basis, combining literature surveillance and internal safety database analyses.

Discussion / Conclusion

Implementation of such tools may contribute to improved anticipation, documentation and management of safety signals in our service. However, heterogeneity in RMP quality was observed, with some marketing authorisation holders merely reproducing the full SmPC without adequate prioritisation or synthesis of safety concerns.

Reference(s)

Medicines | European Medicines Agency (EMA)

Heads of Medicines Agencies: RMP

Keywords

Clinical trials safety - Risk Management Plan (RMP) - Important Identified risk - Important Potential risk - Safety monitoring tool

00077
Guillain-Barré Syndrome in an AML patient on ivosidenib: hematology–neurology–pharmacovigilance collaboration ensuring safe treatment continuation

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Guillain–Barré syndrome (GBS) is a rare but serious immune-mediated polyradiculoneuropathy. Its occurrence in a patient receiving ivosidenib raises a therapeutic challenge, as US prescribing information recommends permanent discontinuation in case of GBS. We report a case in which hematology–neurology–pharmacovigilance collaboration supported continuation of the only disease-controlling therapy after individualized benefit–risk assessment.

Materials and methods

Imputability was assessed using the time relationship to ivosidenib intake and exclusion of alternative diagnoses. Data from the French pharmacovigilance network (BNPV) and the manufacturer were scrutinized. Hematology, neurology, and

pharmacovigilance teams jointly evaluated the benefit–risk balance. Cofactors, including recent influenza vaccination and Lyme serology, were considered.

Results

A 79-year-old man receiving azacitidine plus ivosidenib for IDH1-mutated acute myeloid leukemia (AML) developed progressive gait instability, distal sensory loss, proximal weakness, and areflexia four months after ivosidenib initiation and 2–3 weeks after influenza vaccination. CSF showed albumin-leucocyte count dissociation. A positive CSF Lyme serology was found, but neuroborreliosis was excluded. Electroneuromyography confirmed acute demyelinating polyradiculoneuropathy. Ivosidenib discontinuation, intravenous immunoglobulins and physiotherapy led to rapid improvement. Azacitidine was not suspected, as it is not associated with SGB.

Pharmacovigilance review identified five GBS cases occurring 15 days to 4 months after starting ivosidenib but documentation was limited and/or causality weak. In our patient, idiopathic or vaccine–triggered GBS were the most plausible hypotheses, with temporality favouring vaccination. Published cases with permanent ivosidenib discontinuation showed rapid AML progression and death. Neurological advice judged recurrence risk low while hematology team highlighted the major loss of chance associated with discontinuation. Ivosidenib was reintroduced at full dose without recurrence at one month.

Discussion / Conclusion

Strict application of US discontinuation recommendations would have led to an unjustified loss of survival opportunity. Close collaboration between clinicians and pharmacovigilance experts enabled a personalized, evidence-based decision allowing safe continuation of essential therapy.

Keywords

ivosidenib, IDH1 inhibitor, Guillain-Barré syndrome, multidiscplinary pharmacovigilance collaboration

00080
Optimization of Literature Surveillance for Academic Sponsors Using Artificial Intelligence: An Organizational Lever for Clinical Trial Safety

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Literature surveillance conducted by clinical trial sponsors is a regulatory requirement aimed at the early detection of safety signals related to investigational medicinal products. Regular searches of PubMed generate a large volume of publications, whose selection currently relies on time-consuming and potentially variable expert review. The objective of this study was to develop and validate an artificial intelligence (AI)-based tool to support the automated selection of safety-relevant articles for clinical trial pharmacovigilance.

Materials and methods

Twelve clinical trials sponsored by Rennes University Hospital were included (26 investigational drugs). Structured queries (“drug name” AND “adverse effects”) identified 36,656 potentially relevant articles using the BIBOT program. Abstracts were segmented into sentences and preprocessed using natural language processing (NLP) techniques, including concept extraction and dimensionality reduction.

Two complementary approaches were implemented: (1) manual annotation of sentences and titles retrieved from the queries into three categories (+1 selection, 0 neutral, −1 exclusion) with inter-reviewer reconciliation; and (2) identification of informative sentences and keywords from preselected relevant articles.

An agent-based architecture was developed, with a central aggregator coordinating multiple specialized agents (Keep/Reject) built on open-source large language models. More than 80 configurations were benchmarked. Model performance was assessed using cross-validation with F1-score as the primary metric

Results

A total of 36,656 articles were automatically screened. Overall, 1,189 sentences and 273 titles were annotated by three reviewers and used for training, complemented by an expert corpus derived from 10 relevant articles. The best-performing model was based on Qwen3 within a 5-agent architecture. The optimal configuration achieved an F1-score of approximately 0.7 for classifying texts according to pharmacovigilance relevance. Comparative validation at the article level is ongoing.

Discussion / Conclusion

Integrating AI into literature surveillance represents a major organizational improvement for academic sponsors, potentially reducing workload, standardizing practices, enhancing traceability, and supporting earlier detection of safety signals. Real-world validation will determine its operational applicability.

Keywords

Clinical trials - Literature surveillance - Artificial Intelligence

00095
A case of Ogilvie Syndrome induced by antipsychotics

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Gastrointestinal disorders like constipation are well-known adverse drug reactions of antipsychotic. However, Ogilvie syndrome (OS), also known as colonic pseudo-obstruction, is rarely described.

Materials and methods

We present a case of OS occurring with sulpiride and aripiprazole, registered in French Pharmacovigilance Database with numbers NY2025001046 and NY2025001063, and completed by an analysis of Vigibase® (January 08, 2026).

Results

A 61-years-old man, with history of appendectomy and Diogene syndrome, was treated with sulpiride orally (50 mg every 6 hours) since 1990 for deficit schizophrenia. In March 2024, he was hospitalized with community-acquired pneumonia. Sulpiride was stopped for 4 days, then gradually reintroduced at the initial dose. One week after, he presented an OS with drowsiness, dystonia, and hypersalivation. Sulpiride was stopped and neostigmine introduced. Symptoms resolved after 9 days. Sulpiride was reintroduced combined with tropatepine. Sulpiride was stopped again due to OS recurrence with septic shock. Neostigmine was reintroduced and exsufflation was required.

Sulpiride was replaced with aripiprazole (5 mg per day). Three days later, neostigmine was discontinued, and a recurrence of OS was observed the fourth day. Aripiprazole was stopped and neostigmine reintroduced again for 9 days. Finally, 2 months after these events, aripiprazole was reintroduced without recurrence of OS.

In Vigibase®, using preferred term “Intestinal pseudo-obstruction”, we found no other reports with sulpiride, and only one other case with aripiprazole but with other suspect drugs (clozapine, venlafaxine, loxapine, and atropine). Overall, the most frequently reported substance is clozapine (137 reports, including 70 reports where clozapine is the only suspect drug).

Discussion / Conclusion

Few cases of OS with antipsychotic have been reported to date [1-4], but none with sulpiride. To our current knowledge, this is the first case of diagnosed OS with sulpiride with a recurrence following reintroduction. Here, the occurrence of a cross-reaction is difficult to assert, considering the negative rechallenge with aripiprazole.

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Keywords

Adverse drug reaction, pharmacovigilance, Ogilvie syndrome, antipsychotic, sulpiride

00097
Behind the counter: a snapshot of melatonine dispensing practices

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Melatonin is currently available in France in numerous dietary supplements (daily doses < 2 mg), and also in medicines (Slenyto®, Circadin®; daily doses from 2 to 10 mg); The main distribution channels are community pharmacies . We aimed to study dispensing practices of melatonin in community pharmacies.

Materials and methods

We sent a questionnaire to community pharmacies in the Hauts-de-France region registered by the Regional Union of healthcare professionals (URPS) pharmacists. It consisted of four parts: characteristics of the pharmacy, dispensation characteristics of melatonin-based drugs, preparations, and dietary supplements, adverse effects observed with melatonin and pharmacists' knowledge about it.

Results

Among the 67 pharmacies that responded to the questionnaire, a varied profile emerged in terms of both type and size. With regard to prescriptions, it came from general practitioners or specialists (neurology, paediatrics, psychiatry) and concerned patient of all ages, mainly adults. The standard daily dosage is 2 mg daily, but daily doses exceeding 10 mg are observed by 1.5% of respondents. Melatonin-based preparations are dispensed at least one per month by 40 respondents. The monthly dispensing of dietary supplements containing melatonin ranged from 2 to more than 100 per month with 62 % dispensing more than 10. Capsules and tablets

were the most frequently dispensed, while gummies remained in the minority. 4.6% of respondents had already reported adverse effects related to melatonin use.

Discussion / Conclusion

This study highlighted the reality of melatonin consumption in our region and probably in France, whatever the form, with potentially high doses. However, adverse effects reported to pharmacists are limited. This is consistent with the increase in the consumption of dietary supplements by French people (61% in 2024 compared to 46% in 2018) (1). It could be interesting to study whether the increase in melatonin consumption is accompanied by a decrease in the consumption of other medicines (e.g. Antihistamines, benzodiazepines).

Reference(s)

(1) https://www.synadiet.org/les-complements-alimentaires/leur-consommation/

Keywords

Melatonin ; dietary supplements ; community pharmacies ; dispensing ; adverse effects

00098
Comparative Safety of Lithium in Adolescents and Adults: A Disproportionality Analysis Using the WHO Pharmacovigilance Database

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Lithium is commonly recommended as a first-line treatment for adults with bipolar disorder and has shown significant efficacy in pediatric populations. However, its use remains limited in adolescents due to concerns about its safety profile. We aim to assess the comparative safety of lithium in adolescents aged 12-17 years, using international pharmacovigilance data.

Materials and methods

Using data from the World Health Organization's pharmacovigilance database, VigiBase, we conducted case / noncase analyses to compare the reporting of serious adverse drug reactions (ADR) between adolescents and adults prescribed with lithium. Cases were reports of serious ADR of interest and non-cases were reports of any other serious ADR. Reporting Odds Ratios (ROR) and 95% confidence intervals were calculated to assess disproportionate reporting.

Results

We retrieved 2108 serious ICSRs in adolescents exposed to lithium and 23,537 corresponding adult cases. Compared to adults, lithium use in adolescents was associated with increased reporting of suicide attempts (ROR 2.51 [1.38; 4.59]) but decreased reporting of completed suicides (ROR 0.22 [0.09-0.53]). Other significant disproportionate reporting included increased reporting of gynecomastia (ROR 8.63 [3.78-19.69]) and polyuria (2.23 [1.17- 4.22]) and decreased reporting of cardiorespiratory arrests (ROR 0.42 [0.21-0.85]). No signals were found for hypothyroidism, encephalopathy, renal impairment, bradycardia or diabetes insipidus.

Discussion / Conclusion

Current literature indicates that lithium exhibits a comparable safety profile in adolescents and adults. Our study identified variations in the reporting rates of certain ADRs among adolescents, which may be linked to age-specific factors. These observations highlight the need for further pharmacoepidemiological research to explore these potential signals.

Keywords

lithium; pediatric bipolar disorder, adverse drug reaction, pharmacovigilance

00107
When generative AI goes off the rails and leads to adverse drug reactions

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

As Large Language Models (LLMs) become part of everyday life, patients increasingly seek medication-related advice from generative artificial intelligence (AI). Although these systems may facilitate access to health information, unsupervised reliance on AI-generated advice may contribute to medication errors and subsequent adverse drug reactions (ADRs), despite built-in safety safeguards. We aimed to investigate whether LLMs use could be associated with ADRs reported in the French National Pharmacovigilance Database (FNPV).

Materials and methods

We searched the FNPV for ADR cases recorded between January 2023 and February 10, 2026, containing the terms “ChatGPT,” “Anthropic,” “Claude,” or “Gemini” in the narrative field.

Results

We identified six cases mentioning “ChatGPT”; no other LLMs were reported. Five cases (three serious) involved ADRs potentially related to AI-generated content and were categorized into three patterns : 1/medication errors (n=3; zolmitriptan dosing error in an 18-year-old pregnant woman leading to vomiting, chest pain, and paresthesia; cotrimoxazole dosing error in a 47-year-old patient resulting in abdominal cramps; and a prescription error due to mistranslation of a hospital discharge report by the healthcare team causing drowsiness and confusion); 2/anxiety triggered by alarming information (n=1; a 25-year-old female was told she was at risk of death after excessive intake of Humex Gorge®, an over-the-counter throat medication); 3/response to inappropriate request (n=1; atropinic syndrome following diphenhydramine overdose in a 16-year-old male seeking advice for psychotropic effects). Lastly, one case was not an ADR induced by ChatGPT but an appropriate advice with recommendation to consult a healthcare professional after mild paracetamol overdose in a 37-year-old female.

Discussion / Conclusion

LLMs may contribute to ADRs by generating inappropriate advice (dosing errors, mistranslation), alarmist responses or handling of inappropriate requests. As AI tools are increasingly integrated into our daily life, both patients and healthcare professionals should assess critically AI-generated content.

00108
Iatrogenic consequences of incorrect inhalation device use : a retrospective study based using the French National Pharmacovigilance Database

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

In France, nearly 70 inhalation devices are available, mainly indicated for asthma and chronic obstructive pulmonary disease. This wide diversity, involving different administration techniques, can lead to handling errors that compromise disease control; 70–80% of patients use these devices incorrectly. However, the iatrogenic consequences of such administration errors remain poorly described.

Materials and methods

A retrospective descriptive study was conducted using data from the French national pharmacovigilance database(BNPV) from 1985 to March 14, 2025. Cases were

identified by combining suspected inhaled drugs: corticosteroids, bronchodilators (including β2 adrenegic agonists and anticholinergics) with the MedDRA preferred terms “device difficult to use” and “product use issue.” An additional search using the case types “medication error(ME)” and “medication error without adverse event(AE)” was performed, followed by case by case analysis of files.

Results

Seventy-five cases corresponding to 92 AEs were included. Children and the elderly account for 56% of cases. Most AEs were non-serious (n= 71; 95%) and had favorable outcomes. MEs were involved in 97.3% of cases, with AEs occurring in 58.7% of cases mainly during administration (91.8%), and most commonly associated with human factors (75%) and incorrect administration techniques (41.8%). The drug classes most frequently involved were inhaled corticosteroid/β-agonist combinations, followed by β-agonists alone and inhaled corticosteroids alone. The most commonly reported AEs were neurological (n=24, 26%, e.g dizziness), cardiac (n=17, 18.5%, e.g tachycardia), and gastrointestinal disorders (n=10, 10.9%, e.g dry mouth).

Discussion / Conclusion

This study highlights AEs resulting from incorrect use of inhalation devices. Almost all of AEs are not serious and consistent with expected atropinic or adrenergic effects in some cases. Several contributing factors, some preventable, were identified; including high-risk patient populations, insufficient patient education, and the prescription of multiple inhalation devices for the same patient. These findings support the development of a practical tool to help healthcare professionals promote the safe use of inhalation devices.

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Keywords

inhalation devices ; medication error ; adverse drug reaction

00109
Hepatobiliary safety of pharmacotherapies for alcohol use disorder in real-world practice: a pharmacovigilance study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Alcohol use disorder (AUD) is a major cause of liver-related morbidity and mortality. Despite proven efficacy, medications for AUD (MAUD) remain under-prescribed, particularly in patients with chronic liver disease, due to concerns about hepatotoxicity. We aimed to assess the hepatobiliary safety of MAUD using real-world pharmacovigilance data.

Materials and methods

We conducted a retrospective pharmacovigilance study using the French national pharmacovigilance database. Hepatobiliary adverse drug reactions were identified using the MedDRA System Organ Class “Hepatobiliary disorders” in reports involving MAUD (disulfiram, acamprosate, naltrexone, baclofen, or nalmefene). Disproportionality analyses and individual case review were performed for clinical and biological characterization.

Results

Among 187 individual case safety reports identified, 124 were included for detailed analysis. The median age of patients was 48 years (IQR 40.3–58.8 years), and 52.4% were male. Chronic liver disease was reported in 8.9% of cases. Baclofen was the most frequently reported drug (n=58), followed by disulfiram (n=32), acamprosate (n=29), naltrexone (n=13), and nalmefene (n=5). The median time to onset was 28 days [10.5–89.5]. More than half of cases (52.4%) resulted in hospitalization. Life-threatening cases (8.1%) were mainly associated with disulfiram in patients with cirrhosis. Disproportionality analyses showed a modest increase in reporting of hepatobiliary adverse reactions for MAUD overall (ROR 1.19 [95%CI 1.03–1.38]), which was no longer observed after exclusion of disulfiram. No excess reporting was observed in patients with documented alcohol use, and no significant signal was detected in patients with cirrhosis once disulfiram was excluded.

Discussion / Conclusion

In this real-world pharmacovigilance study, hepatobiliary adverse drug reactions associated with MAUD were uncommon and rarely life-threatening, except for disulfiram. These findings challenge the fear-driven under-prescription of MAUD in patients with liver disease. Given their proven efficacy in reducing alcohol consumption and improving liver-related outcomes, we believe that these drugs should be integrated into hepatology care rather than avoided because of hepatotoxicity concerns.

Keywords

Alcohol use disorder; Hepatobiliary adverse drug reactions; Drug safety; Cirrhosis

00110
Is Melatonin Really Safe? Signals of Impulsivity and Self-Harm in VigiBase®

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Melatonin is widely prescribed for insomnia, particularly in children and adolescents, and is often perceived as a safer alternative to Z-drug hypnotics. However, recent reports suggest the possible occurrence of neuropsychiatric adverse effects, including impulsivity, aggression, and suicidal behaviors. This study aimed to assess the presence of a disproportionality signal for impulsivity/aggression, intentional self-harm, and suicidal ideation associated with melatonin compared to Z-drugs, using the WHO global pharmacovigilance database (VigiBase®).

Materials and methods

A disproportionality analysis was conducted using reports recorded in VigiBase® between January 2000 and December 2024. Cases mentioning melatonin or a Z-drug as a suspected or interacting drug were included. Adverse avents of interest were defined using MedDRA preferred terms: (i) impulsivity/aggression, (ii) intentional self-harm, and (iii) suicidal ideation. To enhance the robustness of the results, only reports from healthcare professionals were analyzed. Reporting odds ratios (RORs) and their 95% confidence intervals (CIs) were calculated.

Results

Among 39,367 reports from healthcare professionals (3,066 involving melatonin; 36,301 involving Z-drugs), melatonin was associated with a significant signal for intentional self-harm (ROR 3.87; 95% CI 3.12–4.77) and impulsivity/aggression (ROR 2.04; 95% CI 1.53–2.69) compared to Z-drugs. A trend for moderate signal was observed for suicidal ideation (ROR 1.45; 95% CI 0.99–2.07; p = 0.046). Cases associated with melatonin more frequently involved individuals aged 8–17 years.

Discussion / Conclusion

This pharmacovigilance study highlights a disproportionality signal for impulsivity/aggression and intentional self-harm associated with melatonin, particularly in younger individuals. While no causal link can be established, these findings call for vigilance and further investigation into the neuropsychiatric safety of melatonin.

Keywords

Melatonin; Pharmacovigilance; Suicidal ideation; Impulsivity; Aggression, Hypnotics, Drug safety

00118
Pathological gambling associated with levetiracetam in a patient with frontal lobe epilepsy: a pharmacovigilance case report

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Levetiracetam is a widely prescribed antiseizure medication known to induce behavioural adverse drug reactions such as irritability, aggression, and mood disturbances. Impulse control disorders, including pathological gambling, are rarely reported and remain insufficiently characterized.

Materials and methods

We report a case of pathological gambling occurring in a patient treated with levetiracetam, reported to our pharmacovigilance centre.

Results

A 33-year-old man was treated with levetiracetam for focal epilepsy secondary to a left prefrontal arteriovenous malformation, following a first generalized tonic-clonic seizure. Levetiracetam was initiated at a dose of 500 mg twice daily. Within the first month of treatment, the patient developed marked irritability, which gradually improved. Within six months after treatment initiation, a severe pathological gambling behaviour emerged, characterized by compulsive sports betting, financial losses exceeding €100,000 and the subscription of multiple consumer loans. The patient

had no prior psychiatric history, addictive behaviour, or concomitant medication. Due to concerns regarding adverse effects, he spontaneously reduced the dose to 500 mg once daily. A specialized follow-up was initiated, leading to a progressive improvement of gambling behaviour despite continuation of levetiracetam. This case contributed to a subsequent update of the Summary of Product Characteristics for levetiracetam in September 2025, with the addition of obsessive–compulsive disorders.

Discussion / Conclusion

This case supports a possible association between levetiracetam and impulse control disorders. An observational study reported problematic gambling behaviours, including betting and lying, in patients with epilepsy treated with levetiracetam or brivaracetam, particularly in frontal lobe epilepsy, with a prevalence approximately tenfold higher than in the general population (1). A genetic association study suggested that negative psychotropic effects of levetiracetam, such as irritability and aggressiveness, may be related to polymorphisms affecting dopaminergic activity, potentially through reduced D2 receptor availability and increased impulsivity (2). Our case report highlights the need for careful behavioural monitoring, especially in patients with frontal lobe involvement.

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Keywords

case-report; levetiracetam; pathological gambling; addiction; pharmacovigilance

00119
Ribociclib-induced cutaneous reactions: allergology and pharmacovigilance complementary approaches to explore potential cross-reactivity within the CDK4/6 inhibitors class

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i), ribociclib, palbociclib and abemaciclib, used in advanced HR+/HER2- breast cancer, are known to induced cutaneous adverse reactions. However, validated diagnostic tools and recommendations for selecting safe alternatives remain limited. Understanding the underlying mechanisms and potential cross-reactivity is crucial for treatment optimisation, for which pharmacological approaches combined with allergology work-ups are insightful.

Materials and methods

An in-depth pharmacovigilance analysis was conducted to assess the imputability of ribociclib in the occurrence of maculopapular eruption (MPE), alongside a synthesis of the literature on potential cross-reactivity between CDK4/6i, combined with a full allergological work-up.

Results

A 67-year-old woman with advanced breast cancer developed a maculopapular exanthema 94 days after initiating ribociclib. This drug was subsequently withdrawn and symptoms resolved within three months with topical corticosteroids. Given the oncological necessity, identifying a safe alternative within this class became essential. Considering the potential for cross-reactivity, abemaciclib appeared to be the most suitable option due to its better cutaneous safety profile, likely related to its higher CDK4 selectivity and lower structural similarity than other CDK4/6i. An allergological workup, including patch and photopatch testing, was performed and yielded negative results. Ribociclib was reintroduce leading to recurrence, strengthening the causal relationship. Ultimately, abemaciclib was initiated without reported subsequent cutaneous reaction.

Discussion / Conclusion

Although a class effect has been suggested, evidence for cross-reactivity among CDK4/6i remains limited. The negative predictive value of skin testing, recommended in suspected delayed hypersensitivity reactions, remains uncertain, particularly for ribociclib. A positive rechallenge supports drug imputability, whereas negative skin tests may point toward non-immunological mechanisms or metabolite involvement. According to available data, switching within the class has been successfully reported with limited evidence of cross-reactivity. Negative skin tests and the pharmacological profile of abemaciclib makes it a relevant alternative. Further standardised evaluations are needed, and management should remain individualised based on clinical context and benefit-risk assessment.

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Keywords

CDK4/6 inhibitor; cutaneous adverse reaction; skin test; patch test; breast cancer; cross-reactivity; pharmacology; allergology.

00121
Pharmacovigilance analysis of neuropsychiatric disorders in children post Elexacaftor-Tezacaftor-Ivacaftor initiation in cystic fibrosis

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

CFTR-modulator improved cystic fibrosis management, especially with Elexacaftor/Tezacaftor/Ivacaftor (ETI). Neuropsychiatric disorders (NPDs) are documented in CF adolescents and adults (1) and with ETI use, but their presentation seems different in preschoolers (2). This study analyses in depth, ETI-related NPDs case series in all pediatric age groups

Materials and methods

Retrospective study (2022-2025) using data from regional pharmacovigilance centre of Marseille. NPDs cases ETI-related from a pediatric cystic fibrosis reference centre were analyzed. Time to onset (TTO), dechallenge/rechallenge outcomes, sweat

chloride concentration (SCC, inversely related to CFTR activity, CFTR-modulator major efficacy <30 mmol/L) and ETI plasma concentrations (Ceti) were analyzed.

Results

Thirty-three children, 93 NPDs analyzed (mean of 2.8/child). Median age was 6 years [2-17]. Sex-ratio M/F=0.5. Median SCC was 69 mmol/L pre-ETI and profoundly reduced post-ETI initiation <30 mmol/L.

In the 2-5 year age group (n=13), mood and anxiety disorders were predominant. In the 6-11 year group (n=14), mood, anxiety but also behavourial and attention-deficit disorders were predominant. In the >12 year age group (n=6), mood disorders were predominant with one case of suicidal behaviour. Sleep disorders were identified across all age groups. Median TTO was 1,3 and 8 months for each age group, respectively.

Dechallenge (dose reduction or wash out) improved 65.6% of NPDs. Twenty-three children required individualized dosing schemes. 5 had positive rechallenge. Of 22 C_{eti} (peak or residual) measured during NPDs, 14 were above reference range.

Discussion / Conclusion

NPDs clinical spectrum and TTO evolved with age, with mainly behavourial and attention-deficit disorders in younger children and mood/anxiety disorders progressing to complex presentations in adolesents. NPDs occured at both supra- and therapeutic concentrations, supporting the mechanism hypothesis of CFTR-modulator distribution in CNS (3). The depth of SCC provide ETI dose adjustment to minimize the occurrence of NPDs and conserve efficacy, restoring the benefit/risk balance. A individualized approach to dose adjustment should be warranted.

Reference(s)

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Keywords

CFTR-modulator / rare disease / cystic fibrosis/ CNS adverse effects / Pharmacovigilance / Therapeutic Drug monitoring

00123
Is it reasonable to initiate hydroxyurea in patients with current or past skin cancer history?

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Hydroxyurea, used for myeloproliferative neoplasms, inhibits DNA synthesis. Its association with increased skin cancer risk may limit long-term use.[1, 2] While dermatologic monitoring and photoprotection is recommended due to enhanced susceptibility to UV-induced DNA damage, no guideline addresses the management of patients with a present or past history of skin cancer, leaving therapeutic strategy uncertain in this population.

Materials and methods

To assess the impact of a history of skin cancer on the reporting rate of hydroxyurea-related skin cancers, disproportionality analyses by calculating Reporting Odds Ratios (ROR) were performed using the documented cases reported in the French Pharmacovigilance Database, up to 18 February 2026.

Results

Among 1,616 individual case safety reports (ICSRs) listing hydroxyurea as a suspected drug, 82 cases were reports of skin cancer. According to this known risk,

skin cancer was 28 time more frequently reported with hydroxyurea compared to other drugs used for neoplasm indications (ROR 28.63; 95% CI: 21.73-37.73). Considering patients with indicated skin cancer history, this disproportionate reporting rises to about 54 times (ROR 54.37; 95% CI: 23.31–126.82). Interestingly, within hydroxyurea-related skin cancers ICSR, reports mentioning history of skin cancer were about 9 times more frequently reported than without (ROR 8.88; 95% CI: 3.93–20.08).

Discussion / Conclusion

This analysis highlights a significant association between hydroxyurea exposure and increased reporting of skin cancer, especially in patients with history of skin cancer, who already face a higher recurrence risk.[3] Hydroxyurea might represent another additional risk factor though it remains unclear whether this risk is cumulative or synergistic. In the absence of a formal contraindication, initiating hydroxyurea in patients with prior skin cancer should be based on a close benefit-risk assessment, considering expected efficacy, treatment duration, therapeutic alternatives, and the generally favorable prognosis of non-melanoma skin cancers mainly reported with hydroxyurea[1].

Reference(s)

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Keywords

hydroxyurea, disproportionality, pharmacovigilance, skin cancer history

00125
Safety Profile of Biologic Therapies in Severe Asthma: An Observational Study Based on the French Pharmacovigilance Database

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Advances in the pathophysiological understanding of asthma, particularly the involvement of type 2 inflammatory cytokines, have led to the development of biologic therapies, transforming the management of severe asthma. In light of the recent introduction of these agents, close monitoring of their safety profile is imperative.

Materials and methods

This descriptive observational study was based on data from the French pharmacovigilance database for the five biologic agents approved for asthma (omalizumab, dupilumab, mepolizumab, benralizumab and tezepelumab), from their market introduction up to September 17, 2024. These data were combined with exposure data derived from the national health insurance system.

Results

A steady increase in biologic therapy use was observed, with more than 90,000 patients treated in 2024. A total of 1,830 cases were analyzed, corresponding to 3,299 adverse drug reactions (ADR), with 43% of cases classified as serious. Median age varied according to the drug (37 years for benralizumab and 57 years for mepolizumab). Female-to-male ratio ranged from 1.2 (dupilumab) to 2.6 (pmalizumab).

Most adverse drug reactions (ADR) were common to all biologics and were consistent with their known safety profile, including asthenia, injection-site reactions, cutaneous reactions, headache, and arthralgia. Several distinctive findings were identified. Arthralgia appeared delayed and was often associated with inflammatory joint disorders with mepolizumab. Hypereosinophilia with dupilumab was sometimes associated with severe clinical manifestations. Thromboembolic events were reported with omalizumab. Some ADR were specific to certain indications, such as acquired hemophilia with omalizumab in bullous pemphigoid and organizing pneumonia with dupilumab in chronic rhinosinusitis with nasal polyps.

Discussion / Conclusion

While numerous ADR are shared among biologic therapies, several molecule-specific ADR have been identified. Additionally, some previously unreported and occasionally severe ADR were observed, supporting the need for continued enhanced pharmacovigilance.

Keywords

Asthma, pharmacovigilance, biotherapies, safety

00126
Retrospective descriptive study of adverse events recorded in the French National Pharmacovigilance Database with LUTATHERA®

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Lutathera® therapy is an internal radiotherapy targeting well-differentiated, inoperable, or metastatic gastro-entero-pancreatic neuroendocrine tumors expressing somatostatin receptors.

Materials and methods

The aim of this study was to characterize adverse events (AEs) associated with Lutathera® in real-life clinical use using data from the French National Pharmacovigilance Database (BNPV) up to March 5, 2025, particularly unexpected AEs (UAES).

Results

142 cases were identified, comprising 218 AEs (88 serious, 130 non-serious). Patients: 60 males and 81 females; mean age: 64 years. Four deaths reported: related to tumor progression (3), possibly Lutathera® or a co-suspect drug (1).

AEs occurred after first injection (50.7%), second (13.4%), third (13.4%), fourth (7%).

After the first dose, skin and subcutaneous tissue (SCT) disorders: 20 AEs, mainly alopecia (12), pruritus (6). Hematological disorders: 22 AEs, primarily thrombocytopenia (11), lymphopenia (6). Gastrointestinal disorders: 29 AEs, mainly nausea (13), vomiting (10). The most involved SOCs: gastrointestinal (65), hematological/lymphatic (62), skin/SCT (30).

Most frequent AEs: thrombocytopenia (25), nausea (24), vomiting (22), alopecia (15), lymphopenia (11), anemia (7).

33 positive rechallenges (R+): involving alopecia(2), pruritus(2), thrombocytopenia(13), worsened neutropenia(1), neutropenia (1), lymphopenia(5), leukopenia(1), cytopenia(1), anemia(2), vomiting(6), nausea(3), abdominal pain(1), ascites(1), hepatic cytolysis(1), partial seizure(1).

4 negative rechallenges: pituitary apoplexy (1), carcinoid crisis (1), pruritus (2).

16 AEs not listed in the summary of Product Characteristics (SmPC): Cushing syndrome, pituitary apoplexy, photophobia, decreased libido, partial seizure, pruritus-associated hepatic injury, oral hypoesthesia, pruritic erythematous, infectious enteritis, subsegmental pulmonary embolism, Raynaud syndrome, tooth loss (3), thrombotic microangiopathy (2).

Discussion / Conclusion

Most AEs primarily hematological and gastrointestinal are listed in the SmPC, 7% are not listed in which 2 R+ (seizure, ascitis) highlighting the importance of a close surveillance.

Keywords

PHARMACOVIGILANCE

LUTATHERA

adverse effect

gastro-entero-pancreatic neuroendocrine tumors

somatostatin receptors

00130
Drug-associated posterior reversible encephalopathy syndrome (PRES) in critically ill patients: an ancillary analysis of the prospective XPRESSE study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological condition characterized by acute neurological symptoms associated with vasogenic brain edema. Toxic causes account for up to half of reported cases and mainly involve anticancer agents, immunosuppressants, and illicit substances. However,

drug-associated PRES in intensive care unit (ICU) patients has not been prospectively compared with non-toxic etiologies.

Materials and methods

XPRESSE (NCT04950270) is a multicenter prospective observational biomarker study conducted in four French ICU. Adults were eligible if PRES was confirmed by MRI within 48 hours. Clinical, biological, and radiological data were prospectively collected, including demographics, comorbidities, blood pressure, organ failure, and therapeutic management. PRES etiology (medical, toxic, or mixed) was determined by the intensivist with systematic input from a pharmacologist from a regional pharmacovigilance center. Three-month outcomes were assessed by telephone using modified Rankin Scale (mRS); poor outcome was defined as mRS ≥4 defined. This ancillary analysis compared medical versus toxic/mixed PRES.

Results

Twenty-four patients were included over 18 months: medical PRES (n=16), toxic (n=5), and mixed (n=3). Medical PRES was predominantly related to malignant hypertension (n=11). Toxic/mixed cases involved anticancer drugs (n=5), triptan overuse (n=1), and alcohol-related conditions (n=2 withdrawal syndrome and alcohol/disulfiram poisoning). Toxic/mixed PRES occurred in a similar proportion of females (63% vs 75%, p=0.6), but in older patients (median 64 vs 40 years, p=0.046), with less frequent acute hypertension (50% vs 85%) and acute kidney injury (63% vs 81%). Poor functional outcome at 3 months was significantly more common in toxic/mixed PRES (63% vs 13%, p=0.021).

Discussion / Conclusion

PRES is a heterogeneous syndrome with frequently overlapping etiologies in ICU patients. Drug exposure rarely acts as an isolated cause, supporting a “multiple-hit” hypothesis. This complexity challenges causality assessment and may contribute to greater severity and poorer functional outcomes in vulnerable patients.

Reference(s)

-XPRESSE study: The arginine Vasopressin aXis as a Potential Therapeutic Target for Posterior REverSible Encephalopathy SyndromE, https://clinicaltrials.gov/ct2/show/NCT04950270

-Largeau et al., Stroke 2023: “Experimental Models of Posterior Reversible Encephalopathy Syndrome: A Review From Pathophysiology to Therapeutic Targets” - PMID: 38126184

Keywords

Posterior reversible encephalopathy syndrome, pharmacovigilance, neurology, anticancer drugs

00131
Collaboration between general practitioners and the Regional Pharmacovigilance Center: a mixed study in the Centre-Val de Loire region.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

General practitioners (GPs) play a pivotal role in the diagnosis and management of adverse drug reactions (ADR). Yet, their contribution to the French pharmacovigilance system remains limited, representing only 7% of ADR reports in 2014. The reasons for this under-reporting have been poorly explored. This study aimed to describe interactions between GPs and the Centre-Val de Loire Regional Pharmacovigilance Center (RPVC) before to explore factors influencing this collaboration.

Materials and methods

We conducted a sequential mixed study (QUAN→QUAL). First, we performed a descriptive analysis of all requests submitted to the Centre-Val de Loire RPVC by ambulatory practitioners in 2023. Second, a qualitative study inspired by grounded theory methodology was conducted to interpret and contextualize the quantitative findings.

Results

In 2023, interactions between GPs and the RPVC Centre-Val de Loire were limited, accounting for 2.6% (81/3076) of all requests and 5.1% (81/1603) of physician requests. Substantial geographical disparities were observed: 85% (57/67) of GP requests originated from three of the region's six departments. GP requested advice from the RPVC three times less frequently than specialists (advice-to-report ratio of 2.4 vs. 7.1), supporting a predominantly declarative rather than consultative use of the center. Qualitative findings highlighted limited awareness of the pharmacovigilance system, and other barriers (fear of legal action, feelings of guilt, concern about harming professional relationships). GPs also expressed a preference for autonomous and pragmatic ADR, alongside an implicit referral hierarchy favoring organ specialists, which partly explains the low level of collaboration.

Discussion / Conclusion

Collaboration between GPs and the RPVC remains limited and largely confined to ADR reporting. Reducing identified barriers, clarifying the RPVC's role as a partner in pharmacological management, and streamline the process may enhance engagement and improve medication safety in primary care.

Reference(s)

-Durrieu et al., Drug Saf. 2016 "Completeness of Spontaneous Adverse Drug Reaction Reports Sent by General Practitioners to a Regional Pharmacovigilance Centre: A Descriptive Study - PMID: 27688025

Keywords

adverse drug reaction, pharmacovigilance, general practice

00132
Acute tubulointerstitial nephritis induced by proton pump inhibitors: impact of time to diagnosis on renal prognosis, a systematic review of published case reports and French pharmacovigilance data

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Proton pump inhibitors (PPI)-induced acute tubulointerstitial nephritis (ATIN) appears to differ from antibiotic-associated ATIN, with fewer hypersensitivity features, a more insidious onset, and delayed diagnosis (often ~3 months vs. <1 month for antibiotics). Such delay may impair renal recovery. We aimed to compare 3-month renal outcomes in biopsy-proven PPI-induced ATIN according to time to diagnosis, dichotomized at 35 days (early vs. late diagnosis).

Materials and methods

We retrospectively analysed biopsy-proven-ATIN attributed to a PPI, reported between 1989 to January 1, 2026, identified through a systematic search of Medline and reports from French Regional Pharmacovigilance Centers. Inclusion criteria were: PPI as the main suspected drug, documented time to onset, exclusion of

alternative aetiologies, and available follow-up serum creatinine (>1 month). Renal outcomes at 3 months were classified as complete recovery (serum creatinine <25% above baseline), partial recovery (>25% above baseline but ≤50% of peak creatinine), or no recovery (all other cases).

Results

Among the 586 cases identified, 115 (20%) met all eligibility criteria. The median age was 70 years [IQR 63-77], with a male-to-female ratio of 0.92. Omeprazole was the most frequently implicated PPI (59%). The median time to onset was 78 days [IQR 35-180], and 74% of cases occurring after >35 days of exposure. At least one hypersensitivity feature (rash, fever, eosinophilia) was reported in 19%. Corticosteroids were prescribed in 88% of cases, and 8% required dialysis. At 3 months, 100% (12/12) of patients in the early-diagnosis group achieved complete or partial recovery, compared with 60% (18/30) in the late-diagnosis group (p=0.0268).

Discussion / Conclusion

Our findings suggest that PPI-induced ATIN is not intrinsically more severe than other drug-induced ATIN. The poorer renal outcomes observed in some cases are more likely explained by delayed diagnosis, possibly due to its insidious presentation and lack of consistent hypersensitivity signs.

Reference(s)

[1] S. Farid, M. Mahmood, O.M. Abu Saleh, A. Hamadah, S.H. Nasr, Z.E. Garrigos, N. Leung, M.R. Sohail, Clinical Manifestations and Outcomes of Fluoroquinolone-Related Acute Interstitial Nephritis, Mayo Clin Proc 93 (2018) 25–31. https://doi.org/10.1016/j.mayocp.2017.08.024.

[2] B. Lazarus, M.R.P. Davies, J.A. Trubiano, R. Pellicano, Time to Acute Kidney Injury in β-Lactam−Induced Acute Interstitial Nephritis, Kidney International Reports 5 (2020) 1068–1070. https://doi.org/10.1016/j.ekir.2020.04.008.

[3] B. Sanchez-Alamo, C. Cases-Corona, G. Fernandez-Juarez, Facing the Challenge of Drug-Induced Acute Interstitial Nephritis, Nephron 147 (2023) 78–90. https://doi.org/10.1159/000525561.

Keywords

Keywords: acute tubulointerstitial nephritis, proton pump inhibitors, pharmacovigilance, systematic review

00137
Secondary cancer after CAR-T cell therapy: a French pharmacovigilance analysis

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Cases of secondary cancers (SC) associated with Chimeric Antigen Receptor (CAR) T cell therapy have been reported in the literature prompting safety alerts from both the Food and Drug Administration and the European Medicines Agency after reports of T-cell lymphomas. Establishing causality between CAR-T therapy and SC in patients previously heavily treated for a hematological malignancy is challenging. To clarify this risk, we evaluated SC cases reported to the Regional Pharmacovigilance Centers in France in patients with hematological malignancy treated with one of the six authorized CAR-T therapies.

Materials and methods

A query in the French Pharmacovigilance Database conducted on 01/24/2025 identified 20 SC cases in 19 patients where a CAR-T specialty was considered a suspected cause.

Results

Most patients were males (63%), with a mean age of 65.2 + 6 years. Of these, 79% had received CAR-T treatment for B-cell lymphoma, while 21% were treated for myeloma. Only 3 CAR-T currently available were reported as associated with SC: tisagenlecleucel, axicabtagene ciloleucel and idecabtagene vicleucel.

The mean interval between CAR-T administration and SC diagnosis was 11 months (median 9.5 months). Of the 20 SC, 11 were secondary hemopathies (6 acute myeloid leukemias, 4 myelodysplasias, and one cutaneous T-cell lymphoma with CAR-T cells detected in the blood and skin). The remaining 9 cases were secondary solid tumors including 3 skin neoplasms, 2 colon adenocarcinomas, one breast cancer, one relapse of oral squamous cell cancer, one jejunal leiomyosarcoma, one manubrial bone sarcoma (the latter two in the same patient). Most patients had established risk factors for these cancers, making CAR-T causality difficult to assess, except for the cutaneous T-cell lymphoma.

Discussion / Conclusion

Continuous long-term monitoring is essential to further evaluate the benefit-risk profile of CAR-T therapies, especially in settings with poor prognosis.

Keywords

secondary cancer; Chimeric Antigen Receptor T; adverse drug reaction; pharmacovigilance

00148
Iodide mumps/sialadenitis: a Pharmacovigilance study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Iodinated contrast media (ICM) injections are associated with infusion-related reactions (linked to increased plasma osmolarity) and hypersensitivity reactions (allergic or not). More rarely, the administration of ICM can also cause an acute inflammation of the salivary glands, known as sialadenitis, which may affect the parotid, submandibular, or sublingual glands. The clinical presentation and lack of knowledge of this type of impairment may, however, wrongly lead to the diagnosis of an allergic reaction.

The aim of the study was to describe the ICM induced sialadenitis reported through pharmacovigilance databases (PVDB).

Materials and methods

All reports of ‘inflammation of the salivary glands’ reported with iodinated contrast media (ATC V08A) in the French PVDB and in the WHO PVDB (Vigibase) from their inception to June 8th, 2025 (date of the query) were considered. An analysis of scientific literature (PubMed) was also performed.

Results

Over this period (>35 years), 148 and 26 reports (43% and 25% of seriousness) were respectively registered in Vigibase and in the French PVDB. The most frequently reported products were iomeprol, iohexol, and ioversol with a time to onset generally

within 24 hours (usually between 4 and 12 hours) after injection. The outcome is generally favorable within three days. Several reports document positive rechallenges with the same or another ICM. The disproportionality analysis shows a statistically significant association between sialadenitis and all ICM compared to other contrast media, suggesting a “class” effect.

Discussion / Conclusion

Of all the products marketed in France, only two (Optiray® and Optiject®=ioversol) clearly mention the very rare risk of sialadenitis. Given the probable “class effect”, it seems necessary to harmonize the product information for all ICMs. Although clinical presentation and allergy tests consistently rule out an immune-allergic reaction, a thorough individual analysis must be carried out, ideally with dermatological, otolaryngological, and pharmacological opinions sought.

Keywords

Iodide mumps

Sialadenitis

Iodinated contrast media

00171
Clinical Trials Vigilance : Using Artificial Intelligence to compare reference documents

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

A study was conducted to evaluate the use of artificial intelligence (AI) to compare two successive versions of a Summary of Product Characteristics (SmPC) for an experimental treatment. The main objective was to identify the most relevant AI tool for performing a detailed, section-by-section comparison as an alternative to the reference method based on manual analysis of changes. Another issue was practical feasibility, particularly in terms of the ability to upload large files (up to 10 per day) in Word or PDF format.

Materials and methods

Four AI tools were evaluated: ChatGPT, Mistral, Text.Cortex and Perplexity. Comparisons were made between previous and updated versions of the SmPCs for three medicines: Aubagio® (7 mg and 14 mg), Copaxone® (20 mg/mL, pre-filled syringe) and Novatrex® (2.5 mg). A specific prompt was developed with the support of NotebookLM in order to obtain a structured and comprehensive comparison of the two versions of the same SmPC. The results provided by the AI tools were compared with the manual analysis method.

Results

AI tools demonstrate remarkable speed of execution and the ability to generate concise and highly informative tables. The format of the analysis generated complies

well with the conditions set out in the prompt. However, not all changes to SmPC are identified by the four AI tools, and when queries are repeated several times, the results may change. Furthermore, the free versions have significant limitations: download thresholds (file size or number of files), daily query quotas, etc.

Discussion / Conclusion

AI is a promising tool for comparing SmPC, particularly for speeding up the identification of changes and producing structured summaries. However, technical constraints and variability in results limit its routine use. A hybrid approach, combining traditional tools and AI, appears to be the most appropriate strategy at this stage.

Keywords

Clinical trials - Artificial Intelligence - Analysis - SmPC - Comparison

00177
Lichenoid dermatitis after pembrolizumab exposure: French pharmacovigilance data.

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

During a multidisciplinary team meeting focusing on immunotherapy-related toxicities, a life-threaning case of lichenoid dermatitis (LD) following pembrolizumab exposure was presented (about 80% body surface involvement and hypovolemic shock). Our Centre was asked whether similar cases had been reported. In this context, we investigated data from the French Network of Regional Pharmacovigilance Centres.

Materials and methods

We reviewed serious reports of LD involving pembrolizumab recorded in the French Pharmacovigilance Database up to October 15, 2025. LD reports were identified using the MedDRA® Preferred Term “lichenoid keratosis”.

Results

Forty-nine serious LD reports related to pembrolizumab were analyzed. Median patient age was 65 years (range: 18 – 82 years), male/female sex-ratio was 0.53. Most cases were classified as serious because of hospitalization. Pembolizumab was

mainly used for non-small lung cancer and triple negative of breast cancer. Diagnosis was based on skin biopsy and direct immunofluorescence studies. Median time to onset was 75 days (range: 1 day – 1 year). Data on body surface area or CTCAE grade were limited. The outcome was favorable in 36 reports after pembrolizumab discontinuation and corticosteroid therapy: half required only topical corticosteroids, while the other half required systemic corticosteroids. A positive rechallenge was observed in two cases.

Discussion / Conclusion

Lichenoid eruptions occur in about 0.5-6 %of patients receiving anti-PD-1 or anti-PD-L1 therapy (1). The time to onset in our series aligns with published data (between 6 and 12 weeks after initiation) (1). Clinical severity in our cohort can be inferred from the management data, and it is significant in half of the reports (those requiring systemic corticosteroids). Our aim is to inform healthcare professionals about this potential adverse reaction. Early recognition and adapted management are essential to improve outcomes. Reintroduction of immunotherapy should be carefully considered on a case-by-case basis.

Reference(s)

1. McCormick BJ, Zieman D, West-Santos C, Phillips MB. Immune checkpoint inhibitor lichenoid eruption due to pembrolizumab. BMJ Case Rep. 2023 Jun 20;16(6):e254692.

Keywords

pembrolizumab; lung cancer; breast cancer; lichenoid dermatitis; pharmacovigilance

00178
Polyradiculoneuritis after nivolumab use: a cohort description from the French Pharmacovigilance Database.

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

During a multidisciplinary team meeting focusing on immunotherapy-related toxicities, a case of polyradiculoneuritis following nivolumab exposure was presented. Our Centre was asked whether similar cases had been reported. In this context, we investigated data from the French Network of Regional Pharmacovigilance Centres.

Materials and methods

We reviewed reports of polyradiculoneuritis involving nivolumab recorded in the French Pharmacovigilance Database up to October 02, 2025. Polyradiculoneuritis cases were retrieved using the MedDRA® Low-Level Term including the word “polyradiculoneuritis”.

Results

Twenty-nine polyradiculoneuritis reports related to nivolumab were analyzed. Median patient age was 65 years (range: 23 – 84 years), male/female sex-ratio was 1.63. All cases were classified as serious, mainly because of hospitalization. Nivolumab was mainly used for melanoma and thus its association with ipilimumab was predominant.

Median time to onset was 52 days (range: 2 – 240 days). Other concomitant immune-related adverse events were often observed. The majoritarian management consisted in nivolumab discontinuation, systemic corticosteroid therapy and intravenous immunoglobulins therapy. Some patients required a symptomatic treatment susch as pregabalin, gabapentin or amitriptyline. The outcome was favorable in half of reports (n=14), as patients were not followed over a long period.

Discussion / Conclusion

Immune-related polyradiculoneuritis represents a rare but a potentially serious adverse reaction with niovlumab. The outcome was favorable in half of reports, althought long-term follow-up was limited. Early diagnosis and apporopriate management are key to improve patient ouctomes. Clinicians should be aware of this possible complication during immunotherapy exposure.

Keywords

nivolumab; ipilumab; melanoma; polyradiculoneuritis; pharmacovigilance

00179
Sodium-glucose co-transporter-2 inhibitors (SGLT2i) and diabetic ketoacidosis (DKA): is the surgical setting a predisposing factor?

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

SGLT2i have been increasingly prescribed in France since their marketing in 2020. Recommendations for their use are not always sufficiently precise or not known, particularly in the surgical setting. This study aims to provide a descriptive analysis of spontaneous reported cases of SGLT2i-associated DKA in a surgical setting recorded in the French Pharmacovigilance Database (FPVD). This analysis follows on from in 2024 that included only six cases (1).

Materials and methods

A retrospective, descriptive study was conducted on all DKA with a SGLT2i notified in FPVD up to January 15, 2026, with MedDRA High Level Term (HLT) “Diabetic complications NEC”. We manually excluded cases not in a surgical setting or not informative.

Results

A total of 164 cases were extracted, with 22 cases occurred in a surgical context. The sex ratio is 1.2, with a median age of 65 years [43-83]. Dapagliflozin was the most SGLT2i represented (59%), then empagliflozin (32%) and canagliflozin (9%); indicated in diabetes possibly associated with heart or renal failure (n=20) or heart failure only (n=2). Metformin was coded as a co-suspect drug in 5 cases, and semaglutide as a co-suspect drug in one case. No deaths were reported.

Three main contexts were identified: 1/ in the absence of perioperative discontinuation (n=8), 2/ after “too fast” postoperative reintroduction (n=10), in a fasting context; 3/ despite preoperative discontinuation (n=4) 72 hours before surgery (n=3). In 6 cases, SGLT2i was reintroduced without recurrence of DKA.

Discussion / Conclusion

The surgical setting appears to be a high-risk situation for DKA in patients treated with SGLT2i. Our results indicate that, in 36% of cases, discontinuation is not performed as recommended. The most common scenario is the early postoperative reintroduction of SGLT2i without a normal diet. These findings highlight the need for clearer communication regarding perioperative recommendations for the discontinuation and resumption of SGLT2i.

Reference(s)

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Keywords

SGLT2 inhibitor

Diabetes ketoacidosis

Surgical settings

00186
Severity of Linezolide Induced Lactic Acidosis : Additional Clinical Mechanisms and Risk Factors : A French Pharmacovigilance Database Study.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Linezolide is indicated for the treatment of infections by susceptible Gram-positive bacteria : nosocomial pneumonia, complicated skin and softs tissus. Objective : investigate whether linezolid-induced lactic acidosis(LA) is influenced by additional clinical mechanisms and risk factors beyond direct drug-induced mitochondrial inhibition.

Materials and methods

Retrospective descriptive analysis of pharmacovigilance reports of French Pharmacovigilance Database up to june 2025, in which linezolide was reported as sole "suspected" medication.

Results

37 cases were identified. Median age : 65 years (range : 20 days to 85 years) ; sex ratio : 0.8. The primary clinical indication was respiratory distress in a context of sepsis. Route of administration : intravenous (15), oral(18) , unkown(4) . Lactic

acidosis occurred with a median delay of 15 days. Onset faster in patients receiving intravenous treatment. Laboratory findings : mean lactate level :10 mmol/L (median 9 mmol/L). The main associated risk factor of LA for each case : renal and/or hepatic impairment (17), hypoxia(3), catecholamines administration(5) ; choc and/or severe sepsis were noted (9), unknown (3). Outcome after discontinuation of treatment : favorable(28) unknown(4), deaths[5= multiorgan failure(1), hepatic encephalopathy(1) rhabdomyolysis(1), choc(2)].

Metabolism implicated : Mitochondria regulates lactate flux. Linezolid inhibits mitochondrial respiratory chain activity. Hypoxemia and catecholamines increase glycolytic flux, while renal and hepatic dysfunction compromise gluconeogenesis. Hyperlactatemia results from a profound metabolic imbalance between accelerated glycolysis and diminished gluconeogenesis lactate clearance.

Discussion / Conclusion

In our cases : Linezolid-induced lactic acidosis was exacerbated by : liver/ kidney impairment, hypoxia, catecholamines ; These risk factors are observed in at least74 % of our informative reported cases. In care unit, several of them are often associated. Assessment of these associated risk factors must be taken into account by clinicians regardless the route of administration, in order to avoid defavorable outcome

Keywords

Linezolide - Lactate clearance - Mitochondria - glycolysis / gluconeogenesis imbalance - liver/ kidney impairment, hypoxia, catecholamines.

00187
Severe ulceronecrotic reaction to mogamulizumab in a patient with primary cutaneous T-cell lymphoma not otherwise specified

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Mogamulizumab, an anti-CCR4 monoclonal antibody indicated for primary cutaneous T-cell lymphomas, commonly induces drug eruptions, but ulceronecrotic lesions have not been reported.

Materials and methods

We report the first case of severe ulceronecrotic reaction associated with mogamulizumab.

Results

A 55-year-old man presented with primary cutaneous T-cell lymphoma not otherwise specified, characterized by nodular vascular-appearing lesions affecting the lower limbs. Lesions initially responded to repeated electron beam therapy but progressed despite multiple systemic treatments, either ineffective or associated with significant toxicity: methotrexate, liposomal doxorubicin, pegylated interferon and bendamustine. Mogamulizumab was introduced as a fifth-line therapy due to CCR4 positivity. Three days after the first infusion, painful ulceronecrotic changes developed in some lesions, while others remained stable or enlarged. Treatment was permanently discontinued after 8 infusions (2 months). Three months later, ulceronecrotic lesions persisted, some requiring skin grafting. As the disease continued to progress, brentuximab plus CHP was initiated, leading to progressive re-epithelialization and flattening of most skin tumours.

Discussion / Conclusion

Mogamulizumab-associated rash (MAR) is very common and clinically heterogeneous, but typically benign and non-necrotic. Rare cases of Stevens–Johnson syndrome and toxic epidermal necrolysis have been reported. Only one case of ecthyma gangrenosum has been described, with a favourable outcome under antibiotic therapy and without treatment discontinuation. To our knowledge, our case is the first report of ulceronecrotic transformation of cutaneous lymphoma lesions with mogamulizumab.

A query of the global pharmacovigilance database identified nine other cases of “skin and subcutaneous tissue ulcerations (HLT)” or “cutaneous necrosis” (PT) reported with mogamulizumab, including 2 ecthyma cases, 2 skin erosions, 2 cutaneous necroses and 1 perineal ulceration. While the mechanism remains unknown, hypotheses include a particularly aggressive MAR or a direct cytotoxic effect related to high local CCR4 expression limited to certain lesions.

This case highlights the importance of close clinical monitoring upon initiation of mogamulizumab.

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Keywords

Cutaneous T-cell lymphoma; mogamulizumab; Adverse drug reaction

00188
Adverse events reported with homeopathic products: exploring the nocebo effect in the French pharmacovigilance database

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Drug treatments can elicit effects unrelated to their mechanism of action, known as placebo or nocebo effects. While placebo effects are beneficial, nocebo effects lead to negative health outcomes. Homeopathic products (HP) lack pharmacologically active substances; therefore, adverse events (AEs) reported with HP likely reflect nocebo responses, harmful outcomes driven by negative expectations rather than pharmacological mechanisms. This study aims to investigate this phenomenon by analyzing HP-related AEs reported to the French pharmacovigilance system.

Materials and methods

We conducted a retrospective analysis of all AEs involving HP reported in the French national pharmacovigilance database. Exclusion criteria included miscoding (non-HP), reports without AEs in specific contexts (e.g. drug errors), cases not exclusively attributed to HP, and cases with alternative product-related causes (possible active ingredient, possible contamination) or other possible non-product-related etiologies.

Remaining cases were described according to demographics, reporting source, clinical features, and causality elements.

Results

We retrieved 607 AE reports involving HP. A substantial proportion of cases were excluded, notably 17 confirmed allergy cases and 58 cases attributed to excipients, such as reactions to alcohol-containing mother tinctures. After applying all exclusion criteria, 184 cases with 320 AEs were included in the analysis: 61.4% involved women, mean age was 37.5 years, and 62.4% came from healthcare professionals. The most common MedDRA System Organ Classes were skin (25.9%), gastrointestinal (20.0%), general (12.2%), nervous system (10.9%), and psychiatric disorders (5.3%). Overall, 48 cases were classified as serious (25.9%). When available, a positive dechallenge was noted in 56.5% of cases, and a positive rechallenge in 8.7%.

Discussion / Conclusion

This study provides the first descriptive account of pharmacovigilance reports related to HP consistent with nocebo-type responses, offering exploratory insights into a topic rarely addressed in drug safety research. While some methodological limitations remain, these findings provide a basis for future nocebo researches.

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Keywords

Homeopathy, Nocebo effect, Pharmacovigilance, Adverse effect

00192
Corneal ulceration associated with pembrolizumab : a case report and pharmacovigilance data analysis ?

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Immune checkpoint inhibitors (ICIs) are widely used in oncology but they can induce immune-related adverse drug reactions (ADRs). The development of corneal ulcers is rare, but potentially serious, complication compromising visual prognosis.

Materials and methods

We present a case of corneal ulceration associated with pembrolizumab, recorded in the French pharmacovigilance database (NY2025001717). A complementary analysis of VigiBase, the WHO global pharmacovigilance database, was performed up to February 2026 using the preferred terms “ulcerative keratitis” and “corneal perforation”. Disproportionality was evaluated using the Information Component (IC).

Results

A 51-year-old man with chronic graft-versus-host disease following allogeneic transplantation, in the context of chronic myeloid leukemia transformed into acute myeloid leukemia was treated with pembrolizumab for squamous cell carcinoma. A corneal abscess occurred after the 8th cycle. Bacteriological tests were negative.

Clinical improvement was observed with oral corticosteroids. Pembrolizumab was continued, but the lesion became excavated, jeopardizing the functional prognosis of the eye. Two amniotic membrane grafts were required. Pembrolizumab was discontinued due to the risk of recurrence and ocular perforation, leading to ulcer regression.

VigiBase reports 14 cases of ulcerative keratitis and 4 cases of corneal perforation with pembrolizumab (significant disproportionality: IC025=0.2). For all ICIs, 37 cases of ulcerative keratitis and 15 cases of corneal perforation are identified.

Discussion / Conclusion

Cases of corneal ulceration are rarely described with ICIs, the literature reports cases occurring in the setting of dry eye disease or sicca syndrome(1–3). The clinical course may lead to decreased visual acuity or even corneal perforation(3,4). Onset may occur after several injections. These ocular ADRs are mainly reported with anti-CTLA agents, although a few cases involve other ICIs(1–3,5). The mechanisms involved may include increased dryness as well as an immune-mediated mechanism, causing corneal inflammation progressing to ulcers with or without perforation(5). The decision to continue immunotherapy should be assessed on a case-by-case basis.

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Keywords

ocular ulcer, corneal perforation, pembrolizumab, immune checkpoint inhibitors, pharmacovigilance

00198
Denosumab-induced hypocalcemia: detection of drug-drug interactions using disproportionality analysis in VigiBase®

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Denosumab-induced hypocalcemia has been reported more frequently in real-world studies than in pivotal clinical trials; this is probably due to a closer monitoring of medication regimens in trials. Here, we sought to detect signals for drug-drug interactions (DDIs) between denosumab and other hypocalcemia-inducing drugs.

Materials and methods

We performed a disproportionality analysis of data in VigiBase® between January 1st, 2011, and February 7th, 2024. The frequency of hypocalcemia reports for all drugs known to induce hypocalcemia was compared with that for all other drugs and was quoted as the reporting odds ratio (ROR) [95% confidence interval (CI)]. Generalized linear models were used to test for additive and multiplicative DDIs with denosumab.

Results

Of 3,076,045 reports recorded in Vigibase®, 2,638 concerned hypocalcemia. The ROR [95%CI] values for co-exposures of denosumab with calcimimetics (850.5 [397.6–1819.6]), loop diuretics (251.6 [204.5–309.4]), proton pump inhibitors (164.5 [142.2–190.3]), calcitonin (462.5 [171.5–1247.1]), H2 receptor antagonists (157.2 [114.6–215.7]), aminoglycosides (134.7 [41.5–437.4]), cisplatin (464.1 [256.8–839.0]), sodium bicarbonate (510.4 [296–879.9]), and calcium channel blockers (175.3 [143.7–213.7]) were higher than the sum of the RORs for each drug taken individually. The δ coefficient of additive models of these co-exposures was significant, while that of multiplicative models was not.

Discussion / Conclusion

We found significant signals for hypocalcemia associated with DDIs between denosumab and a range of other hypocalcemia-inducing drugs, suggesting an increased risk of hypocalcemia. With a view to providing guidance on safe prescribing, the hypotheses generated in our disproportionality analysis need to be confirmed by further studies.

Keywords

Denosumab

Drug-drug interaction

Hypocalcemia

Pharmacovigilance

00226
Tooth discoloration after amoxicillin exposure: French pharmacovigilance data

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Tooth discoloration is a well-known adverse effect of antibiotics, particularly tetracyclines. This dental effect is less frequently described for amoxicillin, although it is mentioned in the Summary of Product Characteristics for oral formulations. This study aims to characterize the occurrence of tooth discoloration following exposure to amoxicillin.

Materials and methods

We reviewed all spontaneous reports of tooth discoloration with amoxicillin registered in the French Pharmacovigilance Database (FPVD) from its inception to January 23, 2025. Cases were identified using the Preferred Term “tooth discoloration”. For all identified cases, we studied population data (age, sex), drug characteristics (pharmaceutical form), and the adverse effect details (time to onset, outcome).

Results

One hundred and eighty-one cases were registered in the FPVD. Eight percent of reports were serious. Mean age was 30 years and median age was 26 years old (range: 0.6-94). Sex ratio M/F was 0.85. When the pharmaceutical form was specified (n=85), the majority involved oral formulations (n=69). Amoxicillin was the sole suspected drug in 51 cases; and in 65 cases, it was combined solely with

clavulanic acid. Concomitant suspected antibiotics included metronidazole (n=6), linezolid (n=3), and rifampicin (n=3). The average time to onset was 15.2 days, with a median of 6 days (range: 1 to 365 days). The molecule was stopped in 123 cases, with a marked improvement in 43 cases. There was one positive rechallenge.

Discussion / Conclusion

This analysis suggests that amoxicillin may be associated with tooth discoloration, predominantly with oral formulations. The underlying mechanism remains poorly understood. Wang et al. (2023) identified amoxicillin among 25 drugs showing a positive pharmacovigilance signal for tooth discoloration and hypothesized that disruption of the oral microbiota secondary to antimicrobial activity could contribute to this effect (1). These findings underscore the need for increased awareness of this potential adverse reaction and further investigations to clarify its mechanism, true incidence, and reversibility.

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Keywords

amoxicillin, tooth discoloration, pharmacovigilance

00235
Fetal safety threshold of low-dose aspirin (>100 mg/day) during pregnancy: pharmacological rationale and pharmacovigilance data

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Low-dose aspirin (LDA) is widely recommended (100–160 mg/day) for the prevention of preeclampsia and other placental vascular disorders. However, in France and in some other countries, any dose >100 mg/day remains contraindicated from 24 weeks' gestation due to concerns of NSAID-related fetal toxicity (ductus arteriosus constriction (DAC) and renal impairment (RI)). This regulatory cut-off conflicts with current obstetrical recommendations. Our objective was to assess whether there is any evidence of fetal toxicity for aspirin doses above 100 mg/day and below 300 mg/day.

Materials and methods

A review of the literature and international guidelines was performed, focusing on cardio-renal fetal outcomes after LDA >100 mg/d during pregnancy. Safety data from randomized controlled trials using LDA >100 mg/d during pregnancy were analyzed. French pharmacovigilance cases (BNPV, extracted in July 2025) and international reports (VigiBase, September 2025) of fetal toxicity following in utero exposure to LDA>100 mg/d were analyzed.

Results

Pharmacodynamically, LDA preferentially inhibits COX-1, whereas cardiac and renal fetal toxicity are primarily associated with COX-2 inhibition. Among approximately 2,353 pregnant women exposed to LDA 150–160 mg/day in clinical trials up to 28–36 weeks' gestation, no cardio-renal fetal toxicity was reported, although studies were underpowered to detect rare events. In French pharmacovigilance database (22 eligible cases), no case supported a causal role of aspirin after expert assessment. In VigiBase, no confirmed cases of fetal toxicity were identified. Isolated published case reports of fetal toxicity remain confounded.

Discussion / Conclusion

Although the fetal safety of LDA up to 160 mg/day is not yet demonstrated due to the lack of study with high-level evidence, current data suggest the absence of fetal cardio-renal toxicity signal for this dose. Reconsideration of the regulatory threshold may be warranted to align dosage recommendation of aspirin up to 160 mg/day according to contemporary obstetrical practice.

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Keywords

low-dose aspirin

pregnancy

fetal toxicity

00236
Serious adverse effects related to medication name confusion: analysis of data from the French pharmacovigilance database.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Numerous cases of medication errors (ME) involving confusion between drug names with serious consequences are reported each year. The aim of this study was to describe these errors in order to better prevent them.

Materials and methods

This retrospective study was conducted using the French pharmacovigilance database on January 2, 2026 applying the selection criteria: serious case, name confusion (PT). Cases without adverse drug reaction (ADRs) were excluded.

Results

Thirty-nine serious cases (20 men and 19 women, mean age 54 years) related to medication name confusion were analyzed. Three deaths (cardiac arrest : "Bleu de methylene=>Bleu patenté", sudden death : "effient=>effizinc", bronchial congestion : "oxynorm=>morphine"), 5 life-threatening situations (inhaled pneumonia : "oxynormoro=>oxycodone", cardiac arrest : "ephedrine 30mg/mL=>adrenaline0,5mg/mL", prolonged QT : "hydrochlorothiazide=>hydroxyzine", anaphylactic shock : "ferinject=>venofer") and respiratory decompensation"selebri=>sabril"), and 27 hospitalizations were reported. In 31 cases (79%), the ADR was due to the medication received in error. A worsening of the disease related to the discontinuation of the usual treatment was observed in 8 cases (21%).

The error occurred during dispensation (n=19, 49%), administration (n=15, 38%)), or prescription (n=5, 13%) and mostly involved newly prescribed drug (n=24, 61%). The errors were facilitated by name similarity between the two drugs (n=33, 85%) (mainly brand names), an identical first letter (n=28, 72%) or an identical prefix (n=21, 54%), rather than by similarities in packaging. The ATC classes and indications of the drug administrated in error differed from those of the intended drug in 21 and 27 cases, respectively.

Discussion / Conclusion

This study highlights the seriousness of ME due to name confusion and the importance of brand name sound-alike as contributing factor (1). Several measures could help reduce this risk, including the use of capital letters on packaging (2). Based on our findings, checking the indication at the time of dispensing could serve as an effective preventive tool (3).

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Keywords

pharmacovigilance

medication error

sound-alike drugs

00261
Brodalumab - What about depressive adverse effects in pharmacovigilance databases?

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Brodalumab is an anti-IL-17 inhibitors indicated for the treatment of moderate to severe plaque psoriasis in adults requiring systemic therapy. The Warnings and Precautions section of the Summary of Product Characteristics (SPC) mentions cases of suicidal behavior and ideation, even though no causal relationship has been established. We received a report of depressive ideas under brodalumab . This prompted us to conduct a descriptive retrospective study to explore French Pharmacovigilance (FPD) and WHO databases .

Materials and methods

A VigiBase query was performed on January 19, 2026, including cases of adverse events classified as “Depressed mood disorders and disturbances” (MedDRA HLGT) associated with brodalumab. Cases involving co-suspected medications were excluded.

Results

A total of 106 cases (only one in FPD) were analyzed (male/female ratio: 0.88; median age: 53 years [25–88]; median time to onset: 73.5 days [0–2161). Among these cases, 78 (74%) presented depressive symptoms, 18 (17%) presented suicidal

behaviors with only one attempted suicide, and 10 (9%) presented mood disorders. Among 45 dechallenges with known outcomes, improvement is reported in 75%. Outcomes were unknown for the 17 rechallenges reported in total.

Regarding the attempted suicide case, the dechallenge resolved this AE, whereas the associated depression hasn't been resolved.

A disproportionality signal was identified in VigiBase for depression associated with brodalumab (IC025 = 1.3).

Discussion / Conclusion

Depressive and suicidal disorders associated with brodalumab account for approximately 70% and 20% of reports in VigiBase within our criterias, respectively, with a notable disproportionality signal for the term depression. Rare epidemiological studies give discordants results, interclass difference is raised with a lower association with Anti-IL-17 inhibitors and depression, excepted for brodalumab. This can be induced by a reporting bias following warnings in SPC for this drug, and indication bias as psoriasis is associated with an increased of depression (1-2). Epidemiological studies taking into account these biases are needed.

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00272
Hepatic angiosarcoma after trioxyde arsenic therapy in acute promyelocytic leukemia type 3: a case report

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Acute promyelocytic leukemia type 3 (APL) is a rare but often curable hematologic malignancy which treatment includes arsenic trioxide and tretinoin. The adverse events include secondary cancer, and their occurrence should be monitored according to the Summary of Product Characteristics of arsenic.

Materials and methods

We report the case of a hepatic angiosarcoma occurred a few months after an arsenic treatment.

Results

A 44-year-old patient with APL, characterized by a high-level of PML-RARα transcript without hyperleukocytosis, revealed by splenomegaly was and treated with tretinoin and arsenic trioxide (one induction course followed by two consolidation courses).

Pre-treatment liver function tests and imaging including abdominal tomodensitometry and PET scanner revealed no abnormalities. Complete remission from APL3 was obtained. However, 4.5 months after the beginning of arsenic therapy, unexplained abnormal liver function tests and hepatomegaly led to a liver biopsy, which revealed a hepatic angiosarcoma. The patient received chemotherapy but died 15 days after the diagnosis. The patient had no professional exposure.

Discussion / Conclusion

Hepatic angiosarcoma is a very rare vascular malignancy. It has been associated with exposure to certain substances, including arsenic, for which the causal link is well established. Indeed, hepatic angiosarcoma is recognized as an occupational disease in individuals exposed to arsenic, and cases have been reported in patients treated with Fowler's solution, previously used to treat disorders such as leukemia and psoriasis. The association between hepatic angiosarcoma and exposure to arsenic trioxide may be suspected in this case, despite the unusually short latency period and the absence of previously reported cases in the literature.

Hepatic angiosarcoma may represent a new and extremely rare adverse effect of arsenic trioxide and could constitute a potential pharmacovigilance signal.

Keywords

Hepatic angiosarcoma

Trioxyde arsenic

Acute promyelocytic leukemia type 3

00275
Sex differences in LDL-C response to evolocumab

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Evolocumab is a human immunoglobulin G2 monoclonal antibody directed against human proprotein convertase subtilisin/kexin type 9 (PCSK9). An increase in liver serum low-density lipoprotein receptor levels results in associated reductions in serum low-density lipoprotein cholesterol (LDL-C). In the follow-up of evolocumab, the available data suggest that LDL-C reduction is lower in women than in men for the same dose administered.

Materials and methods

The French pharmacovigilance database (FPVD) and international pharmacovigilance Vigibase database (IPVD) were consulted accessed on February 12, 2026: all suspected " drug ineffective», « drug effect less than expected», « therapeutic response decreased », «drug resistance », « therapy partial responder » and « therapy non responder » (MedDRA Preferred Term PT) reported with "evolocumab" were extracted and analysed in the FPVD. A literature review was conducted.

Results

With the PT terms of the method, only three women cases were compiled in the FPVD. In the IPVD, the percentage of women who do not respond well to treatment is higher than that of men. For example, with the term “ineffectiveness” in Vigibase, women represent 53.4%, men 35.4%, and people of unknown sex 11.1%. Other

examples include non-responders to treatment, who represent 54.9% of women, 30.1% of men, and 15% of people of unknown sex. In the literature, anti-PCSK9 antibodies are less effective at reducing LDL-C levels in women than in men and are equally safe.

Discussion / Conclusion

Three cases in the FPVD reflects the fact that these cases are not reported. Fogacci et al. suggest that men and women may have different inflammatory responses to evolocumab, which could reflect underlying biological differences in immune regulation and lipid metabolism. The problem is that gender differences are not taken into account in the targets to be achieved with identical recommendations. Studies conducted specifically in women would be necessary to determine the most appropriate therapeutic strategy.

Reference(s)

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Keywords

evolocumab , sex difference, LDL-C reponse

00276
AI Identification of Profiles of Pregnancies at Risk of Major Congenital Anomalies after Medication Intake: the France-Quebec Project INuTERO

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

It takes time to identify the teratogenic effect of a medication, which is a complex multifactorial process. Large language models (LLM) make it possible to consider the vast amount of information contained in medical files, across large populations.

Step one of INuTERO study aims to find a validated LLM to identify as accurately and quickly as possible profiles of pregnant women at risk of having a foetus/baby with a major congenital malformation (MCM), to better anticipate and provide adequate care.

Materials and methods

The French cohort EFEMERIS (2,3), has been used. Medication exposures and pregnant women characteristics were considered. Traditional machine learning (ML), recent models based on generative AI, such as language models (LMs) and LLMs, were used. These approaches were trained on EFEMERIS to “learn” how to identify a profile at risk of MCM. Considering the low presence of positive cases, we used appropriate metrics for highly unbalanced datasets to evaluate the performance of the predictive models.

Results

Fine-tuned LMs trained on EFEMERIS achieve the best performance for MCM prediction compared to ML methods, with improvements up to 3% and 2.1% in terms of AUCPR and AUCROC, respectively. In contrast, raw LLM performance shows that these models require better adaptations.

Model	AUCROC	AUCPR
Random	50	2.32
Traditional Machine Learning Methods		
LigthGBM	56.81	5.91
RandomForest	56.67	5.75
XGBoost	56.52	5.53
Logistic Regression	54.25	3.65
Zero-shot LLMs		
Llama-3.1-8B	50.24	2.4
DeepSeekR1-14B	51.66	2.34
Fine-tuned LMs		
BioMedBERT	56.69	6.09
ModernBERT	58.01	5.99

Discussion / Conclusion

Fine-tuned LMs obtain better performance than traditional ML methods in MCM prediction. Currently, raw LLMs are being optimized to achieve better performance, with major challenges identified.

In a second step, federated learning will be performed in two geographically distinct locations, France and Canada, thus including the large Quebec Pregnancy Cohort (4), to improve overall performance of the model, while preserving confidentiality.

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Keywords

Artificial Intelligence, pregnancy, congenital anomalies, medications

00278
Fenfluramine (Fintepla) associated pulmonary arterial hypertension (PAH) : a study of adverse events reporting systems FAERS

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Fenfluramine was first marketed as an appetite suppressant drug and then withdrawn due to severe cardiovascular events. A new fenfluramine formulation (Fintepla) received marketing authorization in 2020, as a treatment for genetic epilepsy. To reduce the risk of cardiovascular toxicity, the drug is available through restricted programs with mandatory echocardiograms. During clinical and safety studies, among 374 patients, no case of pulmonary hypertension (PH) nor persistent valvular heart disease was reported. In 2024, a 4-year-old child presented with increased right pulmonary pressure 6 months after the introduction of Fintepla.

Materials and methods

The main objective of this work was to describe narratives of the reported cases of pulmonary arterial hypertension (PAH) with Fintepla, in the FDA Adverse Event Reporting System database, through the US Freedom of Information Act, we requested access to the narratives of cases reporting Pulmonary Arterial Hypertension with Fintepla.

Results

On June 2025, 2,984 cases of adverse events were reported with Fintepla, and 150 for valvular outcomes or pulmonary pressure abnormalities. The number of cases increased from 8 in 2022 to 72 in 2024. Fifteen cases reported the term PAH, even though no confirmation by right heart catheterization was mentioned. These 15 echocardiographic PH were for 10 adults, with a median time to an increase pulmonary pressure of 380 days; and 5 children with a median time of 363 days. Three echocardiographic PH cases improved after drug discontinuation (unknown information for the others). There was a heterogeneity in dose and time-to-onset of PH, suggesting a poor dose- and time-dependence effect. For the 3 patients with documented follow-up, echocardiography showed a return to normal pressures, suggesting a potential toxicity reversibility.

Discussion / Conclusion

These results confirm the plausibility of PH onset in patients exposed to Fintepla, and reinforce the importance of careful monitoring.

Keywords

PAH

Fintepla

Fenfluramine

Adverse events

00279
Fine-Tuned Biomedical Transformers to Verify MedDRA Coding Related to Guillain–Barré Syndrome in Individual Case Safety Reports Database.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Confirming that MedDRA codes accurately reflect the underlying diagnosis is a critical first step in validating pharmacovigilance cases, particularly for complex conditions such as Guillain–Barré syndrome (GBS). Because GBS is characterised by progressive motor, sensory, and autonomic symptoms, pharmacovigilance officers must reconstruct this clinical logic from fragmented narratives to assess whether the assigned code is appropriate. The study aimed to evaluate how well ICSR narratives support the appropriateness of MedDRA coding for GBS.

Materials and methods

Data from a French Regional Pharmacovigilance Center were used to identify ICSRs potentially related to GBS. A supervised binary classification pipeline was built using the GBS Standardised MedDRA Query, with narrow Preferred Terms as positive controls and broad-term ICSRs as negative controls. The primary model fine-tuned CamemBERT-bio, a French biomedical transformer pretrained on large domain-specific corpora. Narrative text was the main input, with extended models incorporating age and sex. For comparison, contextual embeddings were combined with LightGBM and linear support vector machine classifiers. Performance was assessed using five repeated stratified train–test splits, with results averaged across repetitions, and bootstrap resampling was used to estimate 95% confidence intervals.

Results

Fifty-two positive and 60 negative controls were included. Across five repeated 80/20 stratified train-test splits, fine-tuned CamemBERT-bio achieved the best performance, with mean accuracy 0.96 (95% CI: 0.93–0.98), precision 0.97 (0.91–1.00), recall 0.94 (0.91–0.98), F1-score 0.95 (0.93–0.98), ROC-AUC 0.98 (0.97–0.99), and AUPRC 0.99 (0.97–1.00). Hybrid models with frozen embeddings performed less well.

Discussion / Conclusion

Fine-tuned CamemBERT-bio effectively analyses pharmacovigilance narratives and captures clinically meaningful patterns consistent with GBS with a low number of ICSRs. By helping verify whether narrative information supports the assigned MedDRA coding, it can assist pharmacovigilance officers during ICSR triage in cumulative reviews and provide a scalable framework for evaluating complex cases.

Keywords

Pharmacovigilance, natural language processing, CamemBERT-bio

00288
Eptinezumab-induced alopecia: a safety signal?

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Eptinezumab (Vyepti®) is a humanized monoclonal antibody inhibiting calcitonin gene-related peptide (CGRP), like erenumab (Aimovig®), galcanezumab (Emgality®), and fremanezumab (Ajovy®). Approved for the prevention of migraine in adults experiencing at least four migraine days per month, these therapies are well-tolerated with mainly hypersensitivity reactions and infusion-related reactions (generalized or localized). Alopecia is not an expected adverse drug reactions.

Materials and methods

We report three cases of hair loss after treatment with eptinezumab (Vyepti®) and propose safety data review on this topic.

Results

Case 1: a 25-year-old female patient reported a significant hair loss with eptinezumab, the onset was one week after each the first infusion, the effect persisted for five weeks before improving with recurrence after each rechallenge. Despite alopecia persisting, treatment was remained upon benefit.

Case 2: a 45-year-old female patient reported important hair loss starting fifteen days after the first infusion of eptinezumab for high-frequency episodic migraine. Eptinezumab was pursued and the effect persisted without aggravation.

Case 3: a 29-year-old male patient reported important hair loss which began one month after the first administration of eptinezumab.

Discussion / Conclusion

The occurrence of alopecia with CGRP inhibitors remains an unexpected risk, excepted for erenumab. However, literature analysis retrieves data suggestive for a drug-induced adverse effect. Cases have been reported in the post-marketing pharmacovigilance studies and in the WHO International safety database with positive disproportionality for the class and for each drug individually. Physiopathological mechanism supports a class effect, as CGRP promotes hair growth and protects against hair follicle collapse. The cases we reported with strong imputability score reinforce this safety signal. Clinicians and patients should we aware of this potential effect, which affects patients' quality of life, to better consider the benefits and risks.

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Keywords

Migraine

CGRP antagonists

Alopecia

Pharmacovigilance

00294
Pristinamycin-associated SDRIFE: a case report with atypical bullous presentation and analysis of the French Pharmacovigilance Database

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Pristinamycin is a streptogramin antibiotic commonly used to treat ENT (Ear Nose Throat) and cutaneous infections. Although various toxidermias have been reported, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) is not currently listed in the summary of product characteristics (SmPC).

Materials and methods

We report a case of SDRIFE occurring shortly after initiation of pristinamycin, with favourable evolution following drug withdrawal. To further document this association, we reviewed cases of SDRIFE reported after pristinamycin exposure in the French Pharmacovigilance Database (FPVDB).

Results

Case description: A 59-year-old man received pristinamycin 1 g/day for sinusitis. Within hours of the first dose, he developed an erythematous rash initially localized to the left inguinal fold, with a few bullous lesions. The following day, the eruption extended to both axillae, cubital fossae, and the right inguinal fold. Pristinamycin was discontinued after a single dose. Treatment with topical corticosteroids and local care led to complete resolution. The drug was subsequently contraindicated, and allergy testing was scheduled.

FPVDB analysis : FPVDB analysis identified 16 cases (7 men, 9 women). The median time to onset was 1 day (range: 1 hour–11 days). Outcomes were favourable in all cases, with resolution within a mean of 7.5 days (range: 1–15 days) after drug withdrawal and symptomatic treatment. Allergy testing was performed in several cases and confirmed sensitization in five patients.

Discussion / Conclusion

Although SDRIFE is not currently listed in the SmPC of pristinamycin, our case and pharmacovigilance data, including positive allergy tests, support its inclusion among the potential adverse reactions of this drug.

Keywords

SDRIFE

Pristinamycin

Pharmacovigilance

00299
Adverse Drug Reactions reporting by General Practitioners: analysis of the French Pharmacovigilance Database

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

General practitioners (GPs) manage most primary care prescriptions but are believed to under-report adverse drug reactions (ADRs) compared to medical specialists (SPs). This study investigates if this discrepancy is an intrinsic behavioral difference or a statistical artifact driven by practice settings.

Materials and methods

We analyzed 522,289 ADR reports from the 2024 French pharmacovigilance database (BNPV). Volumes and clinical profiles were cross-referenced with DREES demographics to calculate reporting rates by specialty and setting (private vs. hospital).

Results

GPs accounted for only 8.1% (n=42,179) of total reports, confirming a massive quantitative under-representation compared to SPs (91.9%). Clinically, GPs primarily reported ADRs for ambulatory treatments: lipid-modifying agents (17.9% GP share)

and renin-angiotensin system drugs (13.7%). Vaccines were the only major class dominated by GPs' reporting (52.1%). Regarding System Organ Classes, GPs predominantly identified musculoskeletal (27.7% GP share) and vascular disorders, reflecting chronic care symptoms. Conversely, SPs dominated reports for systemic antibacterials, skin disorders, and immune system reactions. The low global GP reporting rate is heavily confounded by practice demographics: around 65.7% of GPs work in private practice, whereas 51.9% of SPs operate in hospitals. When standardized by setting, private practice GPs actually report slightly more than private practice SPs (0.504 vs. 0.422 reports/physician/year). The global deficit is entirely driven by hospital-based SPs (4.959 reports/physician/year).

Discussion / Conclusion

The perceived overall under-reporting by GPs is a confounding illusion. In ambulatory care, GPs report at rates slightly higher than their specialist counterparts. As the French network of Regional Pharmacovigilance Centers (RFCRPV) celebrates its 50th anniversary, it is essential to find new mechanisms to better engage primary care physicians by extending pharmacovigilance beyond the walls of university hospitals.

Keywords

Pharmacovigilance

General Practitioners

00301
Pregnancy exposure to vortioxetine: a series of eight cases

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Vortioxetine, a serotonergic antidepressant available in France since 2016, is prescribed to nearly 200,000 patients each year, two-thirds of whom are women. Its action results from enhancement of central serotonergic activity through reuptake inhibition combined with 5-HT3 receptor antagonism and 5-HT1A receptor agonism.

Data regarding its use during pregnancy remains scarse, with only one independent publication reporting 17 pregnancy outcomes and one isolated case report. This case series provide additional real-world data on pregnancy outcomes following exposure to vortioxetine.

Materials and methods

Between 2019 and 2024, the Montpellier Regional Pharmacovigilance Centre was consulted about nine pregnant women treated with vortioxetine, with documented outcomes for eight patients.

Results

All eight pregnancies resulted in live births with no apparent congenital malformations, with a mean birth weight of 3.4 kg. All patients were exposed to vortioxetine during the first trimester, and five continued vortioxetine throughout pregnancy, with an average dose of 11.4 mg/d. One late preterm delivery occurred at 36+2 weeks of gestation. Seven patients received concomitant treatments, each taking at least one additional psychotropic drug. Three reported tobacco use. Four newborns presented transient neonatal symptoms: respiratory distress, central apnea, and grunting. These symptoms are frequently associated with cardiopulmonary immaturity at birth; they were mild and regressive.

Discussion / Conclusion

This small case series does not suggest an increased risk of congenital malformations or prematurity with vortioxetine. Neonatal manifestations were observed in four cases, but all involved concomitant psychotropic medications, including hydroxyzine in every cases, and in two cases, maternal smoking, both confounders for respiratory adaptation at birth. These co-exposures limit the ability to attribute neonatal symptoms to vortioxetine alone. Interpretation must therefore remain cautious due to the small sample size, polymedication and confounding factors, highlighting the need for larger studies and long-term follow-up.

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Keywords

pregnancy, pharmacovigilance, vortioxetine

00303
Sex differences in adverse drug reactions following vaccination: analysis of cases from the French Pharmacovigilance Database

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Immune responses to pathogens and inflammation pathways differ between sexes. These differences may be reflected in responses to vaccines, including adverse drug reactions (ADR). This study aimed to describe sex-related differences in reported ADRs after vaccination.

Materials and methods

A retrospective descriptive analysis was conducted using vaccine-related ADR cases reported in the French Pharmacovigilance Database from 01/01/1985 to 19/09/2025.

Exclusion criteria were: undetermined sex, pregnancy/lactation cases, medication errors without ADR, vaccines coded as concomitant or interacting, and incompatible chronology.

Results

Overall, 238,124 cases including at least one vaccine as a suspected drug were analyzed, corresponding to 473,449 vaccine-ADR pairs. 69% (n=164,589) of cases occurred in females. 23% of cases were serious in females, 33% in males.

Considering 95,671 vaccine-ADR pairs other than COVID-19 vaccines, 60% were reported in females. Modest sex differences were observed in ADR types: general disorders and administration site conditions (38.5% vs 36.2%), and musculoskeletal and connective tissue disorders (10.4% vs 8.3%) were more frequently reported in females than in males, whereas infections/infestations were more frequently reported in males (4.7% vs 3.4%). Serious cases represented 32% in female and 37% in males.

Among COVID-19 vaccine-ADR pairs, 74% involved females. Notable sex differences emerged across specific ADR categories: reproductive system and breast (11.6% vs 0.5%), and gastrointestinal disorders (7.7% vs 6.2%) were more reported in females. In contrast, cardiac (5.7% vs 3%), nervous system (14.5% vs 12.5%), respiratory, thoracic and mediastinal disorders (4.9% vs 3.3%), and infections/infestations (4% vs 2.5%) were more frequently reported in males. 22% of cases were serious in females and 32% in males.

Discussion / Conclusion

Vaccine-related ADRs were more reported in females and were proportionately less serious in this preliminary analysis. However, ADR types varied according to biological sex and vaccine type. Post-immunization ADRs should be analyzed in a sex-specific manner to better consider adverse effects without compromising vaccine-conferred protection.

Reference(s)

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Keywords

sex differences, vaccines, adverse drug reaction, pharmacovigilance, personalized medicine

00308
Bexsero® vaccine: 10 years of pharmacovigilance monitoring

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

BEXSERO, first recombinant meningococcal vaccine designed to protect against serogroup B, was used in hyperendemic areas before getting available in the general population for infants and young adults, and became mandatory in March 2024 for young children with reimbursement for 15-24 year olds maintained in 2025.

A strengthened surveillance was first initiated based on electronic vaccination record to optimise data collection, switched for a more traditional pharmacovigilance monitoring with the end of the vaccination campaign in July 2014.

Materials and methods

We come back to the adverse effects of concerns (AE) added to the SPC over the 10 years of this follow-up and those of current interest.

Results

The main AEs of BEXSERO, described in the SPC, were symptoms of reactogenicity, convulsions and a rare cases of Kawasaki disease.

As experience grew, lymphadenopathies and local allergic reactions, as well as nodules at the vaccination site appeared on the SPC. The neurological disorders section was reinforced with the introduction of a meningeal irritation risk; also, in adolescents population, the vasovagal syncope was added as were, in children, headaches and hypotonic-hyporesponsive episodes.

Some potential pharmacovigilance signals, relating to non-serious but potentially alarming effects for parents due to their presentation, are being evaluated, among which the acute hemorrhagic edema of infancy and the pigmentations/hypertrichosis at vaccination site.

Furthermore, the follow-up highlighted medication errors, storage issues, timing errors, and, more strikingly, errors in the vaccines administered.

Discussion / Conclusion

This vaccine has undoubtedly helped to curb the hyperendemicity of invasive meningococcal B infections that was rampant in some French areas and over the years, neither in France nor elsewhere has its effectiveness been questioned.

This extended follow-up confirms its relatively standard and reassuring safety profile, the most frequently reported AE being potentially significant reactogenic effects and neurological disorders, such as convulsions, hypotonic-hyporesponsive episodes and headaches.

Keywords

meningococcal vaccine, strengthened surveillance, adverse effects, safety profile.

00311
Serious infections with anti-BCMA/CD3 bispecific antibodies in real life: a retrospective study on the French Pharmacovigilance Database

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Anti-BCMA/CD3 bispecific antibodies (teclistamab, elranatamab) represent a breakthrough in oncohematology. Being powerful immunomodulatory agents, they expose patients, often elderly and frail, to an increased risk of infections[1]. Even if this risk increase is well-established, real-life data are still too scarce to accurately characterize it.

Materials and methods

A descriptive analysis of serious cases of infection cases with teclistamab and elranatamab recorded in the French Pharmacovigilance Database (BNPV) was performed.

Results

As of February 17th, 2026, 54 serious infections were reported in 44 patients, mainly treated with teclistamab (n=31/44). Infections were, by descending order, viral (n=24; including PML/JC virus n=7, CMV n=4; COVID-19 n=3), bacterial (n=21; including E.coli n=5, P.aeruginosa n=3), fungal (n=6; Aspergillus n=3, Pneumocystis n=2, Candida n=1) and parasitic (n=2: toxoplasmosis, cryptosporidiosis), 2 cases were undocumented. The initial site was most frequently the lower respiratory tract (n=21), the central nervous system (n=11) and the digestive system (n=8). Secondary generalization was reported in 16 cases, and bacterial superinfection in 2/24 viral infections. Time-to-onset after C1D1 was shorter than 3 months in 29 cases (median 45 days; median 10.7 months in the other cases). Thirteen patients (29.5%) died from the infection or from related complications. Risk factors could be identified in several cases: hypogammaglobulinemia (n=8), leuko-neutropenia (n=7), history of autologous bone marrow transplant (n=5), and teclistamab weekly or bimonthly dosing (n=18/31).

Discussion / Conclusion

In line with the available data[2;3;4], patients presented most frequently with respiratory tract infections occurring within the first months of treatment. The cases of opportunistic infections (PML, pneumocystosis…) were often associated with a poor prognosis. The infection risk appears multifactorial: immunosuppression, hypogammaglobulinemia and/or leukopenia that could either be related to the hematological disease or to the bispecific antibody. It can be significantly mitigated with adequate preventative measures that should be discussed before starting treatment, like vaccination and prophylactic treatment including polyvalent immunoglobulins.

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Keywords

Pharmacovigilance

Infections

Bispecific antibody

Teclistamab

Elranatamab

00316
Heparin-induced isolated eosinophilia: not so isolated with unfractionated heparins?

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

French Regional Pharmacovigilance Centers (FRPVCs) are regularly consulted about the role of drugs in cases of isolated eosinophilia in hospitalized patients, raising questions about the imputability of ongoing heparin therapy. We aimed to describe the clinical features of heparin-induced isolated eosinophilia and compare unfractionated heparins (UFH) with low-molecular-weight-heparins (LMWH).

Materials and methods

We performed a retrospective analysis of cases of eosinophilia (> 0.5 G/L) notified to FRPVCs until December 31, 2025 with heparins as the only suspected drug. Cases with cutaneous allergic manifestations, insufficient data, unknown outcomes, or duplicates were excluded. Demographic characteristics, heparin type, eosinophil peak, time to onset, outcomes, rechallenge and switch data were analyzed descriptively.

Results

Among the 8,210 cases of drug-induced eosinophilia registered in the FRPVCs database, 606 (7%) involved a heparin and 94 cases without cutaneous manifestations were included. Patients were predominantly male (n=53, 56%), median age of 65 years (IQR 52–77). UFH accounted for 47 cases (50%) and LMWH for 47 cases (50%). Median time to onset was 11 days [4-32]. Median eosinophil peak was higher with UFH (2.9 G/L) than LMWH (1.7 G/L)(p=0.04). Heparin was discontinued in 71 cases, with improvement within 7 days [4-11]. Rechallenge with the same drug was positive in 100% (8/8). Switching from UFH to LMWH led to improvement in 70% of cases (7/10).

Discussion / Conclusion

Despite lower clinical use of UFH compared with LMWH, a similar number of cases was reported, suggesting a potential increased risk of eosinophilia with UFH. Eosinophilia also appeared more severe with UFH and switching to LMWH may represent an effective management strategy. The underlying mechanism remains unclear, but time to onset and positive rechallenge suggest a possible immune-mediated reaction, potentially reflecting the greater immunogenicity of UFH, as described for heparin-induced thrombocytopenia. These findings may improve recognition and management of eosinophilia during heparin therapy.

Keywords

Heparin ; Eosinophilia ; Pharmacovigilance

00319
Neuropsychiatric ADRs associated with melatonin: Evidence from national reports in France

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Few melatonin-containing medicines are available in France since 2012 (CIRCADIN®), 2020 (SLENYTO®), and 2025 (ADAFLEX®). Their use is growing, with the number of reimbursed boxes of SLENYTO® increasing elevenfold between 2020 and 2024. Due to heterogeneous safety profiles, the aim of this study was to further describe the safety profile of melatonin.

Materials and methods

We conducted a retrospective, descriptive analysis of cases of adverse effects associated with melatonin reported to the French pharmacovigilance database (FPVD) up to 31/12/2025. We excluded cases of overdoses and medication errors without adverse effects. We focused on cases involving nervous system and psychiatric disorders (according to System Organ Class from MedDRA classification), being the 2 most common SOCs concerned in the overall analysis.

Results

193 (out of 485) cases concerned neuropsychiatric effects, including 110 cases with nervous system disorders and 108 cases with psychiatric disorders. The male-to-female ratio was 1.17 and mean age was 36.9 years, with 81 cases occurring in paediatrics (18 years and under). Off-label use (age) was identified in 44 cases. Regarding psychiatric disorders: 65% (n = 70) of cases described unexpected effects, such as pharmacodependence (n = 16), hallucinations (n = 14), confusion (n = 10), and behavioural disorders (n = 9); melatonin was the only suspected drug in 63% (n = 68) of cases, 31% (n = 33) were serious. Regarding nervous system disorders: 53% (n = 58) of cases described unexpected effects, such as epileptic disorders (n = 10), tremors (n = 7) or movement disorders (n = 4); 42% improved after discontinuation and they affected more women (n = 56).

Discussion / Conclusion

Neuropsychiatric effects with melatonin represented nearly half of the reported cases in FPVD and including unexpected ones. Their occurence must be considered in relation to underlying pathologies. Updating on these risks and harmonisation of SPCs should be considered for melatonin-containing medicines.

Keywords

Pharmacovigilance ; drug safety ; melatonin ; adverse drug reaction

00321
Retrospective descriptive study of adverse effects reported in the French National Pharmacovigilance Database associated with Pluvicto®

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

[^177Lu]Lu-PSMA-617 (Pluvicto®) is a targeted radioligand therapy approved for metastatic castration-resistant prostate cancer after failure of androgen receptor pathway inhibitors and taxane-based chemotherapy, with limited real-world safety data. This study aimed to characterize adverse effects (AEs) associated with Pluvicto® during early access authorization using data from the French National Pharmacovigilance Database (BNPV).

Materials and methods

A retrospective descriptive analysis of all pharmacovigilance reports recorded in the BNPV up to March 5, 2025, in which Pluvicto® was reported as a suspect drug, using MedDRA terms, and comparison with Summary of Product Characteristics (SmPC) were performed.

Results

91 cases were identified, including 89 cases reporting AEs and 2 medication errors without AEs. The mean patient age was 73 years. In total, 145 AEs were reported.

The main disorders were hematological the most frequent (66.9%), gastrointestinal (6.2%), renal/urinary (5.5%). The main hematological AEs were anemia (20.7%), thrombocytopenia (18.6%), neutropenia (8.3%), leukopenia (6.9%) and pancytopenia (6.9%). Serious AEs accounted for 70.8% of cases (63/89), mainly: prolonged hospitalization and medically significant AEs. Three deaths were reported, accounting for 4.8% of serious cases. Treatment discontinuation (42.7%) or dose reduction (9%) was frequently required. Symptom improvement occurred in 31.6% of cases after discontinuation and in 50% after dose reduction. Time to onset ranged from day 0 to day 584 after first administration (median 30.5 days; mean 80.8 days). Unexpected effects were identified, including thrombotic microangiopathy, disseminated intravascular coagulation, neurological events and ocular disorders.

Discussion / Conclusion

This study confirms a safety profile of Pluvicto® consistent with data from clinical trials, particularly regarding hematological toxicity. The identification of unexpected AEs highlights the importance of continuous post-marketing surveillance, especially in a fragile and comorbid population, and contributes to refining the benefit–risk assessment of radioligand therapies in clinical practice. Multicenter clinical cohorts could complement clinical trials by providing more comprehensive real-world data on treatment effectiveness and safety.

Keywords

Pharmacovigilance; Pluvicto®; prostatic; radioligand therapy; metastatic castration-resistant prostate cancer; adverse effects.

00354
Serious neuropsychiatric adverse drug reactions to montelukast in children: evidence from the French Pharmacovigilance Database

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Montelukast has been linked to severe neuropsychiatric adverse drug reactions (ADRs) in paediatrics [1-6], prompting safety warnings (ANSM, FDA). After observing, in our hospital, a case of prolonged exposure marked by the emergence of aggressive behaviour, we reassessed its neuropsychiatric safety profile in children using the French Pharmacovigilance Database (FPVD).

Materials and methods

We retrospectively analysed FPVD reports in patients <18 years up to 26 January 2026, including only cases with montelukast as the sole suspected drug and excluding medication errors. ADRs were extracted from the MedDRA SOCs “Psychiatric disorders” and “Nervous system disorders.”

Results

The query identified 201 cases of neuropsychiatric ADRs (M/F ratio 1.7; median age 5 years [7 months – 17 years]; median dose 5 mg/day); median time to onset 3 days [0 – 668]). Montelukast was discontinued in 180/184 cases with dechallenge data, with improvement in 148/160; when reported, recovery was generally rapid (mean 9.5 days [0 – 180]). Fifty-one patients (25%) experienced at least one serious neuropsychiatric ADR (mean: 1.3 ADR/patient). The most frequent were sleep disturbances (24/51; nightmares, insomnia), behavioural disturbances (24/51; irritability, agitation, self/hetero-aggressiveness, anger, screaming), anxiety-depressive symptoms (16/51) and hallucinations (12/51; auditory and/or visual, nocturnal or daytime). Suicidality was reported in 9/51 cases (5 suicide attempts, 4 suicidal ideation). Nineteen cases required hospitalisation and four were life-threatening. In 10 cases, symptoms were initially misattributed to primary psychiatric disorders, leading to psychotropic initiation. Two positive serious rechallenges (aggressive behaviour) were documented (no rechallenge n=30; missing data n=19). Notably, none of the patients with serious neuropsychiatric ADRs had a prior psychiatric history.

Discussion / Conclusion

FPVD paediatric reports highlight early-onset, occasionally severe neuropsychiatric ADRs with montelukast (primarily sleep and behavioural disturbances) in children without prior psychiatric history, often resolving after discontinuation. Despite inconsistent epidemiological data [5], any new psychiatric or behavioural symptom should prompt immediate medication review and careful exposure-symptom evaluation.

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Keywords

Montelukast; Paediatric pharmacovigilance; Neuropsychiatric adverse drug reactions

00365
Is it still relevant to maintain continuous remote assessments with the rise of generative AI? Example of the Pharmacovigilance university diploma of Lyon 1 University?

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The Pharmacovigilance university diploma is structured into nine modules. Following each module, students are given one week to complete an online set of questions, with a strict time limit. Internet access and consultation of course materials are permitted during this assessment. Over the past five years, student performance has progressively improved. However, the rise of generative Artificial Intelligence (gAI) since 2022 raises concerns regarding the validity and sustainability of this continuous assessment format. The objective of this study was to evaluate the feasibility of using gAI systems to complete these timed evaluations and to determine whether their performance is superior to that of students.

Materials and methods

Student assessments were administered on the University of Lyon 1 platforms, (Claroline and Moodle). We compared students' continuous-assessment results for

five modules over five academic years with the performance of four generative AI systems (ChatGPT, Gemini, Copilot, and OpenEvidence). The AI-generated responses were entered into Moodle under real examination conditions, by the coordinators. Data are presented as mean ± SD.

Results

From 2021/2022 to 2025/2026, 83 students completed the diploma. Twenty-five modules were assessed with an average of 20 questions per module. Student scores more than doubled over this period rising from 7.4/20 ± 3.6 to 16.6/20 ± 1.6. Under identical timed conditions, mean AI completion time was 13 ± 6 minutes per module. Across the four AI models evaluated, the mean performance scores obtained exceeded those of the student cohort, with average scores of 18.0 for Gemini, 17.5, for Copilot, 17.2 for ChatGPT, and 16.9 for OpenEvidence.

Discussion / Conclusion

Generative AI systems performed at least as well as students while respecting the time constraints. As it is currently impossible to verify whether students use AI during online assessments and existing monitoring tools such as Safe Exam Browser are not suited to this context, this form of continuous assessment appears increasingly unsustainable in the era of gAI.

Keywords

pharmacovigilance, education, generative artificial intelligence

00368
Risk analysis applied to potential signal in pharmacovigilance

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The French Medicines Agency (ANSM) receives and detects potential signals from a wide range sources (pharmacovigilance reports, medication errors, misuse, etc.). A safety signal in pharmacovigilance is an information on a potential new or known adverse drug reaction that needs further investigation. Each potential incoming signal is subject to a risk analysis that allows risk reduction measures to be put in place tailored to the level of risk. Some signals require more in-depth analysis using additional tools to better characterize them (e.g., conducting a pharmacovigilance investigation, a pharmacoepidemiological study, an impact study, or a utilization study)

Materials and methods

The ANSM has implemented a risk analysis grid that has been tested from 2017 to December 2020 and validated on significant cases from Regional Pharmacovigilance Centers, scientific literature, non-compliant use, and significant medication errors. A set of criteria is scored to assign a risk level from among four predefined levels (low risk, medium risk, significant risk, and high risk). The risk analysis criteria used to assign a risk level to a signal have been ranked (seriousness, unusual nature of the event, sensitive population criteria, existence of similar signal in France or Europe, exposure to the drug, and presence of a potential statistical signal). Each criterion is weighted, and an overall composite score is obtained.

Results

Risk analysis is a decision-making tool for assessors, introduced in 2017, whose main objective is to assess risk by cross-analyzing all available data in order to implement appropriate risk reduction measures. In 2024, 949 potential signals were processed, 27 of which were high risk.

Discussion / Conclusion

All incoming signals are processed in order to prioritize their handling, then analyzed collectively within the ANSM's bodies (Scientific Committee) using the medical, scientific, and technical expertise available to confirm or refute the potential signal.

Keywords

pharmacovigilance; signal; risk analysis ; ANSM

00383
Never events: A survey of community pharmacists' knowledge and practices in Nouvelle- Aquitaine

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Never events are serious, preventable medication errors (MEs) that should never occur if prevention measures are implemented. Although historically developed for healthcare facilities, many medications on this list (e.g., methotrexate, colchicine, anticoagulants) are frequently dispensed in community pharmacies. This study aims to evaluate the knowledge and practices of community pharmacists regarding these critical safety events.

Materials and methods

A descriptive survey was conducted among community pharmacists in the Nouvelle-Aquitaine region (France) using an questionnaire. Knowledge of definitions, the official list, and additional Risk Minimisation Measures (aRMMs) were assessed, alongside practical management of two clinical scenarios (methotrexate and colchicine).

Results

Only 15% of pharmacists correctly identified the complete definition of a never event. While 56% could spontaneously name at least one never event (primarily vitamin K antagonists and methotrexate), only 11% were aware of the recent list update. A significant gap was identified regarding aRMMs, with over 80% of participants unable to cite specific prevention tools like patient cards or brochures. In practice scenarios, although immediate patient management was generally appropriate, only 37% and 19% of pharmacists proposed formal reporting of the ME to their regional pharmacovigilance centre for methotrexate and colchicine cases, respectively.

Discussion / Conclusion

There is a substantial lack of knowledge regarding never events in primary care. The current top-down alert system from the French National Medicines Agency appears suboptimal, as these multiple communications fail to effectively reach community pharmacists. Enhancing the visibility of never events through integrated software alerts and targeted training is essential to bridge this information gap, improve medication safety, and increase pharmacovigilance reporting in community practice.

00386
Pulmonary alveolar hemorrhage with Direct Oral Anticoagulants versus Vitamin K Antagonists in the French Pharmacovigilance Database: is there a difference?

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Pulmonary alveolar hemorrhage (PAH) is a rare, life-threatening condition potentially drug-induced. The risk is described in the Summary of Product Characteristics (SmPC) of warfarin but not for direct oral anticoagulants (DOACs). Nevertheless, few case reports are found in the literature [1]. This study aimed to identify and characterize PAH cases reported with DOACs in the French Pharmacovigilance Database (FPVD) and compare them with those associated with vitamin K antagonists (VKAs).

Materials and methods

An observational, retrospective study based on the FPVD was performed up to February 11, 2026. Anticoagulants included DOACs (apixaban, rivaroxaban, dabigatran) and VKAs (warfarin, acenocoumarol, fluindione). PAH was identified using the Preferred Term of the MedDRA classification.

Results

A total of 74 cases were included (39 DOACs, 35 VKAs), all serious, with fatal outcomes in 10% and 20%, respectively. Clinical and radiological features were comparable. Time to onset ranged from days to years in both groups. The anticoagulant was withdrawn in all cases. Reintroduction was performed in 41% of DOACs cases and 54% of VKAs cases, with no recurrence observed in 69% (≤3 months of follow-up) and 89% (≤2 months), respectively. Among DOACs cases, potential overexposure factors (renal impairment, older age, low body weight) were present in 38%, although documented plasmatic overdose was rare (5% vs 69% with VKAs). Pre-existing pulmonary disease was reported in 28% of DOACs cases and 46% of VKAs cases. Concomitant suspected drugs, mainly antiplatelet agents and amiodarone (46%), and acute infections (23%) were reported at similar rates in both groups.

Discussion / Conclusion

From a public health perspective, although VKAs carry a higher overall risk of bleeding, particularly intracranial and gastrointestinal hemorrhages [2], our pharmacovigilance data suggest that PAH profiles are similar for DOACs and VKAs, prompting harmonization of their SmPC.

Reference(s)

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[2] Zirlik A, Bode C. Vitamin K antagonists: relative strengths and weaknesses vs. direct oral anticoagulants for stroke prevention in patients with atrial fibrillation. J Thromb Thrombolysis. 2017 Apr;43(3):365-379. doi: 10.1007/s11239-016-1446-0. PMID: 27896543; PMCID: PMC5337242.

Keywords

Pulmonary alveolar hemorrhage; direct oral anticoagulants; vitamin K antagonists; pharmacovigilance

00395
INTERNATIONAL PHARMACOVIGILANCE ASSESSMENT OF SEMAGLUTIDE: FDA Adverse Event Reporting System (FAERS) vs European database of suspected adverse drug reaction reports (ADRReports)

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Semaglutide, a GLP-1 receptor agonist initially indicated for type 2 diabetes then weight loss, has seen a sharp increase in use and significant media coverage since 2021. In a context of significant increase in adverse reaction reports, international pharmacovigilance databases were analysed. Thus, this study compares semaglutide's safety profile reported in United States (FDA Adverse Event Reporting System [FAERS]) and Europe (Adverse drug reaction reports [ADRReports]).

Materials and methods

A descriptive comparative analysis of semaglutide's adverse reactions (ADRs) was performed using data extracted from FAERS and ADRReports between 2017 and February 18, 2026. ADRs were analysed according to MedDRA System Organ Classes (SOCs), Preferred Terms (PTs), by gender, age and type of reporter. The percentages of occurrences reported in each database were compared and PTs were matched with the Summary of Product Characteristics (SmPC).

Results

Three SOCs predominate in the overall FAERS (144,990) and ADRReports (100,179) reactions: Gastrointestinal disorders (18% vs 25%), Injury, poisoning and procedural complications (13% vs 12%), and General disorders (12% vs 9%), respectively.

For gastrointestinal disorders, 42% and 43% of ADRs correspond to three PTs (nausea, vomiting, diarrhoea). For complications, reactions related to misuse and medication error have 59% vs 63% of ADRs. Finally, for general disorders, no PT emerges except fatigue represented by 10% vs 14%.

The majority of reports concern adults aged 18 to 64 (32% vs 44%), nearly 60% are women. They come mainly from healthcare professionals in Europe (32% vs 51%).

Discussion / Conclusion

Semaglutide's safety profile appears similar with SmPC. The high frequency of reactions related to misuse or medication errors reflects the growing off-label use outside diabetology, and certain diversion. General disorders remain heterogeneous, encompassing predominant PTs that may be diverse and variable depending on the context. The differences observed in reporting are likely explained by healthcare communication models, patient-professional dynamics, and the organization healthcare system.

Keywords

Semaglutide; Pharmacovigilance; FAERS; ADRReports; Adverse drug reactions; MedDRA; Safety profile; SmPC

00412
Prevalence and Preventability of Adverse Drug Reactions Related to Toxic Anti-Infective Levels: a pilot study.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic drug monitoring (TDM) aims to optimize efficacy while limiting adverse drug reactions (ADRs). Exceeding toxic thresholds is associated with an increased risk of ADRs, particularly for frequently monitored anti-infective agents. Early identification of toxic concentrations may improve ADR detection and pharmacovigilance reporting. Preventability of such ADR has never been assessed. This study evaluated the prevalence and preventability of toxic ADRs associated with anti-infective overexposure over two years of TDM activity in a general hospital.

Materials and methods

A retrospective study was conducted by extracting all anti-infective drug concentrations exceeding predefined toxic thresholds from GLIMS® software for patients hospitalized at the Bordeaux University Hospital between January 1, 2023 and December 31, 2024. For each stay, the highest toxic concentration was retained. Assuming a 30% expected ADR rate and a 10% margin of error, 81 randomly selected stays were required. Medical records were reviewed to identify ADRs.

Causality was assessed using the Naranjo algorithm (1), and preventability using the French ADR preventability scale (2).

Results

During the study period, 48,705 anti-infective assays were performed across 24,491 stays; 1,565 (6.4%) involved at least one toxic anti-infective concentration. Eighty-five toxic exposures were analyzed. The exposures involved amikacin (n=38), vancomycin (n=29), cefepime (n=11), and gentamicin (n=7). Overall, 18 toxic exposures (21.2%) were associated with ADRs. ADRs occurred in 2/38 amikacin cases (5.2%; only acute kidney injuries), 10/29 vancomycin cases (34.5%; including 8 acute kidney injuries), and 6/11 cefepime cases (54.5%; including 5 neurotoxicity cases). No ADRs were observed with gentamicin. Most ADRs were unpreventable; only two cefepime cases without renal dose adjustment were considered preventable.

Discussion / Conclusion

Prevalence of ADR associated with toxic concentrations aligns with literature data. ADRs were rarely preventable. Further studies should assess whether similar findings apply to other monitored drugs.

Reference(s)

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Keywords

therapeutic drug monitoring, pharmacovigilance, anti-infective agent, anti-bacterial agent, drug toxicity

00413
Blunting the peak: do proton pump inhibitors reduce lorlatinib-induced hyperlipidemia?

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Lorlatinib markedly improves outcomes in *ALK*-positive advanced NSCLC, with 60% of patients being progression-free at 5 years.(1) However, approximately 70% of patients develop hypercholesterolemia and/or hypertriglyceridemia. Pharmacokinetic modeling has shown that higher lorlatinib peak concentrations (C_{max}) are associated with increased risk of hypercholesterolemia.(2) Proton pump inhibitors (PPIs) reduce lorlatinib C_{max} by ~30% without affecting total exposure,(3) and could therefore potentially mitigate hyperlipidemia increase.

Materials and methods

In this prospective biomarker study (NCT05221372), 56 patients treated with lorlatinib for *ALK*- or *ROS1*-positive NSCLC were included. Cholesterol and triglyceride levels, PPI use, and baseline characteristics were extracted from medical records. Primary outcome was the association between PPI use and lipid levels at week-4 after lorlatinib initiation (before statin therapy), assessed by multivariable linear regression.

Results

For cholesterol, 40 patients had baseline levels available, of whom 48% (19/40) used a PPI. In multivariable analysis, PPI use was independently associated with a smaller increase in cholesterol levels at four weeks (B=–1.00; 95%CI –1.87 to –0.14; p=0.024) compared with non-PPI use. For triglycerides, 35 patients had baseline values, and 49% (17/35) used a PPI. PPI use was again independently associated with a smaller increase in triglyceride levels at four weeks (B=–1.16; 95%CI –2.19 to –0.14; p=0.028). This corresponds to relative reductions of 12% and 34% compared with the week-4 means for cholesterol (8.4 mmol/L) and triglycerides (3.4 mmol/L), respectively. Both models were adjusted for age, BMI, WHO performance status and baseline lipid values. Our C_{trough} and survival data did not show a significant difference between PPI and non-PPI users.

Discussion / Conclusion

Concomitant PPI use during lorlatinib treatment was associated with a smaller increase in cholesterol and triglycerides at week four, with differences of -1.0 mmol/L and -1.2 mmol/L, respectively. PPIs may represent a clinically relevant interaction to attenuate lorlatinib induced hyperlipidemia, particularly in patients refractory or intolerant to lipid lowering therapy.

Reference(s)

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2. Chen J, Ruiz-Garcia A, James LP, et al. Lorlatinib Exposure-Response Analyses for Safety and Efficacy in a Phase I/II Trial to Support Benefit-Risk Assessment in Non-Small Cell Lung Cancer. Clin Pharmacol Ther 2021;110:1273-1281.

3. Xu H, O'Gorman MT, Nepal S, et al. Phase 1 Study Evaluating the Effects of the Proton Pump Inhibitor Rabeprazole and Food on the Pharmacokinetics of Lorlatinib in Healthy Participants. Clin Pharmacol Drug Dev 2021;10:1395-1404.

Keywords

Lorlatinib; proton pump inhibitor; toxicity; hyperlipidemia; drug-drug interaction

00416
Psychiatric adverse drug reactions associated with antiepileptic drugs in children and adolescents

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Despite their long-term consequences on neurodevelopment, academic performance, and social integration, data on psychiatric adverse drug reactions (ADRs) associated with antiepileptic drugs (AEDs) in children and adolescents remain limited. In this study, we aimed to describe AED-associated psychiatric ADRs specifically in children (2–11 years) and in adolescents (12–17 years) using data from the French PharmacoVigilance Database (FPVD) and to compare age-specific patterns within these groups.

Materials and methods

We performed a descriptive analysis with expert review of psychiatric ADRs associated with AEDs in children and adolescents from the FPVD. After review,

ADRs occurring after in utero exposure to AEDs, or resulting from the abuse or misuse of AEDs, or in patients treated for psychiatric disorders or with specific neurological conditions were excluded.

Results

A total of 215 cases were included, of which 140 involved children (44.3% female, median age 6 years) and 75 adolescents (57.3% female, median age 14 years). Among children, the most frequent psychiatric ADRs were agitation (21.2%), behavioural disorders (11.1%), and aggression (10.7%). In contrast, adolescents primarily experienced agitation (10.6%), depressed mood (10.6%), and aggression (9.8%). Regarding AEDs, valproate and levetiracetam were frequently implicated, accounting for 23.0% and 18.2% of cases in children, and 11.4% and 19.3% in adolescents, respectively. Notably, clonazepam was more commonly suspected in children (13.9%), whereas lamotrigine featured more prominently in adolescents (21.6%). Almost half of the cases were serious, most often resulting in hospitalisation, with higher proportions of fatal and life-threatening ADRs in adolescents. Although two-thirds of ADRs resolved after dose reduction or AED discontinuation, 10.6% of children and 20.3% of adolescents respectively were prescribed psychotropic treatment.

Discussion / Conclusion

Psychiatric ADRs associated with AEDs are common and frequently serious in children and adolescents, with distinct age-related patterns. These findings highlight the need for systematic psychiatric screening and regular reassessment of antiepileptic treatment throughout childhood and adolescence.

Keywords

Epilepsy; children; adolescents; antiepileptic drug; psychiatric adverse drug reaction, pharmacovigilance

00420
Lupus after exposure to immune checkpoint inhibitors: French pharmacovigilance data

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Drug-induced lupus is well described, but immune checkpoint inhibitors (ICIs) were not highlighted in earlier large-scale analyses [1]. Given the central role of PD-(L)1 and CTLA-4 pathways in immune tolerance, ICI-associated lupus is an expected immune-related adverse event. We aimed to characterize lupus among patients treated with ICIs for advanced solid tumors.

Materials and methods

We reviewed all spontaneous reports of lupus associated with ICI therapy recorded in the French National Pharmacovigilance Database from its inception to 31 August 2025. Cases were identified using MedDRA High Level Terms: “Lupus erythematosus (including subtypes)” and “Lupus erythematosus and associated conditions”. All retrieved cases were reviewed.

Results

Thirty-four cases were identified. Mean age was 65 years, with a female predominance. No prior lupus history was reported; two patients had potential autoimmune background elements. One patient had prior exposure to ICIs. Underlying malignancies included lung cancer, melanoma, breast cancer, hepatocellular carcinoma, and peritoneal carcinomatosis. Regimens were anti-PD-(L)1 plus chemotherapy (18/34), anti-PD-(L)1 monotherapy (15/34), and dual anti-CTLA-4/anti-PD-(L)1 (1/34). Most cases were serious (29/34). Lupus was cutaneous in 31/34 (subacute n=19, discoid n=1, chilblain n=1, unspecified n=10), including 5 bullous presentations, and systemic in 3/34 (articular n=2; myocarditis with polyserositis n=1). Median time to onset was 3.4 months (range: 1 day–16.2 months); four cases occurred after ICI discontinuation. Autoimmune tests were positive in 24/34 (often ANA and/or anti-SSA positive). Management included topical corticosteroids (27/34), systemic corticosteroids (6/34), and hydroxychloroquine (17/34). ICIs were discontinued in 27 cases and continued in 8. Improvement or recovery was frequent in both groups. Two rechallenges were reported without recurrence under concomitant topical corticosteroids or hydroxychloroquine.

Discussion / Conclusion

Cases of lupus with ICI were predominantly cutaneous, and frequently improving with topical corticosteroids with or without hydroxychloroquine. Continuation or rechallenge may be feasible in selected cases with appropriate co-treatment and monitoring.

Reference(s)

1. Arnaud L, Mertz P, Gavand P-E, et al. Drug-induced systemic lupus: revisiting the ever-changing spectrum of the disease using the WHO pharmacovigilance database. Ann Rheum Dis. 2019. doi:10.1136/annrheumdis-2018-214598. PubMed: https://pubmed.ncbi.nlm.nih.gov/30793701/

Keywords

Immune checkpoint inhibitors; drug-induced lupus; immunotherapy; pharmacovigilance

00422
Localized Acute Exanthematous Pustulosis: a distinct drug reaction? Evidence from the French Pharmacovigilance Database

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Localized acute exanthematous pustulosis (LAEP) is a rare variant of acute generalized exanthematous pustulosis (AGEP). This cutaneous reaction, most often drug-induced (90% of cases), is characterized by the sudden onset of numerous sterile, non-follicular pustules on an edematous erythematous background. In LAEP, the distribution remains localized. This study updates an initial research conducted on cases reported to the French pharmacovigilance system (1) incorporating newly identified cases and allergy testing.

Materials and methods

We conducted a descriptive study of cases recorded in the French National Pharmacovigilance Database (BNPV). All cases coded as “localized acute

exanthematous pustulosis” were extracted from database inception until February 2, 2026.

Results

Twenty-three cases were included, of which 17 were classified as serious. The population was predominantly female (female-to-male ratio 1.55), with a mean age of 57.7 years (SD: 20.1; range: 11–88 years). In more than half of the cases, the suspected drug was an antibiotic (52.2%), mainly a beta-lactam (39.1% of cases). A positive rechallenge (localized recurrence) was reported in three cases. The median time to onset was 24 hours (range: 3–72 hours). The main sites involved were the face/neck (8 cases) and skin folds (inguinal, axillary, or inframammary) (7 cases). Two cases occurred at the drug injection site (with heparin and piperacillin/tazobactam). Histopathological examination, when performed (6 cases), supported the diagnosis of LAEP. Allergy testing was conducted in four cases, with two positive results.

Discussion / Conclusion

This case series is consistent with the limited published data on LAEP, which also identify antibiotics as the main suspected drugs and report short time to onset (<3 days), similar to AGEP. The strictly localized recurrence may suggest local cutaneous immune memory. Allergological investigations were rarely performed. Finally, due to the limited awareness of this entity and the limits of spontaneous notification, underreporting is expected, which warrants greater recognition among clinicians.

Reference(s)

1. Allain-Veyrac G. et al. Revue Française d’Allergologie 2025 ; 65:104486

Keywords

Localized Acute Exanthematous Pustulosis (LAEP); Pharmacovigilance; Cutaneous adverse drug reactions

00427
Comparative evaluation of methods for detecting out-of-context citations in pharmacovigilance publications

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Signal detection in pharmacovigilance primarily relies on the analysis of spontaneous adverse event reporting databases such as VigiBase or FAERS. The increasing accessibility of these databases has led to a substantial rise in publications of low-quality and highly standardized articles.

Out-of-context citations—defined as references lacking semantic relevance to the cited article—may represent a marker of scientific misconduct or fabricated manuscripts. In this meta-research study, we aimed to compare the performance of three natural language processing approaches for detecting out-of-context citations in pharmacovigilance articles.

Materials and methods

We identified all disproportionality analyses using data from FAERS. Citation contexts were extracted from the methods sections through a structured pipeline. Abstracts of cited articles were obtained using the PubMed Central and Crossref APIs. Each citation context was paired with the abstract of the cited article. Citations were classified as either semantically relevant or out-of-context. We compared the performance of three detection methods: Qwen, Mistral, and sentence-BERT (sBERT). For each method, sensitivity, specificity, positive predictive value, and negative predictive value will be calculated.

Results

Among 2127 published disproportionality analyses using FAERS, 1074 have their full text accessible from PMC and 5568 citation contexts were extracted. Overall, 3331 citation contexts from the method section have an abstract. The 3 methods (Qwen, Mistral, and sentence-BERT (sBERT)) yielded different results. Qwen identified 620 citations as out-of-context, Mistral 187 and sBert 84 with only 14 overlapping between the 3 methods. Manual curation of a gold standard reference set is ongoing to compare the performances and the methods and understand their discrepancies.

Discussion / Conclusion

This study will provide a comparative evaluation of three approaches for the automated detection of out-of-context citations in pharmacovigilance publications. By identifying the most accurate and robust method, our findings aim to support the development of scalable tools for screening citation integrity in studies based on spontaneous reporting databases.

Reference(s)

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Keywords

Paper mills;

miscitation;

pharmacovigilance

00430
Adverse effects of alpha-blockers in off-label use for women: a pharmacovigilance analysis

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Alpha-blockers are indicated for the treatment of benign prostatic hyperplasia (BPH) and, for some agents, hypertension. They are also frequently prescribed off-label in women for obstructive urinary disorders and other voiding dysfunctions, despite limited evidence supporting their efficacy in this population. Data regarding adverse drug reactions (ADRs) associated with off-label uses remain limited. This pharmacovigilance study aimed to describe reported ADRs associated with alpha-blockers off-label use in women.

Materials and methods

We conducted a descriptive analysis of ADRs reported in women treated with alpha-blockers (alfuzosin, doxazosin, prazosin, silodosin, and tamsulosin) for non-hypertensive indications, recorded in the French Pharmacovigilance Database up to December 31, 2024.

Results

A total of 322 cases corresponding to 1 092 reported ADRs were identified; 195 cases (60.6%) were classified as serious. The median age was 71 years (IQR 56–83). In 95 cases (29.5%), the alpha-blocker was the only suspected drug, including 42 serious cases (13.0% of total cases). The most frequently affected system organ classes were skin and subcutaneous tissue disorders (18.1%, mainly rash), vascular disorders (10.2%, mainly hypotension), and general disorders and administration site conditions (9.3%, predominantly malaise).

Discussion / Conclusion

This study reveals a significant proportion of serious adverse reports linked to off-label use of alpha-blockers in women. The reported ADRs are consistent with the pharmacological effects of alpha-adrenergic antagonists, particularly hypotension. However, the high proportion of serious cases is notable in an older population potentially vulnerable to falls and cardiovascular complications. The alpha-blocker was the only suspected drug in nearly one-third of cases, reinforcing the plausibility of a causal association. Although these agents are commonly prescribed for female voiding dysfunction, their clinical benefit remains uncertain and is not supported by marketing authorization. These findings highlight the importance of monitoring off-label use in vulnerable populations and support careful benefit–risk assessment, particularly in elderly women.

Keywords

Alpha-blockers; off-label use; women; French Pharmacovigilance Database

00435
Late-onset bradykinin-mediated angioedema induced by ramipril: exploration of potential triggers in the French National Pharmacovigilance Database

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Bradykinin-mediated angioedema induced by angiotensin-converting enzyme inhibitors (ACEi) is a rare but serious complication. Major risk factors include advanced age, female sex, smoking, drug or seasonal allergy, coronary artery disease, and ethnic and/or genetic susceptibility [1-4]. However, cases occur after years of tolerance without an obvious trigger. The aim of this study was to explore potential triggers in patients exposed long-term to ramipril, based on a clinical signal of angioedema under long-term ramipril after recent capecitabine initiation.

Materials and methods

A retrospective observational study analyzed ramipril-associated bradykinin-mediated angioedema cases reported in the French National Pharmacovigilance

Database (2015–2025). Inclusion required ACEi exposure ≥6 months. Early-onset cases, those related to C1-inhibitor deficiency, exposure to drugs already known to induce angioedema (plasminogen activators [5], mTOR inhibitors, vildagliptine, racecadotril), recent dose increases, alternative diagnoses, or poorly informative reports were excluded. Demographic characteristics, time to onset, and potential drug or contextual triggers were identified via narrative review.

Results

Of 503 initial cases, 127 were included (median age 69 years; sex ratio 1.88; median time to onset 36 months). Another suspected or temporally related drug was identified in 37 cases: tacrolimus, ciclosporin, mycophenolate, capecitabine, encorafenib, binimetinib, acitretin, amoxicillin, cefixime, linezolid, azithromycin, sitagliptin, liraglutide, apixaban, acetylsalicylic acid, ticagrelor, enoxaparin, codeine-paracetamol, tramadol, dutasteride, fluoxetine, gabapentin, oxazepam, alirocumab, glucagon, iomeprol, and lidocaine. Contextual factors included surgical procedures, infections, stress, alcohol or allergenic/expired foods, exposure to irritants, travel with fever, heatwaves, and recurrent episodes occurring in the latter part of the night.

Discussion / Conclusion

These findings suggest a multifactorial mechanism in which ramipril could be considered as a contributing factor but drug- or environmental events may trigger episodes. This descriptive study provides a methodological basis for future analysis across ACEi and highlights the need for vigilance: a reporting bias exists, as ACEi is often identified as sole culprit without systematic review of recently introduced medications.

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Keywords

bradykinin-mediated angioedema; ACE inhibitors; potential triggers

00439
Risk of bevacizumab-induced proteinuria: a literature review of meta-analyses across approved oncological indications

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Bevacizumab, an anti-VEGF monoclonal antibody, is widely used in oncology. Proteinuria is a very frequent on-target adverse reaction. This study aims to describe the proteinuria risk in patients receiving bevacizumab in different oncological indications, in order to determine whether the risk varies according to cancer types.

Materials and methods

A systematic literature search using Embase, PubMed, ScienceDirect, and Cochrane Reviews databases was conducted from 2015 to 15 February 2026. For each oncological indication, one reference meta-analysis was selected according to predefined hierarchical criteria: highest methodological quality (assessed using AMSTAR-2 tool), largest pooled sample size, most recent publication, and highest journal impact factor. The primary outcome was relative risk (RR) of clinically significant proteinuria (grade ≥3) versus control (placebo or standard care).

Results

Among nine major bevacizumab indications (classified by tumor localizations), four had no available related meta-analysis. For the five remaining indications, five meta-analyses were selected from 204 screened, encompassing 60 randomized controlled

trials and 32,059 patients. The highest risk was significantly observed in breast cancer (RR 9.22; 95% CI 4.49–18.93) [1], followed by non-small-cell lung cancer (RR 7.55; 95% CI 2.26–25.22) [2], ovarian cancer (RR 4.31; 95% CI 2.15–8.64; I^2=0%) [3], and colorectal cancer (RR 1.89; 95% CI 1.26–2.84; I^2=0%) [4]. In glioblastoma, high-grade proteinuria did not reach statistical significance (RR 4.13; 95% CI 0.80–21.32), although all-grade proteinuria was significantly increased (RR 1.84; 95% CI 1.14–2.96) [5].

Discussion / Conclusion

In our review, bevacizumab-associated severe proteinuria demonstrates substantial heterogeneity, with nearly a fivefold variation in relative risk across tumor localizations. These findings suggest integrating population-specific risk susceptibility alongside therapeutic efficacy, in the precision medicine era. Recently, bevacizumab has been granted compassionate use in hereditary haemorrhagic telangiectasic, a rare vascular disorder [6]. This study indicates cautious extrapolation of bevacizumab-induced proteinuria risk and careful renal function monitoring in such non-oncological off-label setting.

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Keywords

bevacizumab, proteinuria, oncology, meta-analysis, safety, precision medicine, risk extrapolation

00440
Management of anti-infective-induced acute kidney injury in hospitalized patients: a French retrospective observational case series

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Drug-induced acute kidney injury (AKI) accounts for up to nearly 40% of hospital-acquired AKI cases, with anti-infectives (AI) being among the most common suspected drugs. Specific recommendations for AI-induced AKI remain scarce. Thus, we aimed to describe the clinical management and outcomes of AI-induced AKIs at Rennes University Hospital (Brittany, France).

Materials and methods

In this retrospective observational study, using the Clinical Data Warehouse (e-Hop) of Rennes University Hospital, cases of AI-induced AKIs occurring in patients who had been prescribed systemic AI during hospital stay were identified through an ICD-10 diagnoses codes query between January 1, 2022, and December 31, 2023. AKI and its management were described (imaging examinations, urine cytology analyses,

expert advice, biopsy, therapeutic drug monitoring (TDM), clinical decisions regarding antibiotic therapy).

Results

Of the 155 patients initially identified, 29 met the inclusion criteria. The cases involved AI known to induce AKI (especially amoxicillin, amphotericin B, TMP-SMX, vancomycin). Three AKI mechanisms were identified : acute tubular necrosis (69%), tubulointerstitial nephritis (6.9%) and inhibition of tubular secretion (13.8%). Kidney imagery was performed in 62% of cases, urine cytology in 65%, crystalluria analysis in 16.7% (4 out of 21 eligible cases). TDM was carried out in 13 patients out of 24 with measurable molecules. Specialist advice (infectious diseases, nephrology) were often obtained and pharmacovigilance advice rarely. AI discontinuation was mostly performed (60.5%). Supportive therapy mainly consisted of intravenous saline administration, sometimes corticosteroids, bicarbonate therapy or dialysis. No renal biopsy was performed.

Discussion / Conclusion

AKI occurred predominantly in patients with normal or slightly reduced renal function, underscoring the importance of monitoring renal function in this population upon initiation of AI therapy. Especially, in patients receiving high-dose regimens, TDM should be used. The use of imaging and urine cytology were not systematic but this did not hinder decision-making given the clinicians' experience and multidisciplinary consultation.

Keywords

pharmacovigilance, acute kidney injury, Anti-Infective Agents, case management

00443
Immune-Related Adverse Events associated with Immune Checkpoint Inhibitors: Analysis of Cases Discussed at an Expert Immunotoxicity Board

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Immune checkpoint inhibitors are associated with a wide range of immune-related adverse events (irAEs). Although numerous cases have been reported and availability of various management guidelines, the complexity and heterogeneity of these toxicities often require multidisciplinary discussion. In University Hospitals, multidisciplinary immunotoxicity boards brings together organ specialists to assess drug causality, guide therapeutic management, and determine whether immunotherapy should be continued or permanently discontinued. This study presents a one-year overview of irAE cases discussed by the “Immunotox” multidisciplinary board (IMB).

Materials and methods

A retrospective study was conducted by extracting from the French National Pharmacovigilance Database all Individual Case Safety Reports (ICSRs) registered between November 1, 2024 and November 1, 2025, referring to patients discussed during the IMB and corresponding to the population in charge of our

Pharmacovigilance Center. Cases were exhaustively documented in order to provide all elements at disposal for the discussion and decision-making.

Results

During the study period, 114 patients were discussed by the IMB. Among them, 59 patients (52%) were associated with irAEs (51% female; mean age 67 years), 88% of which were considered as serious. Among ICSRs, the most frequently suspected drugs were pembrolizumab (41.2%), nivolumab (38.2%), and ipilimumab (22.1%, always co-suspected). The most common irAEs were myositis (17.6%), hepatitis (14.7%), myocarditis (13,2%), and colitis (11.7%). Notably, 9.6% of events were not described on the Summary of Product Characteristics (SmPCs) of the suspected(s) drug(s), including triple M syndrome (myasthenia gravis, myositis and myocarditis) and Takotsubo syndrome.

Discussion / Conclusion

IrAEs requiring multidisciplinary evaluation display clinical heterogeneity and a high grade of seriousness. Importantly, around 1/10 of the cases reviewed during IMB is not mentioned on drug SmPCs, constituting potentially drug safety signals.

Keywords

Immune Checkpoint Inhibitors, Immunotherapy, Drug-Related Side Effects and Adverse Reactions, Pharmacovigilance, Multidisciplinary Board

00445
Fenfluramine induced cardiac valve disorders: is there any difference in children?

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Fenfluramine has been used as an anorexigenic for obesity management between 1965 and 1997, then was withdrawn from the market due to severe adverse drug reactions (ADR), particularly cardiac valve disorders[1,2]. Since 2021, fenfluramine is back on the market for severe pediatric epileptic disorders. However, the pediatric cardiotoxicity profile of fenfluramine remains unknown.

Materials and methods

On 04/04/2025, we extracted all cases from Vigibase with fenfluramine as a suspected drug and including at least one ADR related in high level group term (HLGT) “cardiac valve disorder” and high-level term (HLT) “cardiac valve disorders congenital”. Cases were separated into pediatric cases (≤17 years-old) and adult cases (>17 years-old). Teenagers taking fenfluramine for weight loss purpose were excluded from pediatric group and included in the adult one. We performed disproportionality analysis (information component, IC) globally and by age group. Disproportionalities between both groups were considered significantly different if their confidence intervals did not overlap.

Results

In total, 4116 cases were extracted, including 157 pediatric cases. Significant disproportionality was observed in pediatric cases globally (IC025 7.18) and for Preferred Terms (PT) “Aortic valve thickening” (IC025 1.40), “Mitral valve thickening” (IC025 1.88), “Aortic valve incompetence” (IC025 5.11), “Heart valve incompetence” (IC025 0.68), “Mitral valve incompetence” (IC025 5.75), “Tricuspid valve incompetence” (IC025 6.68), “Pulmonary valve incompetence” (IC025 5.50), “Mitral valve prolapse” (IC025 1.81), “Aortic valve disease” (IC025 1.37) and “Cardiac valve disease” (IC025 2.48). Compared to adults, pediatric IC was significantly higher for PT “Tricuspid valve incompetence”. However, adult ICs were significantly higher for PTs “Aortic valve incompetence”, “Mitral valve prolapse”, “Aortic valve disease” and “Cardiac valve disease”.

Discussion / Conclusion

Cardiac valve disorders are reported in children taking fenfluramine with a globally similar profile to adults. However, tricuspid valve incompetence seems more specific to the pediatric population and some further studies are needed to clearly understand it.

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Keywords

fenfluramine, cardiac valvulopathy, pharmacovigilance

00447
Linezolid-induced multiple-organ failure in a cirrhotic patient

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Linezolid is an oxazolidinone indicated for Gram-positive infections (600 mg twice daily). Liver function disturbances and lactic acidosis have been widely reported. However, no dosage adjustment is mentioned in the Summary of Product Characteristics for patients with hepatic impairment.

Materials and methods

Following one case of severe lactic acidosis and liver injury reported to the Rennes Pharmacovigilance Center in a cirrhotic patient treated with standard-dose linezolid, a literature review was conducted regarding the use of linezolid in patients with hepatic impairment.

Results

In a 48-year-old man with pre-existing cirrhosis assessed as Child-Pugh B9/MELD 22 (autoimmune hepatitis), linezolid treatment triggered acute decompensation on Day 7

(worsening cytolysis, jaundice, hyperlactatemia), leading to treatment discontinuation. On Day 8, linezolid trough concentration was 37.8 µg/mL (N: 2-7 µg/mL). Clinical deterioration progressed to multiple organ failure and emergency liver transplantation with a favorable outcome.

Discussion / Conclusion

The literature identified 6 cases of linezolid-induced lactic acidosis in patients with preexisting liver failure, leading to death in 4 cases. While no dosage adjustment is recommended for Child-Pugh A or B cirrhosis (1), some authors suggest a dose reduction (to 600 mg/day) for Child-Pugh C patients. (2-4)

This observation illustrates potentially fatal linezolid toxicity in a cirrhotic patient and highlights the importance of close clinical and biological monitoring. In this context, the implementation of Therapeutic Drug Monitoring (TDM) appears justified to secure the prescription.

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Keywords

Linezolid, pharmacovigilance, Liver Cirrhosis, therapeutic drug monitoring

00448
Granuloma annulare and immunization: cross-reactivity with different vaccines

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Granuloma annulare (GA) is a common benign inflammatory dermatosis. Its physiopathology remains poorly understood but supposed to be related to type IV hypersensitivity, immune complex vasculitis, or tissue monocyte abnormality. It is usually idiopathic and have been rarely reported with drugs, including vaccines, in scientific literature. Most of GA vaccine-related literature cases concerned COVID-19 and BCG (Bacillus Calmette Guerin) vaccines.

Materials and methods

We described the case of a female infant presenting GA after two successive different vaccines, completed by VigiBase analysis with disproportionality analysis (information component, IC).

Results

A 12-month-old healthy girl was vaccinated with meningococcal B vaccine (3rd dose) and Measle-Mumps-Rubella-varicella vaccine (MMR-VZV vaccine, 1st dose) on 9th September 2025. Previous vaccines were well tolerated. Two weeks after combined immunization, she presented with generalized GA. On 23th October 2025, while

previous GA's episode was still ongoing, she received her first dose of meningococcal ACYW135 vaccine, leading to another GA flare two weeks later. About 2.5 months later, the patient had not recovered.

On 12th January 2026, 388 cases of GA following immunization were registered in VigiBase. COVID-19 vaccines, mostly RNAs-based, were the most represented (311, 80.2%, IC025 0.7), followed by VZV (28, 7.2%, IC025 1.4) and influenza (20, 5.2%, no significant disproportionality). Regarding vaccines suspected in our cases, MMR was reported in nine cases (2.3%), Meningococcal ACYW135 in two (0.5%) and Meningococcal B in one (0.3%). Overall median time-to-onset was 11 days [45 minutes-10 years]. Positive rechallenge was described in three cases (tozinameran, ChadOx1, tick-borne encephalitis).

Discussion / Conclusion

GA have been rarely described after immunization and mostly after COVID-19 and BCG vaccines. In several cases, GA relapsed after rechallenge with the same vaccine [1–5]. However, to our knowledge, this case is the first one describing a relapse after another vaccine. Nevertheless, we cannot exclude a cross-reactivity between two meningococcal vaccines.

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Keywords

granuloma annulare, vaccine, pharmacovigilance

00450
Description of factors associated with the reporting of Triple M overlap syndrome with immune checkpoint inhibitors in the French Pharmacovigilance Database.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Immune checkpoint inhibitors (ICIs) are associated with immune-related adverse effects (irAEs), including myocarditis, myositis, myasthenia-like syndrome. Their co-occurrence has been reported (1-2), with high mortality reaching up to 60% (3). Although myocarditis, myositis, and myasthenic syndrome are individually described in ICI product information, the pathophysiology underlying their co-occurrence remains unclear. Some clinical data suggest that cases labelled as myasthenic syndrome may correspond to immune-mediated myotoxicity rather than true autoimmune neuromuscular junction involvement. This study aimed to describe cases of triple M overlap syndrome reported in the French pharmacovigilance database.

Materials and methods

We conducted a retrospective descriptive analysis of myocarditis cases associated with myositis and/or myasthenia gravis during ICI therapy, reported in the French pharmacovigilance database up to January 19, 2026.

Results

A total of 194 cases were identified with the lowest level terms: myocarditis-myositis-myasthenia (45 cases); myocarditis-myositis (139 cases); myocarditis-myasthenia (10 cases). The study population comprised 66 women and 128 men, with a mean age of 73.2 years. ICI therapy was used as monotherapy in 152 cases (78%), most frequently pembrolizumab (40%), mainly for melanoma (44%), lung cancer (13%), renal cancer (12%). Triple M syndrome median time to onset after treatment initiation was 27 days, ranging from 1 day to 2.5 years. The suspected ICI was discontinued in 106 cases (54.6%) with an improvement in 36 cases (33.9%), treatment discontinuation being unknown in the remaining cases and 20% of cases resulted in death. One case reported a positive rechallenge. Treatment consisted mainly of corticosteroids (83.5%).

Discussion / Conclusion

These findings are consistent with reported cases in the literature regarding suspected ICIs, mortality, and patient characteristics. Early identification of at-risk patients remains a major prognostic challenge to guide ICI discontinuation and management. Further research is warranted to better characterize the underlying mechanisms, to identify potential risk factors and to improve coding of AEs terms in the database.

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Keywords

Immune-related adverse events ; Immune checkpoint inhibitors ; myocarditis ; myositis ; myasthenic syndrome ; myasthenia gravis

00454
Adverse Drug Reactions associated with Cyamemazine: A Nationwide Analysis of the French Pharmacovigilance Database

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Cyamemazine is currently the second most widely used neuroleptic in France after risperidone. However, no clinical trials are available, it is never mentioned in major international psychiatric guidelines and is marketed in only a limited number of countries. The vast majority of reported adverse drug reactions (ADRs) worldwide originate from France (1). This study aims to describe ADR cases related to cyamemazine registered in the French pharmacovigilance database.

Materials and methods

All Individual Case Safety Reports (ICSRs) reporting cyamemazine as a suspected or interacting drug up to December 31, 2025 were extracted from the French

Pharmacovigilance Database. ICSRs coded as medication errors, overdose, withdrawal, or drug dependence were excluded. Data included demographics, ADR characteristics (nature and seriousness), and concomitant medications (ATC classification).

Results

During this period, 4,428 ICSRs were reported (50.8% male; mean age 44.9 years). Among these 64.5% were considered as serious, mainly due to hospitalization (64.2%), followed by life-threatening events (9.0%) and death (6.8%). All ADRs typically associated with antipsychotics were identified, with the most frequent being anticholinergic ADRs (11.6% of ICSRs, mainly constipation, urinary retention, confusion and tachycardia), hepatobiliary disorders (10.7%), sedation symptoms (9.8%, including falls), cutaneous ADRs (7.7%), Parkinsonism (6.3%), and neutropenia (6.0%). Other antipsychotics, anxiolytic/hypnotic drugs, and/or antidepressants were suspected in 48.2%, 46.0% and 37.7% of ICSRs, respectively. Regarding concomitant drug patterns, the most frequent after cyamemazine alone (15.4%) was its combination with at least one antidepressant and one anxiolytic/hypnotic drug (10.1%), followed by its association with another first-generation antipsychotic (7.1%), without significant differences in reporting profiles.

Discussion / Conclusion

Cyamemazine exhibits a safety profile consistent with first-generation phenothiazine antipsychotics, with all major antipsychotic-related ADR classes represented. Given the limited available safety data, these findings may help prescribers to identify cyamemazine-related ADRs. Comparative studies with drugs used in comparable clinical situation are warranted.

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Keywords

Cyamemazine; Antipsychotic Agents; Antipsychotic Agents, Typical; Pharmacovigilance; Drug-Related Side Effects and Adverse Reactions

00455
Immune checkpoint inhibitor rechallenge after discontinuation for grade ≥2 immune-related adverse events (irAEs): Analysis of spontaneous reports registered in French PharmacoVigilance DataBase

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Immune checkpoint inhibitors (ICI) have substantially improved the clinical management of cancer. However, their use is associated with immune-related

adverse events (irAEs), which may be serious or even life-threatening (1). Currently, limited data are available regarding the safety of rechallenge ICI in patients who previously experienced an irAE during ICI therapy. Nevertheless, rechallenge may be considered in selected clinical situations. We aimed to describe cases of ICI rechallenge in patients who developed an irAE, recorded in the French Pharmacovigilance Database (FPVDB).

Materials and methods

We performed a retrospective descriptive analysis of ICI rechallenge cases recorded in the FPVDB. All adverse drug reactions involving at least one ICI, reported between January 1, 2020, and October 21, 2025, were extracted. Cases were included if patients experienced at least one grade ≥2 irAE resulting in ICI discontinuation, and subsequent ICI rechallenge.

Results

Among 1790 cases, 37 met inclusion criteria. The median age was 63.5 years, 54.1% were men. A total of 50 irAEs leading to first ICI discontinuation were reported, with colitis (22%) and hepatitis (18%) being the most frequent. Following ICI reintroduction, 9 patients didn’t develop further irAEs, whereas 28 experienced at least one grade ≥2 irAE. Among them, 11 developed the same effect, 10 another one, and 7 both the same and another irAE. Seven patients initially had grade 4 irAEs; five experienced recurrence upon reintroduction, with lower severity than initial event. For patients who initially developed colitis or hepatitis, irAE recurred in 55% and 44% of cases, respectively. Among patients with irAE recurrence, 39.3% were receiving corticosteroids or other immunomodulators during ICI reintroduction.

Discussion / Conclusion

According to our data, 75.7% of patients after ICI rechallenge experienced irAE ≥2 again. Our findings are consistent with those reported in the literature (2). This study will be extended to analysis outcomes over a five-year period (20-2024).

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Erratum in: J Immunother Cancer. 2021 Feb;9(2):1. doi: 10.1136/jitc-2020-001622corr1. PMID: 33428586; PMCID: PMC7768965.

00457
Drug-induced Posterior Reversible Encephalopathy Syndrome (PRES): analysis of the French pharmacovigilance database

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Posterior reversible encephalopathy syndrome (PRES) is characterized by various symptoms, including headaches, visual disturbances, encephalopathy, and seizures. Risk factors include acute hypertension, preeclampsia–eclampsia, autoimmune diseases, organ transplantation, renal failure, and some drugs. The main pathophysiological hypotheses involve a hypertensive crisis exceeding the threshold of cerebral autoregulation and immune activation leading to endothelial injury and disruption of the blood–brain barrier. We aimed to identify the main pharmacological classes and specific drugs associated with PRES using spontaneous reports recorded in the French Pharmacovigilance Database (FPDB).

Materials and methods

We performed a retrospective and descriptive analysis of PRES reports registered in the FPDB between 01/01/1985 and 31/12/2025. Reports without Magnetic Resonance Imaging scan confirmation were excluded.

Results

Among 188 reports of PRES, 144 met inclusion criteria, involving 133 distinct drugs. Median patient age was 58.5 years, with a female predominance (2:1). All reports were serious, including six deaths. A total of 57% (82/144) of cases had acute hypertension at the time of PRES. Most patients had at least one risk factor, including renal failure (n=30) and autoimmune disorders (n=26). Suspected drugs were predominantly antineoplastic and immunomodulating agents (60.3%). When a single suspected drug was identified, the most frequently reported were calcineurin inhibitors (tacrolimus n=14, ciclosporin n=5), followed by VEGF/VEGFR inhibitors including protein kinase inhibitors (n=8), human normal immunoglobulins (n=5), other protein kinase inhibitors (n=4), proteasome inhibitors (n=4), glucocorticoids (n=4), and nitrogen mustard analogues (n=4). PRES were an “unexpected” adverse drug reaction for immunoglobulins and corticosteroids.

Discussion / Conclusion

Drugs well known to lead PRES regarding their pharmacological properties were identified in our analysis. Further studies are needed to clarify the role of immunoglobulins and corticosteroids. Given the multifactorial nature of PRES, a drug-induced cause should be systematically considered in the differential diagnosis, particularly in patients exposed to drugs with known vascular effects regarding their pharmacological profile.

00459
Eptinezumab-induced hyperthyroidism: a case report

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Eptinezumab is a recombinant humanized IgG1 monoclonal antibody targeting calcitonin gene-related peptide (CGRP), a key mediator in migraine physiopathology. By inhibiting CGRP activity, it prevents migraine attacks(1). Some animal studies suggest that CGRP may play a role in controlling thyroid hormone secretion(2). However, clinical data regarding thyroid dysfunction associated with anti-CGRP therapies remain limited.

Materials and methods

We present a case of hyperthyroidism occurring with eptinezumab, registered in French Pharmacovigilance Database (NY2025001734). We performed a descriptive analysis of cases reported with eptinezumab and Standardised MedDRA Queries ‘‘thyroid disorder’’ in VigiBase.

Results

A 43-years-old woman with chronic migraine (3 attacks/week to 1/day) was treated with botulinum toxin injections, propranolol, sumatriptan and acetaminophen with codeine. She had a history of total thyroidectomy and was receiving levothyroxine (150 µg/day), with stable thyroid function for several years. Concomitant medications

included prazepam, fluoxetine, rivaroxaban, and dienogest. On May 16, 2025, she received the first eptinezumab infusion. She had no migraines for 3 weeks, then attacks returned. One month after initiation clinical and biological hyperthyroidism has developed, with significant weight loss, suppressed TSH (0.06 mIU/L), and elevated T4 (20.3 ng/L). No triggering factor was identified. Levothyroxine dosage was reduced to 137 µg/day, and subsequently to 125 µg/day, leading to stabilization within 6 months. Further infusions were administered without clinical or biological worsening.

On January 20, 2026, 12 cases of thyroid disorders were registered in VigiBase, including the case above: 6 hypothyroidisms, 3 hyperthyroidisms (including one Graves' disease), and 3 unspecified thyroid disorders.

Discussion / Conclusion

This is the first reported case of hyperthyroidism described as a potential adverse drug reaction of eptinezumab in a thyroidectomized patient receiving levothyroxine. A biologically plausible mechanism may involve CGRP modulation of thyroid hormone regulation. Although causality cannot be established, this signal warrants continued pharmacovigilance monitoring and further investigation.

Reference(s)

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(2) Grunditz T. et al. Endocrinology.1986;119(5);2313–2324

Keywords

adverse drug reaction, pharmacovigilance, hyperthyroidism, eptinezumab

00460
Acute Pancreatitis Associated with Angiotensin-converting-enzyme inhibitors (ACE Inhibitors): A Disproportionality Analysis of VigiBase and a Descriptive Analysis of the French Pharmacovigilance Database

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

ACEi, widely used in cardiovascular diseases, have been associated with acute pancreatitis but its clinical features remain insufficiently characterized (1-3).

Materials and methods

A disproportionality analysis was performed in VigiBase including reports of acute and chronic pancreatitis with ACEi up to July 2024. Reporting Odds Ratios (ROR) and Information Components (IC) were calculated, with sensitivity analysis excluding co-suspected pancreatitis-inducing drugs (4). Cases from the French Pharmacovigilance Database (FPVD) were descriptively analyzed.

Results

In VigiBase, among 38.3 million reported adverse drug reaction, 82872 involved pancreatitis, including 1598 associated with ACEi. A significant disproportionality signal was identified for ACEi class (ROR025 2.89 ; IC025 1.51), strengthening after exclusion of confounding drugs (ROR025 4.11; IC025 2.00). Strong signals were observed for necrotizing pancreatitis (ROR025 11.20 ; IC025 2.76) and hemorrhagic forms (ROR025 19.79 ; IC025 2.86). Patients were predominantly males (56.6%) and elderlies (>65 years: 35.5%). Fatal outcomes occurred in 7.1%.

In the FPVD, 357 cases were recorded (mean age 65±15 years ; 63% male), of which 96.1% were serious. In 285 cases, sufficient data were available for severity assessment using the revised Atlanta criteria, of which 39% were moderately severe and 10% severe. Overall, 173 patients developed complications (48.5%), mainly pancreatic necrosis (53.8% of complicated cases) and acute renal failure (33.5%). Mean time to onset was 121±254 days. ACEi discontinuation (248 ; 69.5%) led to clinical improvement in 85.5% (mean 7.5 days). Rechallenge in 29 patients led to recurrence in 12 (41.1%). Switching to another ACEi (n=4) led to recurrence in half of the patients.

Discussion / Conclusion

ACEi should be considered in the etiological assessment of acute pancreatitis in the absence of other etiological factors. A bradykinin-mediated increase in vascular permeability, leading to pancreatic edema and possible ductal obstruction, provides a plausible mechanism (5). Recurrence after rechallenge and after switching to another ACEi suggests a class effect.

Reference(s)

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Keywords

Acute pancreatitis ; Drug-induced pancreatitis ; ACE inhibitors; Pharmacovigilance ; Disproportionality analysis.

00463
Acalabrutinib-induced sequential limbs lymphoedema

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Chronic lymphocytic leukemia (CLL) is a highly prevalent adult leukemia usually treated with acalabrutinib, a second-generation selective Bruton's tyrosine kinase inhibitor (BTKi) [1]. Common adverse drug reactions include headache, diarrhea, and bruising, but limbs lymphoedema remains poorly described.

Materials and methods

We present a case of sequential limbs lymphoedema during acalabrutinib therapy, reported in the French pharmacovigilance database (NY2025002055, NY2025002057). Additionally, we performed a query in VigiBase.

Results

An 82-year-old man with a history of CLL was treated with acalabrutinib as second-line treatment for two years. He also had arterial hypertension recently treated with nicardipine, cardiac stimulator, chronic renal disease, and benign prostatic hypertrophy. Following a gardening left hand injury, he presented persistent homolateral upper limb swelling. Six months later, he presented with spontaneous

bilateral lower limb oedema. Initially, nicardipine was suspected. However, lymphoscintigraphy performed for all limbs, confirmed lymphatic insufficiency, while doppler ultrasound ruled out venous etiology. Consequently, nicardipine was no more suspected, and acalabrutinib remained the main suspect. In Vigibase, there are 24 reports of lymphoedema associated with acalabrutinib (75% were serious). Gender and age were specified only for 19 patients (11 males: 45.8%; 8 females: 33.3%) and 5 patients (> 75 y.o.), respectively. Time to onset was specified only for one patient: 11 months. Disproportionality analysis showed a significant signal (ROR025: 6.7; IC025: 2.5).

Discussion / Conclusion

Few cases of BTKi-induced oedema are reported in literature, with confirmed lymphatic etiology in some cases [2-5]. Time to onset ranged from 5 months to 2.5 years. The precise mechanism remains unknown, but off-target inhibition of PI3K (impairing lymphangiogenesis and allowing capillary leakage) or PDGF receptors (reducing interstitial fluid pressure and increasing capillary fluid transport to the interstitium) is suspected.

Reference(s)

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Keywords

adverse drug reaction, pharmacovigilance, acalabrutinib, burton tyrosine kinase inhibitor, lymphoedema, chronic lymphocytic leukemia

00465
Depressive disorders and suicidal behaviour with daridorexant

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Daridorexant is an orexin type 1 and type 2 receptor antagonist and the first drug of this pharmacological class to receive marketing authorisation in the European Union (May 2022) for the treatment of insomnia. Clinical trials reported a higher frequency of depressive disorders with daridorexant compared with placebo, as well as four cases of suicide and self mutilation [1]. The aim of this study was to describe and compare the reporting rate of depressive disorders and suicidal behaviour associated with daridorexant in the post-marketing setting.

Materials and methods

Data were extracted from Vigibase, the WHO pharmacovigilance database, up to 31 December 2025. Cases involving daridorexant and the MedDRA High Level Group Term « Depressed mood disorders and disturbances » and the High Level Term "Suicidal and self-injurious behaviour" were included. We performed a descriptive analysis and a disproportionality analysis by calculating reporting odds ratio (RORs) with 95% confidence intervals (CIs).

Results

In Vigibase, 160 cases of depressive disorders and suicidal behaviour were reported with daridorexant. The mean age was 52.7 ± 18.9 years and 57.5% were women. Antidepressant treatment was prescribed in 21.9% of cases. The mean time to onset was 20.2 ± 44.3 days for depressive disorders and 18.6 ± 37.4 days for suicidal

behaviour. Recovery was reported in 31.4% and 43.8% of cases, respectively. Three deaths (suicides) (4.1%) were reported. Significant disproportionality signals were observed for depression (ROR 3.25, 95% CI 2.56-4.11), suicidal ideation (ROR 9.11, 95% CI 7.07-11.73), depressed mood (ROR 4.85, 95% CI 3.34-7.03) and suicide attempt (ROR 2.16, 95% CI 1.16-4.02).

Discussion / Conclusion

A safety signal was identified between daridorexant and depressive disorders and suicidal behaviour. These findings highlight the need to raise awareness among prescribers regarding this potential risk, particularly since the effectiveness of daridorexant has not been compared with other treatments for insomnia in clinical trials.

Reference(s)

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Keywords

depression, depressive disorders, suicidal ideation, suicide, daridorexant, orexin, disproportionality

00467
Daridorexant (QUVIVIQ®): innovative mechanism of action, unusual adverse effects — Focus on sleep paralysis

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Daridorexant is the first dual orexin receptor antagonist marketed in France for the treatment of chronic insomnia. Its adverse drug reaction (ADR) profile, distinct from that of benzodiazepine hypnotics, includes sleep paralysis (SP), a distressing condition characterized by an inability to move or speak for up to several minutes during sleep-wake transitions. We aimed to better characterize this uncommon ADR in a real-world setting using the French Pharmacovigilance Database (FPVD).

Materials and methods

We selected all cases within the "Nervous system" or "Psychiatric disorders" SOCs reported for daridorexant as the suspected or interacting drug in the FPVD between February 2024 and February 2026. We included cases coded with the PT "Sleep paralysis" or that explicitly mentioned SP, or described an ADR strongly suggestive of SP, in the narrative.

Results

Among the 146 neuropsychiatric reports selected, 31 (21.2%) were identified as SP (including 4 cases detected through the narrative) and were included in the analysis. Patients (median age: 56 years; 71.0% female; prior history of SP in 1 case) were treated for unspecified insomnia (58.1%), sleep disorders (25.8%), or chronic insomnia (6.5%), mainly at a dose of 50 mg/day (67.7%). The median time-to-onset of SP was 2 days after treatment initiation, and 30 minutes after drug intake. SP was predominantly hypnagogic (64.5%) and characterized by an inability to move (74.2%) and/or speak (29.0%). Hallucinatory forms were more frequent (64.5%) than purely atonic forms and included visual, auditory, and/or somesthetic hallucinations, with a predominance of incubus phenomena (sensation of chest tightness or suffocation), contributing to marked distress and premature discontinuation of daridorexant. Only six rechallenge cases were identified, including five positive and one negative.

Discussion / Conclusion

SP, as other narcolepsy-like symptoms observed with daridorexant, likely reflects paradoxical sleep intrusions facilitated by orexinergic system modulation. Patients should be adequately informed about this potentially distressing yet fully reversible ADR.

Reference(s)

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Keywords

daridorexant ; dual orexin receptor antagonist ; chronic insomnia ; sleep paralysis

00473
Opioid analgesic-induced hypogonadism : a disproportionality analysis from Vigibase

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Hypogonadism is an opioid-associated uncommon adverse effect, with sexual dysfunctions being reported in 21% to 86% of patients (1). While hypogonadism has been mostly reported with opiate substitution (2), data on opioid analgesic-induced sexual dysfunction (OAISD) remain scarce. Previous French pharmacovigilance analyses identified few cases of "hypogonadism" (3), prompting this investigation into broader OAISD symptoms using Standardised MedDRA Queries (SMQ).

Materials and methods

Using SMQs "sexual dysfunction" and "fertility disorders", disproportionality analyses were performed in the WHO pharmacovigilance database (VigiBase®) stratified by opioid analgesic (OA) strength (strong/weak) and sex, with all analgesics as comparator group. Reporting odds ratios (ROR) and 95% confidence intervals (95% CI) were estimated. Signal of disproportionate reporting (SDR) was defined as ROR and lower 95%CI >1.

Results

Out of 2439 OAISD cases (mean age 49±17.7 years, missing data for 50%), 70% were men. SDR emerged for the SMQs “sexual dysfunction” and “fertility disorders” for all OAs (ROR 1.28 95% CI [1.21–1.35]), strong OAs (ROR 1.35 [1.27–1.44]), and weak OAs (ROR 1.88 [1.78–2.00]). Sex stratification revealed significant SDRs for all OAs in men (ROR 1.47 [1.37–1.57]) but not in women (ROR 0.91 [0.82–1.0]), for strong OAs in both sexes (men: ROR 1.11 [1.02–1.19]; women: ROR 1.30 [1.16–1.47]), and for weak OAs (men: ROR 1.41; [1.27-1.57]; women: ROR 2.44 [2.27–2.61]).

Discussion / Conclusion

Our analysis suggest sex-specific OAISD signals only for men with all OA compared to other analgesics. Both sexes presenting with an SDR when considering strong or weak opioids. Pharmacologically, opioid-induced hypogonadism is mediated by Mu receptor inhibition of the hypothalamic-pituitary axis. But the underrepresentation of women may reflect diagnostic bias or lack of awareness of hypogonadism in theses patients. Clinicians should be aware of OAISD symptoms and monitor for hypogonadism in long-term opioid users especially among women.

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Keywords

hypogonadism, opioids, pharmacovigilance, Vigibase

00496
Angioedema associated with SGLT2 inhibitors: a possible bradykinin-mediated signal from the French Pharmacovigilance Database

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Sodium–glucose cotransporter-2 inhibitors (SGLT2i) are increasingly prescribed due to expanded indications. “Angioedema” is mentioned in their Summary of Product Characteristics, without details on the underlying mechanism. This study aimed to describe possibly bradykinin-mediated angioedema (BMA) cases reported with SGLT2i in the French Pharmacovigilance Database (FPVD), either alone or combined with known angioedema-inducing drugs.

Materials and methods

We conducted a retrospective descriptive study of BMA cases recorded in the FPVD up to July 23, 2025, identified through the Standardised MedDRA Query “angioedema” and screening for SGLT2i among suspected, interacting, and concomitant drugs and within case narratives. Reports were included when a SGLT2i was the sole suspect drug or co-reported with at least one known BMA-inducing medication (angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARBs), gliptins, racecadotril, mTOR inhibitors, sacubitril, or anti-androgens).

Results

Among 124 screened reports, 39 were retained: 4 with SGLT2i as the sole suspected drug, 25 with one concomitant BMA-inducing medication (21 ACEi, 2 ARBs, 2 gliptins), and 10 with more than one. Dapagliflozin was the most frequently reported SGLT2i (n=34). Most patients had no prior history of angioedema (n=30). Time to onset ranged from 4 hours to 2 months when the SGLT2i was the sole suspected drug. In combination cases, onset ranged from 3 days to 3 months when the SGLT2i was added to ongoing angioedema-inducing therapy, but occurred within 24 hours when an ACEi was introduced in patients on long-term SGLT2i (n=2). One positive rechallenge was reported, and recurrence occurred in 4 cases despite continued SGLT2i therapy.

Discussion / Conclusion

To date, only two published cases have described angioedema occurring after empagliflozin initiation in patients on long-term losartan [1-2]. A potential synergistic effect between renin–angiotensin–aldosterone system blockade and SGLT2 inhibition, previously discussed in the context of pruritus through increased bradykinin levels, could contribute to angioedema [3].

Reference(s)

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Keywords

SGLT2 inhibitors ; Angioedema ; Bradykinin-mediated angioedema ; Drug–drug interaction

00539
Impact of the new regulation on tramadol and codeine prescription in France: Feedback from community pharmacists

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Some opioids such as tramadol and codeine, widely used for moderate to severe pain, are associated with increasing risks of misuse, dependence, and diversion. In response to these concerns, French health authorities strengthened their regulatory framework in March 2025, notably by introducing secure prescription forms and limiting prescription duration to 12 weeks [1]. However, the impact of this new regulation on community pharmacy practice remains to be determined.

Materials and methods

Two questionnaire-based surveys were conducted among community pharmacists. Responses were collected from 75 pharmacists between May and October 2025 regarding codeine, and from 91 pharmacists in June 2025 regarding tramadol. The surveys assessed compliance with the new regulation, its impact on dispensing practices, and its influence on relationships with patients and prescribers.

Results

The findings indicate that the majority of tramadol and codeine prescriptions comply with the new requirements; however, approximately ¼ of prescriptions presented are still not written on secure forms. More than half of the pharmacists reported a decrease in prescriptions for both medications, accompanied by a shift toward alternative analgesics (nefopam, Izalgi®, Lamaline®).

Between 25% and 30% of pharmacists identified suspected falsified prescriptions for these substances following implementation of the regulation, and 70% of them reported these cases to a prescription fraud monitoring system.

Finally, pharmacists indicated that prescription non-compliance negatively affected their relationships with patients (70%) and prescribers (55%).

Discussion / Conclusion

These data show that secure prescribing requirements improve traceability and help to reduce high-risk prescribing without increasing prescription falsification. However, a shift toward other analgesics may lead to displacement of misuse. Relational tensions and increased administrative workload highlight the need for supportive measures, including systematic patient information and strengthened interprofessional coordination. Longitudinal monitoring will be essential to assess the real impact of this regulatory change on public health.

Reference(s)

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Keywords

codeine, tramadol, prescription, regulation, survey

00543
Detection Gaps in Drug Related Poisonings

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Background: In France, hospital surveillance of acute therapeutic drug poisonings relies mainly on ICD-10 coding (OSCOUR, PMSI) and pharmacovigilance reports (BNPV). The granularity of ICD-10 may limit accurate identification of the drugs involved, thereby constraining pharmacovigilance signal detection and amplification.

Objectives: To compare three hospital-based detection strategies for acute therapeutic drug poisonings managed in the emergency department (ED): a standard ICD-10 and BNPV–based method reflecting current surveillance practice, an extended ICD-10 method with systematic chart review, and an automated text-mining algorithm developed from a Clinical Data Warehouse (CDW).

Materials and methods

We conducted a single-centre retrospective study including all adult ED visits for acute poisoning at Rennes University Hospital in 2023. Cases were extracted from the CDW (eHOP) and supplemented with BNPV reports, then manually reviewed to define a gold standard dataset (4,625 cases; 7,278 agents). Sensitivity and specificity of each method were calculated at ICD-10 category and subcategory levels.

Results

Therapeutic drugs accounted for 40.4% of agents. At the subcategory level, sensitivity was 23.2% for the standard method, 71.0% for the automated method, and

99.3% for the extended method. Specificity was 99.8% and 98.0% for the standard and extended approaches, respectively. Standard-method sensitivity declined markedly in poly-intoxications (42.6% for single-agent vs 12.8% for ≥4 agents) and during high-workload periods. Psycholeptics, analgesics, and antidepressants were the most frequently involved classes.

Discussion / Conclusion

Routine ICD-10–based hospital surveillance captures only a fraction of acute therapeutic drug poisonings. While systematic review maximises sensitivity, it is not scalable. Automated CDW-based text mining appears to offer a pragmatic balance between feasibility and pharmacological accuracy, supporting future large-scale hospital pharmacovigilance.

Reference(s)

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Keywords

Acute drug poisoning; Therapeutic drug overdose; Pharmacovigilance; Drug safety surveillance; ICD-10 coding; Clinical Data Warehouse; Text mining; Signal detection

00550
Antidepressant withdrawal syndrome : Survey of community pharmacists

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Antidepressant withdrawal syndrome is a clinical underrecognized syndrome that occurs after dose reduction or discontinuation of antidepressant medication. Clinical manifestations may include gastrointestinal symptoms, insomnia, sensory disturbances, dizziness, psychological distress, … and can severely impact quality of life. Despite its prevalence (affecting over 50% of patients), the antidepressant withdrawal syndrome remains poorly understood by both prescribers and patients, leading to mismanagement and prolonged suffering. The aim of this study was to evaluate the knowledge of community pharmacists about this syndrome, associated risk factors (e.g., treatment duration, dosage, and type of molecule), and appropriate management approaches.

Materials and methods

A survey was conducted among french community pharmacists between may and september 2023.

Results

A total of 104 pharmacists completed the questionnaire. The findings indicate that only approximately 70% of respondents correctly identified the symptoms of withdrawal syndrome.

Although pharmacists recognized that prolonged treatment duration and higher doses increase the risk of developing a withdrawal syndrome, 54% identified risk factors (short-half-life drugs, e.g., paroxetine, venlafaxine) and around 70% know appropriate dose-reducing protocols or switching to fluoxetine. Finally, many reported lacking confidence in counseling patients about this syndrome.

Discussion / Conclusion

The antidepressant withdrawal syndrome remains a major clinical challenge due to underestimation by healthcare professionals and patients misinformation. Reporting cases of withdrawal syndrome to French pharmacovigilance centers is therefore absolutely essential.

Patient education, as well as education for prescribers and pharmacists on withdrawal syndrome is essential to improve knowledge of withdrawal-related risks and to optimize the discontinuation protocol. French health authorities have made information notes available online to promote the appropriate use of antidepressants [1].

In addition, it is crucial to evaluate the clinical appropriateness of prescriptions, which remain excessively frequent in France for these medications.

Reference(s)

[1] https://ansm.sante.fr/dossiers-thematiques/antidepresseurs

Keywords

withdrawal syndrome, antidepresseur, survey, community pharmacists

00552
Therapeutic Cannabis: Knowledge of Community Pharmacies

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic cannabis, long stigmatized as a recreational drug, is gaining recognition for its potential in managing chronic pain, neurological disorders, and side effects of cancer treatments. Its key compounds, Δ^9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD), interact with the endocannabinoid system, offering analgesic, anti-inflammatory, and antispasmodic effects. While many countries have integrated cannabis-based therapies, the French Medicines Agency has conducted since 2021 a controlled experimentation program, to assess feasibility, efficacy, and safety of this new therapeutic strategy [1]. The aim of this study was to evaluate the knowledge of community pharmacists in the Vienne region, who are not directly involved in the experimentation.

Materials and methods

A survey was conducted to assess the knowledge of community pharmacists about cannabinoids such as Δ^9-THC and CBD, French legislation and the current experimental framework, including authorized indications and dispensing protocols; and their attitudes toward cannabis dispensing in pharmacies.

Results

A total of 46 pharmacists completed the questionnaire between august and september 2024. The survey revealed that around 70% of pharmacists correctly identified the effects of Δ^9-THC and CBD, while 47% of respondents well knew drug interactions and 70% know risks during pregnancy or for patients with psychiatric disorders.

Regarding legislation and the experimentation, 83% of respondents knew the five authorized indications for medical cannabis, which include neuropathic pain, epilepsy, palliative care, chemotherapy-induced nausea, and spasticity in multiple sclerosis. However, only 60% were familiar with the dispensing protocols, such as patient eligibility and prescription requirements. Finally, 65% of pharmacists supported the idea of dispensing therapeutic cannabis in pharmacies.

Discussion / Conclusion

The survey revealed that most pharmacists were aware of the effects of cannabis, but have significant gaps regarding general pharmacology, interactions, and risks during pregnancy. They point to an urgent need for training programs focused on cannabinoid pharmacology, legal frameworks, and patient counseling.

Reference(s)

[1] Dossier thématique - Mise en place de l’expérimentation du cann - ANSM

Keywords

therapeutic cannabis, survey, Community Pharmacies

00560
CLARMOR: study of clinical and biological consequences of drug interactions with clarithromycin in hospitals.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Drug-drug interactions (DDI) are responsible for preventable adverse effects (AE) that can lead to excess mortality or rehospitalization. Prescriptions analysis by pharmacists can help limit their occurrence. Clarithromycin is an antibiotic that inhibits several cytochromes, including CYP3A4, as well as P-gp and transporters. However, although the scientific literature mentions many Clarithromycin-associated DDI, only a limited number of studies listing the clinical or biological consequences in patients. We wanted to study these clinical and biological consequences in our hospital.

Materials and methods

We conducted a single-center retrospective study on the clinical and biological consequences of Clarithromycin-associated DDI in hospitalized adults who received at least one dose of Clarithromycin and another drug in a contraindicated, non-recommended, or clinically or biologically significant combination described in the literature, based on electronic prescriptions from January 2022 to January 2025. All clinical or biological consequences that occurred during the period of interaction between clarithromycin and the victim drug, and that could be related to a Clarithromycin-associated DDI were recorded. We also collected any evidence of prevention of consequences due to a Clarithromycin-associated DDI by physicians or pharmacists.

Results

We analyzed 135 patients and 92 were included, representing 186 DDI. We found 49 AEs that could potentially be linked to Clarythomycin-associated DDI, for 30 affected molecules. Only two AEs were qualified as serious, with Ticagrelor or Rivaroxaban. Ten DDIs were anticipated by physicians through a note, monitoring, or suspension of the implicated drug. Four alerts were issued by pharmacists responsible for prescription analysis.

Discussion / Conclusion

We show that Clarithromycin-associated DDI could be responsible for serious adverse clinical effects and that they are not sufficiently prevented by physicians and pharmacists. This study has many limitations, including its retrospective nature and the lack of data on plasma concentrations of the molecules concerned, limiting the attribution of the adverse effects found to Clarithromycin-associated DDI.

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Keywords

Adverse effects prevention, drug-drug interactions, Clarithromycin, serious adverse effects

00563
Risk of bias in pharmacovigilance disproportionality analyses: a scoping review

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Disproportionality analyses are statistical methods that aim to identify associations between drug and adverse events by comparing the number of reported events with the number of expected events. Numerous biases that systematically distort estimates from disproportionate measures have been described. Our objective is to identify methodological studies on biases, classify them, and summarise the results of methods developed to mitigate these biases.

Materials and methods

We first performed a systematic literature review on PubMed and Web of Science (WoS) according to PRISMA extension (PRISMA-ScR) for scoping review. We then performed forward and backward citation searches for each included study in the first step following the recommendations from the TARCiS statement. We included all studies that conceptualise a bias or evaluate a mitigation strategy to address it, without restriction on language or date.

Results

We first identified 504 records on PubMed and WoS; after deduplication, 288 records were screened and 36 retained in the first step. Using Scopus database, we identified 1,263 additional records in references and citations. Finally, a total of 67 articles were included in our analysis. We defined 3 main types of bias in disproportionality analyses (bias by differential (under)reporting; confounding and misclassification bias). Among them, 31 aimed to conceptualize and demonstrated these biases, with heterogeneous terminologies (e.g., stimulated/litigation/notoriety bias; competition/masking/cloaking) and 36 studies aimed to evaluate mitigation strategies. Fourteen studies (21%) used a reference dataset in order to evaluate the bias (n=9) or of the mitigation strategy (n=5), among them 4 used the Summary of Product Characteristic.

Discussion / Conclusion

This first scoping review systematically charted the varied approaches to define and mitigate biases in pharmacovigilance disproportionality analysis, thus providing the basis to develop a dedicated risk of bias tool, including recommendations to standardize relevant mitigation strategies.

Keywords

Pharmacovigilance; Bias; Disproportionnality analysis

00565
An exceptional Case of Empagliflozin-induced DRESS Syndrome

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Empagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, is a relatively new antidiabetic agent used in the management of type 2 diabetes. Although generally well tolerated, SGLT2 inhibitors have mostly been associated with mild cutaneous adverse effects. Only one case of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome has been reported in the literature [1]. We herein report, to our knowledge, the second case of DRESS syndrome following empagliflozin intake.

Materials and methods

This case was reported to the department of collection and analysis of adverse effects of the Tunisian National Center of Pharmacovigilance in July 2025. Drug imputability was assessed using the updated French method [2].

Results

A 69-year-old female patient with a history of type 2 diabetes mellitus, hypothyroidism and cardiomyopathy, presented with maculopapular rash, fever and odynophagia. One week prior to presentation, empagliflozin 12.5 mg/day was initiated for uncontrolled diabetes. This was the only recent change to her long-term medication regimen. Physical examination revealed a generalized maculopapular rash and cervical lymphadenopathy. Laboratory investigations were significant for

leukocytosis with marked eosinophilia (15%, absolute count 1611 cells/µL), liver injury (ALT 329 IU/L, AST 215 IU/L, ALP 449 IU/L, GGT 533 IU/L, total bilirubin 55 µmol/L) and elevated C-reactive protein (81 mg/L). An abdomen-pelvis CT scan showed no abnormalities. A RegiSCAR score of 5 confirmed the diagnosis of probable DRESS syndrome. Empagliflozin was permanently discontinued, whereas the other medications were continued. The patient was treated with antihistamines, systemic and topical corticosteroids, leading to a gradual resolution of the rash and normalization of the eosinophil count and liver enzymes within two weeks.

Discussion / Conclusion

Empagliflozin, though generally well tolerated, can exceptionally induce DRESS syndrome. Early recognition and immediate drug withdrawal are crucial for management. This case expands the spectrum of severe cutaneous adverse reactions associated with SGLT2 inhibitors.

Reference(s)

[1] Kaushik A, Jaswal A, Jeewooth A. Empagliflozin-related DRESS syndrome. Eur Heart J Case Rep. 2025 Jun.

[2] Miremont-Salamé G, Théophile H, Haramburu F, Bégaud B. Causality assessment in pharmacovigilance: The French method and its successive updates. Therapie. 2016.

00566
Comparative evaluation of methods for detecting out-of-context citations in pharmacovigilance publications

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Signal detection in pharmacovigilance primarily relies on the analysis of spontaneous adverse event reporting databases. The increasing accessibility of these databases has led to a substantial rise in publications. This expansion has been accompanied by a growing number of low-quality and highly standardized articles, some of which are suspected to originate from paper-mills. Out-of-context citations may represent a marker of scientific misconduct or fabricated manuscripts. In this meta-research study, we aimed to compare the performance of three large language models (LLMs) for detecting out-of-context citations.

Materials and methods

We identified all disproportionality analyses using the FDA Adverse Event Reporting System. Citation contexts were extracted from the methods sections in full texts, if available in PubMed Central. Each citation context was paired with the abstract of the cited article. Citations were classified as either semantically relevant or out-of-context. We compared the performance of three LLMs: Qwen, Mistral, and sentence-BERT (sBERT). Sensitivity, specificity, positive predictive value, and negative predictive value will be calculated. Secondary analyses will describe citation typology (self-citation, same research group citation, or external citation), assess citation relevance, and identify fabricated or erroneous references.

Results

Among 2,127 published disproportionality analyses using FAERS, 1,074 have their full text accessible from PMC and 5568 citation contexts were extracted. Overall, 3,331 citation contexts from the method section have an abstract. The 3 LLMs yielded different results. Qwen identified 620 citations as out-of-context, Mistral 187 and sBert 84 with only 14 overlapping between the 3 LLMs. Manual curation of a gold standard reference set is ongoing to compare the performances and understand their discrepancies.

Discussion / Conclusion

This study will provide a comparative evaluation of three LLMs for the automated detection of out-of-context citations in pharmacovigilance publications. By identifying the most accurate and robust method, our findings aim to support the development of scalable tools for screening citation integrity.

Keywords

Pharmacovigilance; FAERS; Paper mills

00568
Unintentional exposure to GLP-1 receptor agonists in early pregnancy: insights from three cases

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are increasingly prescribed for the management of type 2 diabetes and for obesity or overweight, in individuals with at least one weight-related comorbidity. Their expanding off-label use among women of reproductive age, often for weight loss, increases the risk of inadvertent exposure during early pregnancy.

Given the limited human safety data and potential embryofetal toxicity in animal studies, such exposure constitutes a significant pharmacovigilance concern.

Materials and methods

We report three cases of unintentional early pregnancy exposure to GLP-1 RAs notified to the Tunisian National Center for Pharmacovigilance (CNPV) in a 3 month-period (from Decembre 2025 to February 2026).

Results

All three patients were 35 years old at the time of exposure. GLP-1 RAs were prescribed for weight loss in all cases, with associated prediabetes in one patient. The implicated drug was liraglutide in one case and tirzepatide in two cases.

The patients were taken the drug for 10 months, 5 weeks, and 4 weeks prior to pregnancy recognition. Two patients were exposed during the peri-conceptional period with continued treatment into the first trimester, whereas one patient received the medication exclusively before the conceptional period. Treatment was stopped immediately after pregnancy confirmation in all cases.

Notification of exposure to CNPV occurred at 5 weeks of gestation (WG) in one case and at 10 WG in two cases. No concomitant teratogenic medication was reported.

At the time of reporting, no echographic abnormalities had been identified. A follow-up of these pregnancies is programmed.

Discussion / Conclusion

GLP-1 RAs are not approved for use in pregnancy, with recommendations of discontinuation prior to planned conception[1]

Although current human data do not conclusively demonstrate teratogenicity, animal studies have suggested potential embryofetal toxicity. The lack of robust safety data warrants caution and underscores the urgent need for effective contraception, and strict adherence to prescribing guidelines.

Reference(s)

1. Palmer V, Grunvald E, Sannidhi D, et al. Obesity management: implications for contraceptive counseling and reproductive health. Curr Obstet Gynecol Rep. 2025;14:38.

00569
Inaugural Serious Hepatic Involvement in DRESS Syndrome: A Rare Diagnostic Challenge

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome typically presents with fever and cutaneous eruption followed by systemic involvement. However, in rare cases, visceral involvement may be the initial manifestation, preceding classic features. We report two cases of allopurinol-induced DRESS syndrome initially presenting with hepatic involvement.

Materials and methods

These cases were reported to the Tunisian National Center of Pharmacovigilance in 2025. DRESS syndrome was evaluated based on the RegiSCAR score and imputability was assessed using the updated French method[1].

Results

Case 1:

A 50-year-old woman developed severe acute liver injury (30-fold elevation in transaminases, hyperbilirubinemia, prothrombin time of 51%) two weeks after initiating allopurinol. A generalized maculopapular rash with fever subsequently

occurred. Marked eosinophilia (2,870 cells/µL) and renal impairment were observed, while viral and autoimmune hepatitis were excluded. Skin biopsy confirmed drug-induced hypersensitivity. RegiSCAR score of 5 (probable DRESS). Discontinuation of allopurinol and systemic corticosteroids resulted in resolution of the rash, improvement of renal function within two weeks, and recovery of liver enzymes within six weeks.

Case 2:

A 77-year-old woman presented with acute liver injury (10-fold elevation in transaminases and prothrombin time of 24%) five weeks after starting allopurinol. Two days after admission, she developed a generalized maculopapular rash without fever or lymphadenopathy. Eosinophilia (730 cells/µL) was noted. Viral and autoimmune hepatitis were excluded. RegiSCAR score was 2 (possible DRESS). Allopurinol was discontinued, and topical corticosteroids led to resolution of the rash and partial improvement of liver enzymes within two weeks.

Discussion / Conclusion

Our cases illustrate rare presentations of DRESS in which serious hepatic involvement preceded the rash, as reported in up to 10% of cases [2]. This atypical presentation is likely underestimated, as early liver injury may remain clinically silent. DRESS should therefore be considered in cases of unexplained liver injury following recent exposure to high-risk drugs.

Reference(s)

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Keywords

allopurinol-induced hypersensitivity syndrome; drug reaction with eosinophilia and systemic symptoms; drug eruption; liver injury

00572
Evaluation of the robustness and corroboration of published safety signals generated by disproportionality analyses of spontaneous reporting databases

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

A growing number of disproportionality analyses are carried out by academic researchers and published in medical journals generating a large number of safety signals. However, little is known about the proportion of signals actually corroborated by formal hypothesis-testing studies and about the impact of the robustness of these signals on their validation. Our objectives were to determine how often unknown signals generated by disproportionality analysis were assessed by further studies, determine the proportion of corroborated signals and evaluate the association of the characteristics of studies and the robustness of the signals on their odds to be corroborated

Materials and methods

We extracted all new signals generated by pharmacovigilance disproportionality analyses using individual cases safety reports database from 2016 to 2019, through a systematic literature review performed by Sartori et al. (Drug Safety 2025). We identified all citations in Scopus database of selected publications and we assessed if they were corroborated by further inferential studies (i.e. observational studies, meta-

analysis or clinical trials). A signal was considered corroborated if one of the identified study highlighted a significant association between the drug and the adverse event.

Results

Eighty-nine disproportionality analyses were published during the study period yielding 500 signals of disproportionate reporting considered as previously unknown. These disproportionally analyses were cited by 2331 articles, among them 223 were considered as inferential studies and only 79 evaluated the new signals of interest. Theses 79 studies evaluated only 42 different signals among the 500. In a preliminary analysis, 36 signals were confirmed, 33 infirmed, 10 obtained conflicting results.

Discussion / Conclusion

Only a small part of signal generated by disproportionality analyses are subsequently explored in observational and inferential studies. Among them only few of them are confirmed. Understanding the factors associated with higher probably of being true adverse drug reaction may help in assessing the robustness of published disproportionality analyses.

Keywords

Disproportionnality analysis; Corroboration; Replication

00573
Pulmonary Arterial Hypertension associated with chemotherapies: a nested case-control study on a health data warehouse

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Several studies had already linked chemotherapy to Pulmonary Arterial Hypertension (PAH) using pharmacovigilance database or case series. However, in order to explore and quantify the link between chemotherapies and PAH, given in-hospital exposure to these drugs are often missing from medico-administrative databases, they are not suitable. Our objective was to evaluate the risk of PAH associated with all chemotherapies using a local health data warehouse (HDW).

Materials and methods

We created a retrospective cohort of patients with at least one intravenous chemotherapy using chemotherapy prescription in an HDW. Cases and dates of diagnosis were defined based on the date of PAH diagnosis (I27.0 according to International Classification of Diseases). Each case of PAH was match up to 20 controls according to calendar year, age, type and duration of cancer treatment.

Results

In our preliminary analysis, we were able to identify 42,679 patients who had received at least one course of chemotherapy since 2021. Among them, 189 patients were diagnosed with PAH. The average age at diagnosis was 68.7 years, and 41.2% of patients were women. The three drugs most frequently associated with PAH in our cohort were cyclophosphamide (n = 11, 5.8%), rituximab (n = 9, 4.8%) and cisplatin (n = 8, 4.2%).

Discussion / Conclusion

This study will provide estimates of the odds ratio of PAH following chemotherapies, thereby informing clinical practice and regulatory decision-making.

Keywords

Pulmonary arterial hypertension; Pharmacovigilance; Chemotherapies

00574
Immediate hypersensitivity selective to clavulanic acid

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

β-lactam antibiotics are among the most commonly implicated drugs in hypersensitivity reactions. Although the association amoxicillin–clavulanic acid is widely prescribed, immediate hypersensitivity reactions specifically related to clavulanic acid remain rare and underdiagnosed. [1]

We report herein a case of immediate hypersensitivity reaction to clavulanic acid, confirmed by a positive drug rechallenge.

Materials and methods

This case was notified to the Tunisian National Center of Pharmacovigilance in November 2025. Causality assessment was performed according to the updated French method of imputability. [2]

Results

We report a case of a 39-year-old woman with no significant past medical history who received amoxicillin–clavulanic acid in January 2025 following plastic surgery. Immediately after the first dose, she developed an episode of rhinitis associated to diffuse pruritus and tingling. Symptoms resolved spontaneously within 12 hours after discontinuation of the drug. In May 2025, the patient was treated with amoxicillin (Clamoxyl®) for 6 days for acute tonsillitis. The drug was well tolerated without

recurrence of symptoms. In June 2025, treatment with amoxicillin–clavulanic acid for thigh folliculitis was readministrated with immediate recurrence of symptoms, consisting of rhinitis and dizziness.

The recurrence of the event upon reintroduction of the combined amoxicillin-clavulanic acid treatment and the good tolerance of amoxicillin alone suggested the responsibility of clavulanic acid.

Discussion / Conclusion

This case draws attention to the potential role of clavulanic acid as a causative agent of hypersensitivity reactions occurring during administration of the combination of amoxicillin and clavulanic acid. Hence the importance of appropriate pharmacovigilance and allergological evaluation to ensure the safety of subsequent prescriptions.

Reference(s)

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00577
Development of an evaluation grid for the quality of adverse event notifications in Côte d'Ivoire

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Pharmacovigilance relies on the quality of adverse drug reaction reporting forms, which condition the identification of signals, the assessment of causality, and public health decision-making. However, in resource-limited countries, these forms often have completeness and consistency shortcomings, reducing their usefulness. This study aimed to develop an evaluation grid for the quality of adverse drug reaction reporting forms adapted to the Ivorian context.

Materials and methods

This methodological design study was conducted over a two-month period (September to October 2025) within the pharmacology department of the Bouaké University Hospital, in partnership with the Ivorian Pharmaceutical Regulatory Authority (AIRP) and GSK/Path. The new grid made it possible to properly evaluate the notification forms, and its performance was then compared to that of other grids, particularly the Moroccan grid and the international VigiGrade grid.

Results

The comparison of classifications resulting from the Moroccan grid and the new grid showed a statistically significant association ($\chi^2 = 150.73$; $p < 0.0001$), with moderate agreement (weighted Kappa = 0.52), reflecting partial consistency between the two tools. In contrast, the application of VigiGrade led to classifying all the reports as poor quality, limiting its discriminative power in the studied context. The inter-rater reliability of the new grid was evaluated by two experts, a pharmacist and a physician, who independently analyzed the 213 reports. Perfect concordance was observed, demonstrating excellent reproducibility, ease of use, and absence of ambiguities in the score allocation.

Discussion / Conclusion

The new grid appears as a reliable, reproducible tool suitable for evaluating the quality of notification forms in the studied context, constituting a relevant compromise between international methodological requirements and local operational realities.

Reference(s)

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Benkirane R, Pariente A, Bensouda M, Cherkaoui I, Ouanaimi F, Azzouzi A, et al. Profile of spontaneously reported adverse reactions in Morocco (2010). Fundam Clin Pharmacol. 2013; 27(2): 167-172.

Keywords

Evaluation grid, notification, adverse effect, imputability, pharmacovigilance

00578
Precision Pharmacovigilance: Challenges and Perspectives

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Precision medicine aims to personalize treatment according to individual characteristics such as genetics, environment, and lifestyle. When applied to pharmacovigilance, which is the detection, assessment, understanding and prevention of adverse drug reactions (ADRs), this approach is referred to as Precision pharmacovigilance (PP). PP integrates traditional drug safety monitoring with patient-specific data collection and analysis to identify individuals at higher risk of ADRs.

This overview aims to highlight the concept of PP based on current literature.

Materials and methods

This is a brief overview of the current literature on drug safety monitoring in the context of personalized medicine. Literature search was performed using databases including PubMed, ScienceDirect with keywords such as 'pharmacovigilance', 'drug safety', 'precision medicine' and 'personalized medicine'.

Results

PP aims to minimize pre-exposure risk and optimize post-exposure surveillance [1]. This approach integrates data from electronic health records, national databases, pharmacogenomic testing, and other molecular omics. It is accomplished through

methods like Bayesian inference, knowledge engineering and artificial intelligence (AI), which are used to answer complex questions about causal associations. The application of this approach is particularly impactful in smart hospitals, which aim to design real-time data collection infrastructures, explore new computational methods suitable for drug safety data, and provide a computer-aided framework for distributed clinical decisions [2].

In pediatrics, where children seem to experience ADRs more frequently than expected, PP is crucial. It integrates knowledge of pediatric-specific biology into systems biology approaches to identify age-dependent toxicities and genetic predispositions to ADRs [3].

Discussion / Conclusion

PP represents a promising approach to personalized drug safety, and it could improve the prevention of ADRs. However, it faces significant challenges including ethical and legal issues related to the use of Artificial Intelligence, data complexity, data safety, lack of standardization and resource constraints.

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00593
Rituximab-Induced Serum Sickness in Sjögren's Syndrome: A Case Report

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Rituximab is a chimeric monoclonal IgG1 antibody that targets CD20-positive B lymphocytes, used in the treatment of hematologic and autoimmune diseases. Infusion reactions are the drug's most common and most serious adverse effects. In rare cases, rituximab may induce a delayed immune-mediated reaction such as serum sickness. We report the case of a 48-
year-old woman who developed rituximab-induced serum sickness (RISS).

Materials and methods

This case was reported to the Tunisian National Centre of Pharmacovigilance and evaluated according to the updated French method of imputability 1

Results

A 48-year-old woman followed for Sjögren's syndrome since 2013. The condition was complicated in 2018 by central and peripheral neurological involvement. This required long-term
corticosteroid therapy and immunosuppressants (azathioprine 150 mg/day). She developed severe immune thrombocytopenia with hemorrhagic syndrome. Corticosteroids were therefore discontinued. She was subsequently treated with rituximab (1000 mg IV infusion). Rituximab infusion was well tolerated initially. Eight

days later, she developed fever up to 39°C, diffuse arthralgia, myalgia and generalized macular eruption. Laboratory workup revealed elevated C-reactive protein (CRP; 99 mg/L) with no identified infectious etiology. Complement levels were normal. Based on the temporal profile and characteristic triad of fever, erythematous rash, and arthralgia following drug exposure, a diagnosis of RISS was established. All symptoms resolved spontaneously within two weeks, with normalization of inflammatory markers. Rituximab was not.

Discussion / Conclusion

Delayed immunologic reactions such as RISS are extremely rare 2 . RISS is a type III hypersensitivity reaction mediated by circulating immune complexes. Symptoms typically appear 7-21 days after exposure and classically include fever, rash, and arthralgia. This rare side effect should be considered in a patient receiving rituximab and presenting this symptomatology.

Reference(s)

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Keywords

Rituximab,serum sickness, Pharmacovigilance

00597
An Exceptional vildagliptin induced DRESS Syndrome

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Vildagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, is widely used in the management of type 2 diabetes. Despite its favorable safety profile, rare cases of severe hypersensitivity reactions, including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), have been reported with DPP-4 inhibitors and only one case with vildagliptin.

We report an exceptional case of vildagliptin-induced DRESS syndrome.

Materials and methods

This case was notified to the Tunisian National Center for Pharmacovigilance in March 2025, and analyzed using the updated French imputability method[1].

Results

A 72-year-old man with a medical history of hypertension, type 2 diabetes, and dyslipidemia, treated with irbesartan, dapagliflozin, glimepiride, and fenofibrate, started vildagliptin/metformin in January 2025.

One month later, he presented to the emergency department with fatigue and dizziness. On examination, he was apyretic. Respiratory assessment showed SpO_2 98% on 3L oxygen via nasal cannula. Dermatological examination revealed diffuse,

non-pruritic, erythematous maculopapular lesions. Laboratory tests showed leukocytosis (16 000/mm³), elevated C-reactive protein level (157 mg/L), creatine phosphokinase 506 IU/L, troponin 142 ng/mL rising to 376.8 ng/mL, and creatinine 120 µmol/L. Eosinophil count was unavailable.

During hospitalization, the patient became febrile (up to 40°C) with oxygen desaturation to 90% on room air, and hypoxemic pneumonia was diagnosed. Mild liver test abnormalities were detected with negative hepatitis A and B serologies.

DRESS syndrome was suspected with a RegiSCAR score of 2 (possible case). Vildagliptin was discontinued, while metformin and other chronic medications were continued.

The patient’s condition improved within 6 days after vildagliptin discontinuation, with resolution of skin lesions, progressive weaning from oxygen, and apyrexia.

Discussion / Conclusion

DRESS syndrome is a rare but potentially life-threatening reaction. We report herein the second case of DRESS with vildagliptin. Early recognition, prompt discontinuation of the drug, and supportive care are crucial for favorable outcomes.

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00599
Certolizumab Pegol-Induced Vitiligo-Like Depigmentation in Rheumatoid Arthritis: A Case Report

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Drug-induced vitiligo-like depigmentation has been increasingly recognized as a cutaneous adverse event in recent years. Immune checkpoint inhibitors and immunomodulatory agents are among the most frequently implicated drugs. While Tumor necrosis factor alpha (TNF-α) inhibitors are generally well tolerated, they can also be associated with various dermatologic adverse effects. We describe an exceptional case of skin depigmentation attributed to certolizumab pegol.

Materials and methods

This case was reported to the Tunisian National Centre of Pharmacovigilance and evaluated according to the updated French method of imputability 1 .

Results

A 57-year-old female with a history of rheumatoid arthritis, diagnosed in 2004, had been managed with leflunomide for ten years. In February 2025, she had started certolizumab (Cimzia®, 200 mg: one subcutaneous injection every 2 weeks). Five months after treatment initiation, she developed depigmented lesions around the lips, followed by lesions on the

forehead, forearms, and right leg as treatment continued. She has no personal or family history of vitiligo. Given the unilateral distribution of the depigmented lesions, different from the typical pattern of classic vitiligo, the diagnosis of drug-induced vitiligo-like depigmentation (VLD) was suspected. Certolizumab was subsequently discontinued. After three months, substantial clinical improvement was observed, and the depigmented areas underwent gradual spontaneous repigmentation.

Discussion / Conclusion

Skin depigmentation or VLD is an uncommon adverse reaction of TNFα inhibitors. Two cases of de novo vitiligo occurring during certolizumab therapy have previously been reported 2 . We report, to the best of our knowledge, a first case of VLD specifically attributed to certolizumab. In our patient’s case, certolizumab induced VLD was suspected. The diagnosis was based primarily on the timeline of lesion onset, the unilateral distribution of the lesions, differing from the typical bilateral and symmetrical pattern of classic vitiligo, which is usually associated with a systemic pathogenesis, and on the absence of personal or family history of vitiligo.

Reference(s)

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Clin Pharmacol. 2020 Dec;34((6)):736–42.

Keywords

Certolizumab pegol, Vitiligo, Hypopigmentation

00601
Cutaneous adverse effects of tyrosine kinase inhibitors: a case series of 29 patients

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Tyrosine kinase inhibitors (TKIs) have significantly improved outcomes of several malignancies. However, despite their targeted mechanism of action, they are associated with a wide range of adverse effects, among which cutaneous manifestations are the most frequently reported.

This study describes the clinical features of 29 TKIs-induced cutaneous adverse effects cases, reported to the Tunisian National Centre of Pharmacovigilance.

Materials and methods

A descriptive retrospective study over a nine-year period (January 2016 to December 2024) including cases of TKIs-induced cutaneous adverse effects reported to the Tunisian National Centre of Pharmacovigilance.

These cases were analyzed according to the updated French method of imputability [1].

Results

We collected 29 cases. Age ranged from 35 to 74 years old (mean=55 years, median=57 years) with a M/F ratio of 0.32. A history of atopy was identified in 3 patients. Maculopapular eruption was the most frequently reported (18 cases), followed by psoriasiform and acneiform eruptions (3 cases each), urticaria (2 cases) and xerosis, photosensitivity, hand-foot syndrome (1 case each). The onset delay ranged from 3 days to 1 year.

Mucosal involvement was observed in 2 cases. Systemic signs were associated in 8 patients. Symptomatic treatment was initiated in 19 cases, and TKI discontinuation was required in 14 patients.

Imatinib was the most frequently implicated TKI (16 cases), followed by erlotinib (5 cases) and dasatinib, nilotinib, sorafenib, and sunitinib (2 cases each).

Causality assessment classified 2/3 of cases as doubtful and 1/3 as plausible.

Discussion / Conclusion

This case series highlights the wide spectrum of cutaneous adverse effects associated with TKIs. Despite symptomatic treatment, some cutaneous reactions significantly compromise treatment adherence, requiring drug discontinuation. Early identification and appropriate management are essential to reduce morbidity and avoid unnecessary interruption of an effective anticancer therapy.

Reference(s)

1. Miremont-Salamé G, Théophile H, Haramburu F, Bégaud B. Causality assessment in pharmacovigilance: The French method and its successive updates. Therapie. 2016;71(2):179-186.

00603
Cytarabine and Posterior Reversible Encephalopathy Syndrome: a case report

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Posterior Reversible Encephalopathy Syndrome (PRES) is a rare neurological complication, described with several chemotherapeutic agents. Early diagnosis determines the prognosis due to its potential reversibility under appropriate management.

Materials and methods

The case was reported to the regional pharmacovigilance service of Sfax. Drug causality was assessed using the French Bégaud method

Results

A 6-year-old patient followed for high-risk early relapse B-cell acute lymphoblastic leukemia, treated with cytarabine and idarubicin. The second dose of cytarabine was interrupted due to septic shock. Febrile neutropenia warranted empirical antibiotic therapy with imipenem, teicoplanin, ciprofloxacin, and metronidazole, with a favorable outcome. Eleven days after chemotherapy, she developed bilateral ocular myoclonus associated with generalized hypotonia, controlled by diazepam. The initial antibiotics were discontinued and switched to ceftazidime–avibactam . The brain

scan was normal. The MRI revealed abnormalities suggestive of PRES. The blood pressure was normal. Laboratory tests showed hypomagnesemia at 0.56 mmol/L. The blood cultures were negative. Cytarabine was stopped. A recurrent seizure occurred three days after the introduction of voriconazole, in the absence of antiepileptic treatment. The imputability score of cytarabine is plausible.

Discussion / Conclusion

PRES associated with chemotherapy is likely the result of endothelial toxicity, leading to disruption of the blood-brain barrier and vasogenic edema [1-3]. Hypertension, renal failure, and electrolyte disturbances are contributing factors. The median time to onset after chemotherapy is approximately 8 days. The progression is often favorable within two weeks after stopping the suspected agent and correcting the associated factors [1-2]. Severe forms are still described [1]. Management is based on stopping the triggering agent, controlling blood pressure, correcting electrolyte disturbances, and symptomatic treatment with anticonvulsants [1]..

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Keywords

Keywords: Posterior Reversible Encephalopathy Syndrome (PRES); Cytarabine; Chemotherapy; Pharmacovigilance; Encephalopathy; Neurological toxicity; Pediatrics

00605
Severe Myopathy Induced by Isoniazid: A Case Report

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

First-line antitubercular drugs such as isoniazid and rifampicin are generally well tolerated but can rarely cause serious adverse effects. We report a rare case of severe myopathy associated with isoniazid

Materials and methods

The case was reported to the regional pharmacovigilance center of Sfax. Drug causality was assessed using the French Bégaud method

Results

Patient, a 45-year-old pulmonologist, weighing 60 kg, treated for lymph node tuberculosis with isoniazid 300 mg/day and rifampicin 600 mg/day. A few days after the initiation of treatment, she developed intense muscle pain, characterized by burning sensations, generalized, progressive, and resistant to analgesics, leading to complete functional impairment
The biological tests (antinuclear antibodies, autoimmune assessment), radiological tests (Brain CT scan and MRI), and muscle functional tests were normal.
The plasma concentration of isoniazid was supratherapeutic, at 7 µg/mL (normal values 1.4–2 µg/mL), with a slow acetylator phenotype. Given the severity of the symptoms, the regional pharmacovigilance center advised stopping isoniazid.
After the discontinuation, there was a spectacular improvement within a few days

with complete recovery and no recurrence when continuing treatment with rifampicin alone. The causality of isoniazid is considered plausible.

Discussion / Conclusion

Isoniazid-induced myopathies are rare and often underdiagnosed, particularly in the absence of specific biological signs [1,2]. The mechanism is based on the accumulation of toxic metabolites, favored in slow acetylators, which can lead to intense muscle pain and functional impairment [3]. Clinical vigilance remains essential from the first days of treatment, in order to early recognize this type of adverse effect and avoid major functional complications. This case highlights the importance of pharmacovigilance and individualized monitoring of patients on antitubercular drugs, particularly in at-risk pharmacogenetic profiles

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Keywords

Myopathy, isoniazid, pharmacovigilance, slow acetylation, tuberculosis

00606
Modafinil Safety and ADE Signal Mining in Pediatric Population: A JADER Database Analysis

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Modafinil, a first-line wake-promoting agent for narcolepsy, is increasingly used off-label in adolescents and children. However, real-world safety data in East Asian pediatric populations are scarce, with its risk profile and high-risk subgroups undefined. Using the Japanese Adverse Drug Event Report (JADER) database, this study mined adverse drug event (ADE) signals of modafinil in patients aged ≤18 years, to provide evidence for precise pediatric medication and risk management.

Materials and methods

Modafinil-related ADE reports of children and adolescents (2014–2024) were extracted from JADER, with duplicate/incomplete cases excluded. Positive ADE signals were identified via reporting odds ratio (ROR), proportional reporting ratio (PRR) and Bayesian confidence propagation neural network (BCPNN), defined as detection by ≥2 methods. Signal distribution was analyzed by MedDRA System Organ Class (SOC), with risk differences compared by age stratification (≤12/13–18 years) and medication indications.

Results

A total of 401 valid reports were included, yielding 68 positive ADE signals. The most affected systems were psychiatric/ nervous system (46.2%, insomnia/anxiety) and

skin/subcutaneous tissue (20.6%, rash/Stevens-Johnson syndrome). Children ≤12 years had higher severe skin reaction signal intensity, while 13–18-year-olds had more prominent psychiatric symptoms. Off-label use for ADHD accounted for 58.3% of reports, with significantly higher insomnia/anxiety signal intensity than approved indications; severe skin reactions mostly occurred within 6 weeks of treatment initiation.

Discussion / Conclusion

Modafinil-related ADE reports of children and adolescents (2014–2024) were extracted from JADER, with duplicate/incomplete cases excluded. Positive ADE signals were identified via reporting odds ratio (ROR), proportional reporting ratio (PRR) and Bayesian confidence propagation neural network (BCPNN), defined as detection by ≥2 methods. Signal distribution was analyzed by MedDRA System Organ Class (SOC), with risk differences compared by age stratification (≤12/13–18 years) and medication indications.

Keywords

Modafinil; Adolescents and Children; JADER Database; Drug Safety; ADE Signal Mining

00607
Overview of pharmacists' knowledge and experience regarding the misuse of medicines for weight loss: survey of pharmacists

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Drug misuse for weight loss involve both listed drugs and over-the-counter products. Pharmacists, as local healthcare professionals, play a role in both the prevention and detection of risky behaviour. The objectives of this study are to assess the knowledge of community pharmacists on this phenomenon and to measure their role in addressing this misuse.

Materials and methods

A survey was conducted among pharmacists practising in the Pays-de-la-Loire region. The questionnaire was available in both paper and digital formats. Characteristics of pharmacists, misused drugs, patients profile, tools implemented to address this phenomenon was recensed.

Results

Forty responses were received. Concerning bisacodyl, patients between 40 and 60 year-old (n = 20; 46.5%), women and patients with a normal BMI (n = 25; 47.1%) are the most likely to spontaneously request bisacodyl. The majority of pharmacists agree to dispense bisacodyl. It was difficult to confirm misuse because of doctor

shopping. Concerning GLP-1 analogues, no typical profile of patients was identified. According to pharmacists, patients who misuse the medication are most often overweight (n = 11; 23.4%) or moderately obese (n = 10; 21.3%). Nineteen pharmacists refused to dispense the medication. In 18 cases, pharmacists did not know whether patients presenting with a falsified or off-label prescription for a GLP-1 analogue suffered from an eating disorder (n = 18; 81.8%). Other drugs and health products (14 products) was cited by pharmacists : laxatives, diuretics, antidiabetics…. It was impossible to describe a typical profile and the delivrance was mixed.

Discussion / Conclusion

In conclusion, the misuse of medicines for weight loss raises complex issues, both medically and socially. Although these practices may seem to offer quick solutions to weight problems, they expose individuals to considerable health risks. Pharmacists have a role to play in preventing the risks associated with these drugs and protecting consumer health.

Keywords

misuse, weight-loss, pharmacovigilance, survey

00609
Venlafaxine and the risk of cutaneous hemorrhagic manifestations

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Venlafaxine is a serotonin and norepinephrine reuptake inhibitor, commonly used in the treatment of depressive disorders. It can be the cause of a rare complication (unknown to psychiatrists), which is an increased risk of abnormal bleeding. We report the case of a patient who presented with ecchymotic and purpuric lesions on the thighs after treatment with venlafaxine.

Materials and methods

The case was reported to the regional pharmacovigilance centre of Sfax. Drug causality was assessed using the French Bégaud method.

Results

A 56-year-old patient, with no medical history, has been followed for a depressive disorder since September 2025, manifesting as asthenia, fatigue, memory problems, and insomnia. She was initially treated with Venlafaxine at a dose of 75 mg/day combined with oxazepam. Two weeks later, oxazepam was replaced by quetiapine 25 mg/day. After a month, the dose of quetiapine was reduced to 12.5 mg, and mirtazapine was introduced. Both treatments were discontinued after one month. Since the beginning of December, the patient has been on monotherapy with venlafaxine. Three months after starting Venlafaxine, she developed ecchymotic

lesions and some purpuric spots on her thighs, without affecting her legs. An etiological work-up was performed to exclude other causes, including a complete blood count, PT, aPTT, fibrinogen, liver and renal function tests, thyroid function tests, and an immunological assessment, all of which returned normal results. Drug responsibility was suspected, and the discontinuation of venlafaxine was carried out, leading to the spontaneous disappearance of the lesions after two weeks. The responsibility of venlafaxine was retained with a plausible imputability score (C2S2I2B3).

Discussion / Conclusion

Venlafaxine may cause bleeding by inhibiting platelet aggregation through reduced intraplatelet serotonin or by inducing immune-mediated thrombocytopenia via anti-platelet antibodies. This case highlights the importance of rigorous clinical and biological monitoring when using venlafaxine. Clinicians must remain vigilant in the face of this type of adverse effect.

00613
Lethal and Life-threatening Medication Errors in Early Childhood: A fifteen-year retrospective Analysis

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Medication errors (MEs) are preventable cause of morbidity and mortality. Neonates and infants are particularly vulnerable to ME due to frequent weight-based dosing, off-label use and multiple drug dilution or handling, of which consequence might be severe in relation with physiological immaturity. This study aimed to characterize MEs having lethal or life-threatening consequences in children under 5 years.

Materials and methods

Using the French Pharmacovigilance Database, we conducted a retrospective study of MEs with lethal or life-threatening outcome, reported in neonates (<28 days), infants (1–24 months), and preschool children (2–5 years). Analysis was performed according to child age group, error characteristics (type, medication-use process step, cause), adverse drug reactions and culprit drugs.

Results

Of 1323 deemed serious MEs cases, 207 cases had lethal or life-threatening outcomes, involving neonates (n= 63, 30%), infants (n= 101 ,49%), and preschool children (n = 43 ,21%); 63% were male. Among these, lethal outcome was reported for 19%, 13% 21%, respectively, with no statistical difference according to age group. The most frequently involved drug classes were analgesics (mainly opioids) (n = 50, 19%), anesthetics (n= 27, 10%) and antibacterials drugs (n = 19, 7%). Detailed characterization of error types and medication-use process steps is ongoing.

Discussion / Conclusion

Severe MEs in children under 5 years predominantly involve high-risk medications, often used in intensive care units. These findings highlight the need to strengthen medication-use safety in neonatology and pediatrics, particularly for injectable drugs and medications with a narrow therapeutic index.

Keywords

Pediatrics ; Medication error ; Drug safety ; Neonatology

00628
Immediate hypersensitivity reactions associated with proton pump inhibitors (PPIs): update on data published since 2016

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Immediate hypersensitivity to proton pump inhibitors (PPIs) is rare but potentially serious. The five PPIs currently available in France have a common structure composed of a benzimidazole ring and a pyridine ring(1,2). Two groups can be distinguished based on their molecular chains suggesting a correlation between these structures and cross-reactivity profiles2. We have updated an initial study published in 2018 by Tourillon et al.(3), based on new cases reported within the French National Pharmacovigilance Database (BNPV) of immediate hypersensitivity associated with PPIs.

Materials and methods

A query was performed by the National Agency for the Safety of Medicines and Health Products using the Standardized MedDRA Queries (SMQ) method with the main search criterion being all anaphylactic reactions related to a suspected PPI during the period from March 1, 2015, to February 28, 2025. Cases were included if skin tests or oral provocation tests (OPT) were performed with at least one positive result documented.

Results

The SMQ query yielded 1656 cases. After reviewing each abstract, 60 cases were selected. The male-to-female ratio was 1.5 and the mean age was 47 [range 21-76]. The main indication found was gastroesophageal reflux (n=10). The PPI most commonly involved in IgE-mediated hypersensitivity reactions is pantoprazole, which was found to be positive in 45 cases, omeprazole was present in 42 cases, esomeprazole in 32 cases, lansoprazole in 13 cases, and rabeprazole in 11 cases. Partial cross-reactivity were found in 46 cases (77%). Twelve isolated allergies have been identified (20%), as well as 2 cross-reactivity to all PPIs (3%).

Discussion / Conclusion

The study highlights an increase in allergy investigations since 2015, particularly in the use of the gold standard OPT test, improving the characterization of cross-reactivity profiles among PPIs. An expansion of the study is planned to include cases of delayed hypersensitivity to PPIs, which are often less documented but clinically relevant.

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Keywords

Pharmacovigilance, proton pump inhibitors, immediate hypersensitivity reactions

00632
Implementation of early detection of iatrogenic events in emergency departments

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

According to the 2022 IATROSTAT report, in France, 8.5% of hospital admissions to medical wards are attributable to adverse drug events (ADEs), representing more than 200,000 hospitalizations annually. Approximately 16% of these hospitalizations are considered preventable. In this context, we aimed to implement an early detection system for ADEs in our institution for patients admitted to the medical emergency department, in order to enable earlier corrective interventions.

Materials and methods

The iatrogenesis detection pathway was developed by a multidisciplinary team including an emergency physician, a clinical pharmacist, a pharmacovigilance pharmacist, and a pharmacy resident.

Results

A pharmacy resident was assigned to the emergency department. Patients' prescriptions are reviewed during admission medication reconciliation, with a systematic assessment for potential drug-related iatrogenesis. In collaboration with our regional pharmacovigilance center, it was agreed to record all cases of iatrogenesis in an Excel database. Reports are submitted in cases of serious or unexpected ADEs, and the attending physician is systematically notified. The final

diagnosis of drug-related iatrogenesis is established by the physician in consultation with the pharmacist and the pharmacovigilance team.

Discussion / Conclusion

This iatrogenesis detection pathway is currently being implemented in our institution. This organization will enable the collection of statistics on emergency department visits and hospitalizations related to serious adverse drug events, as well as on patient management and outcomes.

00645
Acute alithiasic cholecystitis during ponatinib treatment with positive rechallenge

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Ponatinib is a tyrosine kinase inhibitor (TKI) indicated in chronic myeloid leukemia (CML)treatment , particularly in cases of resistance or intolerance to previous generations of TKIs.Digestive disorders are among the adverse effects frequently observed with ponatinib. However, acute alithiasic cholecystitis is rare.

We report a case of acute alithiasic cholecystitis occurring during ponatinib treatment, an adverse effect very rarely reported in the literature.

Materials and methods

This case was reported to the National Pharmacovigilance Center in Tunis in December 2025. Drug causality was assessed according to the updated version of the French causality method [1].

Results

This is a 46-year-old woman with a medical history of type 2 diabetes since 2015, high blood pressure since 2013.

She is treated for chronic myeloid leukemia since May 2015.In 2024, she was ondasatinib.But she presented generalized edema, dyspnea, and myalgia at the beginning of the treatment.Thus, ponatinib at a dose of 45 mg/day was initiated in October2025.

On the third day of ponatinib treatment, the patient developed fever associated with abdominal pain as hepatic colic. Laboratory tests revealed an white blood cell count at 12,200cells/mm3 and an C-reactive protein level at 20.4mg/L. An abdominal ultrasound and tomography showed thickening of the gallbladder wall with submucosal edema, but there were no detectable stones or densification of the perivascular fat.

The decision was to stop ponatinib, hospitalize the patient, and start antibiotic therapy. The outcome was favorable within 3 days.

Twenty days later, restarting ponatinib treatment led to a recurrence of the same abdominal pain as soon as the first dose was taken. Ponatinib was therefore discontinued definitively.

Discussion / Conclusion

This observation highlights the importance of increased clinical vigilance when initiating treatment with ponatinib. In particular, in cases of abdominal symptoms, special attention should be given to rule out acute cholecystitis.

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00646
Dose-Dependent Pedal Edema Associated with Valproic Acid: A Three-Case Series

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Valproic acid (VPA) is widely used for epilepsy, bipolar disorder, and migraine prophylaxis. While common adverse effects include gastrointestinal upset, hepatotoxicity, and tremor, peripheral edema is rare. We report 3 cases of VPA-induced pedal edema confirmed by supratherapeutic serum valproic acid levels after excluding other potential causes.

Objectives: To report three cases of valproic acid–associated pedal edema and suggest a dose-dependent mechanism

Materials and methods

Three cases of valproic acid–associated pedal edema were reported with clinical assessment and serum drug monitoring.

Results

The first patient, a 28-year-old woman with intellectual disability, had been on VPA 1200 mg/day for 15 years (irregular adherence) and presented with a five-month history of progressive grade 3+ edema extending to the shins. She had no cardiopulmonary or urinary symptoms, and an extensive workup, including evaluation for nephrotic syndrome, liver disease, hypothyroidism, and congestive heart failure, was unremarkable. Therapeutic drug monitoring revealed a supratherapeutic VPA level of 149 µg/mL. Dose reduction to 500 mg/day led to complete resolution within two weeks, with a subsequent level of 41.5 µg/mL. Re-titration to 600 mg/day achieved therapeutic levels (56 µg/mL) without recurrence of edema.

The two additional patients, males aged 31 and 24 years, developed similar bilateral pitting pedal edema without cardiopulmonary or urinary symptoms. Comprehensive workups excluded cardiac, renal, hepatic, and endocrine causes. Their serum VPA levels were supratherapeutic (147 and 139 µg/mL). Pedal edema resolved following dose reduction, and subsequent re-titration to therapeutic doses allowed maintenance of seizure control without recurrence.

Discussion / Conclusion

These cases highlight a rare adverse effect of valproic acid (Naranjo score = 8). Valproate-induced edema may involve peripheral GABA receptors, as it indirectly affects the GABA system by increasing GABA availability. GABA receptors are present in peripheral tissues, suggesting valproate could influence regional vascular resistance, leading to fluid accumulation. This mechanism has been proposed previously but remains unproven.

5- Addictovigilance, toxicovigilance

00007
Toxicological Profile of Daridorexant in Overdose Scenarios: A Retrospective Study from French Poison Centers

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Daridorexant is a newly introduced dual orexin receptor antagonist used for treating insomnia. It blocks OX1R and OX2R receptors involved in promoting arousal, regulating anxiety, and controlling sleep-wake transitions. Daridorexant offers advantages in terms of reducing sleep latency and improving sleep maintenance, with less risk of sedation, cognitive impairment, and dependence. Despite its growing clinical use, data on overdose and acute toxicity remain limited. This study aimed to evaluate toxicity data and clinical outcomes of daridorexant exposures reported to French Poison Centers.

Materials and methods

This retrospective study analyzed data from the French National Poison Centre database, including daridorexant exposures reported from March 2024 to May 2025.

Key data included age, sex, reported dose, exposure circumstances (e.g., suicide attempt, therapeutic error), and co-intoxication status. Poisoning severity was assessed using the Poisoning Severity Score (PSS). Statistical analyses included ordinal logistic regression and sex-stratified analyses.

Results

Fifty-one cases involving daridorexant were identified, with a median patient age of 32 years, predominantly female (n=36). The majority of cases were suicide attempts (58.8%), followed by therapeutic errors (13.7%) and adverse drug reactions (9.8%). Severity of intoxication, measured by PSS, was mild to moderate in most cases (PSS 0-2), with no fatalities. Co-intoxication with other CNS depressants significantly increased poisoning severity, particularly in female patients. Clinical symptoms included somnolence (47.1%), vertigo, confusion, and tachycardia. A dose-response relationship was not observed.

Discussion / Conclusion

Daridorexant overdose cases, especially mono-intoxications, generally resulted in mild symptoms, with no fatalities. Co-ingestion with other CNS depressants increased the severity of poisoning, particularly in females. These findings suggest that daridorexant has a relatively favorable safety profile in overdose situations, with most patients recovering with supportive care. Clinicians should be aware of the risks of co-intoxication.

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Keywords

central nervous system depression, daridorexant, intoxication, orexin receptor antagonist, poison center

00008
Do I need to go to the hospital? Predicting the need for medical intervention after exposure with AMIGO, an explainable artificial intelligence clinical decision support tool

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Approximately half of the patients Poison Control Centers (PCCs) refer to hospitals solely for medical treatment require no medical care, reflecting the challenge of prognosticating from information usually limited to symptomatology and the circumstances of the exposure. Unfortunately, current clinical decision support (CDS) tools require results from laboratory testing, data someone calling PCC from home does not have. To help PCCs triage public calls, we developed a CDS tool, AMIGO.

Materials and methods

We trained a gradient boosting model, XGBoost, using cases from Lyon PCC from 2000 to 2025, to predict whether the caller should stay at home, stay at their current healthcare facility, or go to a hospital. We evaluated model performance using the F1 score. We used SHapley Additive exPlanations (SHAP) to identify predictive

features. We benchmarked AMIGO against published algorithms optimized for specific exposures.

Results

We screened 549,098 cases, including 215,914 cases involving 1959 unique exposures. The recommended dispositions were: stay at home, 66.6%; stay at facility, 7.4%; and go to hospital 25.4%. The median age was 9 (2-36.5) years, equal male and female. XGBoost obtained an AUC ROC [95% confidence interval] of 0.874 [0.871-0.876], overall accuracy of 0.786 [0.784-0.788], and F1 score of 0.668 [0.665-0.671]. Time between exposure to call, intentionality, and symptomatology were the most predictive features. AMIGO achieved an F1 score of 0.69 [0.66-0.71] for paracetamol versus 0.76 by [1] and 0.64 [0.61-0.67] for diphenhydramine versus 0.75 by [2].

Discussion / Conclusion

We developed AMIGO, a generalist CDS tool that uses clinically plausible variables to predict which exposures to a xenobiotic need medical attention. It covers 1959 exposures and performs comparably to models optimized for specific exposures that require laboratory data, despite only needing information the public can supply. AMIGO's significant but not total agreement with clinician recommendations demonstrates fidelity and provides an avenue to improve PCC home triage recommendations.

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Keywords

Toxicology, Machine Learning, Triage

00028
From Screening to Intervention: Pharmacist-Led Management of Step II Opioid Misuse, Real-World Data from the Pays de la Loire

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

In France, step II opioids represent about 20% of all analgesic prescriptions, with consumption rising steadily. This increase is associated with misuse and overdose risks, tramadol accounting for 40% of analgesic-related deaths according to French addictovigilance data. Since January 2025, community pharmacists can conduct structured support interviews for patients on step II opioids, including administration of the Prescription Opioid Misuse Index (POMI) to screen for misuse. Previous pharmacy-based studies showed that around half of POMI assessments score ≥2, indicating potential misuse. However, as the POMI is a screening tool rather than an intervention in itself, its clinical value relies on the actions implemented following its administration, which remain insufficiently documented in routine community pharmacy practice and warrant further investigation.

Materials and methods

This multicenter, observational, cross-sectional study was conducted in volunteers community pharmacies from an academic and professional network in the Pays de la

Loire region. Adult patients undergoing a support interview with POMI completion were included. Anonymized data from national Health Insurance interview forms (November 2025–April 2026) captured POMI total and items scores and pharmacist-reported alerts and actions. The primary endpoint was the proportion of interviews resulting in at least one intervention. Secondary endpoints included POMI score distribution, the type and frequency of actions, and associations between positive POMI items and actions using multivariate logistic regression.

Results

Approximately 70 interviews are expected; seven have been collected to date. All interviews resulted in at least one pharmacist action. More than half showed a POMI score ≥2. The most frequent positive item was shortened dosing intervals (85%). One interview had a score <2 but reported psychoactive effects. Actions were heterogeneous and not systematically tailored to POMI findings.

Discussion / Conclusion

This study will demonstrate the real-world impact of POMI integration in community pharmacy practice and highlight areas where pharmacist training may enhance prevention of opioid misuse and overdose.

Keywords

Opioid misuse

Step II analgesics

Prescription Opioid Misuse Index (POMI)

Community pharmacist intervention

00090
Sex differences in fatal poisoning among drug users in France: an exploratory analysis of the DRAMES register

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The DRAMES (Décès en Relation avec l'Abus de Médicaments et Substances) register is a French database of drug-related deaths reported by forensic toxicology experts. This study evaluated sex differences in the substances involved in deaths, with the aim of improving public policy on prevention and care for women with addiction disorders.

Materials and methods

We assessed 6,068 drug-related deaths that occurred from January 1, 2010, to December 31, 2023, in France. Subject demographic characteristics and medical history, forensic autopsy findings, and toxicology reports were evaluated. We

endorse the Sex and Gender Equity in Research (SAGER) guidelines, which aim to promote reporting of data by sex and gender. However, information on gender is not currently available in forensic data. Accordingly, the term sex is appropriately used and refers to the external anatomy at the time of autopsy.

Results

The proportion of deaths related to polydrug use was higher in women than in men (39% vs. 28%). Female sex was significantly associated with mortality from taking antidepressants ($p<0.001$), antipsychotics ($p<0.001$), benzodiazepines and z-drugs ($p<0.001$), codeine ($p=0.002$), other anxiolytics and hypnotics ($p=0.029$), pholcodine ($p=0.005$), and tramadol ($p<0.001$), all of which are legal prescription medicines. Male sex was significantly associated with mortality from taking amphetamine-type stimulants ($p=0.044$), buprenorphine ($p=0.042$), cannabis ($p<0.001$), GHB ($p=0.002$), heroin ($p<0.001$) and new psychoactive substances ($p<0.001$). Apart from buprenorphine, all of these drugs are illegal in France.

Discussion / Conclusion

The observed differences in causes of death between women and men, specifically more polydrug related-deaths (especially with pharmaceuticals) highlight the need to address female-specific concerns. Further studies and resources are needed to develop programs dedicated to women with substance use disorders.

Keywords

Addictovigilance, drug-related deaths, sex, prescription drugs, illicit drugs, opioids, cocaine, amphetamine-type stimulants, cannabis, new psychoactive substances

00096
Adulterated cannabidiol-based product: an unexpected but real risk

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Cannabidiol (CBD) products are becoming increasingly common, whether in tobacco shops, CBD shops, or vending machines. However, quality control of these products remains variable. Adulteration with psychoactives substances, such as new synthetic drug, or a different concentration to the one announced represent a specific concern and a public health risk [1].

Materials and methods

We present here two cases of synthetic cannabinoid (SCB) intoxication caused by an adulterated CBD product, registered in French Addictovigilance Database with numbers AVNY2025000238 and AVNY2025000285. Product analysis was performed using the SINTES system [2].

Results

A 21-years-old man, with a history of occasional CBD consumption (at least 10 times per year) and treatments for unknown conditions (cyamemazine, diazepam, methylphenidate, zopiclone, valpromide, loxapine, zuclopenthixol), smoked a CBD product named “THX Harleyqueen” in the form of flower purchased in a CBD shop.

Ten minutes after consumption, he presented muscle relaxation, loss of balance, sweating, and a significant sedation during 2 hours.

The second case concerned a 28-year-old man with a history of regular CBD consumption (0.4 g per dose) to replace his cannabis use, who smoked a CBD product named “TRIME HPC” in the form of flower purchased in an organic store. Following consumption, he presented with a burning sensation in the throat, a feeling of tightness, palpitations, nausea, cold sweats, and a significant drop in motivation. Other consumers of this product report the same symptoms, which resolve spontaneously in 30 minutes.

Both CBD-based products were analyzed using the SINTES system. The analysis identified EDMB-4en-PINACA and Δ^9-THC in both products, and quantified CBD at a concentration of 13% and 8.2%, respectively.

Discussion / Conclusion

EDMB-4an-PINACA is a new SCB, first identified in Germany in February 2025. Adulteration with new synthetic products is a current issue that can have serious consequences for consumers. These cases illustrate the ongoing circulation of adulterated CBD products.

Reference(s)

1. Addictovigilance network bulletin. ABCD du CBD. 2025

2. Cherki S *et al*. Guide méthodologique du dispositive SINTES. OFDT. 2025

Keywords

Addictovigilance, cannabidiol, synthetic cannabinoid, cannabis, adulteration

00101
The State of Morphine Sulfate Misuse in France: Addictovigilance data from 2019 to 2024

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The abuse of Morphine sulfate has been monitored in France by the French Addictovigilance Network (FAN), since the 2000s. As the latest published data date from 2019, this study aimed to provide updated data for 2019–2024.

Materials and methods

Data were extracted from the national spontaneous reporting (SR) database and addictovigilance epidemiological tools: OPPIDUM (Observation of Illegal or Misused Psychotropic Products) and DRAMES (Deaths Related to the Abuse of Medicines and Substances). A descriptive analysis of Spontaneous Reports (SRs) was conducted, followed by a cluster analysis to identify user profiles.

Results

A total of 724 SRs were identified (71.4% men; median age: 39 years). Prolonged-release Skenan® was the most frequently misused (88.3%), with intravenous diversion in 55.2% of cases.

Four user profiles emerged: (1) recreational male injectors of Skenan® (57.5%) ; (2) women injecting Skenan® or Actiskenan® recreationally, with severe outcomes (19.5%) ; (3) older men using oral Skenan® (14.65%) mainly for pain (85.8%) with dependence and (4) women using oral Actiskenan® recreationally (53.4%) or for pain (46.6%), with serious adverse effects (8.35%). Pain-related users were older than recreational users (45 vs. 37 years).

The OPPIDUM survey identified 563 users (78.9% men; mean age: 40 years), with intravenous use in 70.1% of cases.

DRAMES recorded 142 deaths (73.9% men; mean age: 40.6 years). Cocaine, methadone, or buprenorphine were the most frequently associated substances. A history of morphine abuse was documented in 50-75% of cases depending on the year.

Discussion / Conclusion

Morphine sulfate misuse in France mainly involves middle-aged men injecting the prolonged-release Skenan®. Emerging trends include younger users (under 25 years) and dependence associated with pain-related oral use, indicating evolving risk profiles.

Keywords

Morphine sulfate; misuse; addictovigilance

00102
Off-label use and self-treatment of GLP-1 receptor agonists in individuals with cocaine use disorder: clinical observations and underlying mechanisms

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Cocaine Use Disorder (CUD) remains a major public health concern, with high relapse rates and currently no approved pharmacological treatments. Glucagon-like peptide-1 receptor agonists (GLP-1RA), widely prescribed for metabolic disorders, modulate mesolimbic reward pathways and have emerged as potential candidates for addiction treatment. Their increasing accessibility has coincided with reports of off-label and patient-initiated use targeting addictive behaviors. The objective of our study was to describe cases of GLP-1RA use in individuals with CUD identified through French addictovigilance/pharmacovigilance systems and to contextualize these observations through a narrative review of mechanistic and clinical evidence.

Materials and methods

Cases were identified through the French national vigilance system as part of routine signal detection activities. Reports involving intentional GLP-1RA use in individuals

with ongoing cocaine use were descriptively analyzed. A literature review was conducted to identify preclinical and clinical studies examining the effects of GLP-1 receptor activation on cocaine-related outcomes.

Results

Four cases were identified. Two involved patient-initiated off-label use of GLP-1RA to reduce cocaine craving, while two case reports described semaglutide prescribed for metabolic indications with secondary improvements in cocaine-related symptoms. The narrative synthesis included 15 original studies. Across preclinical models, GLP-1 receptor activation consistently reduced cocaine intake, motivation, and relapse-like behaviors through modulation of mesolimbic dopaminergic activity and dopamine transporter regulation. Human evidence remains limited to three clinical reports, including one experimental laboratory study, one open-label case series, and one supervised clinical case report, with heterogeneous and preliminary findings.

Discussion / Conclusion

GLP-1 receptor signaling represents a biologically plausible target in CUD. However, current clinical evidence remains preliminary. The emergence of patient-driven off-label use highlights the need for rigorous controlled clinical trials and continued vigilance.

Keywords

Cocaine use Disorder, Glucagon-Like Peptide-1 Receptor Agonists, Dopaminergic pathways, Addictovigilance

00120
Risks Associated with the Combination of Methadone and Cocaine/Crack: An Assessment of Practices, difficulties and Needs in Addiction specialized centres

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

In addition to its respiratory depressant and sedative effects, methadone can lead to cardiac effects (blockage of hERG potassium channels). The latest national monitoring addictovigilance report on methadone has highlighted an increase in cocaine/crack consumption, leading to serious health consequences. The aim of this study is to assess current practices, difficulties and needs when methadone is combined with cocaine/crack, with a focus on the cardiac effects.

Materials and methods

This national study, conducted by the CEIP-A centers of Marseille and Montpellier, was implemented at the regional level through the French network of addictovigilance. Each CEIP-A center distributed an anonymous online questionnaire to doctors and nurses in addiction specialized centres between 07/04 and 07/05/2025.

Results

A total of 154 doctors and 206 nurses participated. 43% of them reported that cocaine consumption affected between 25% and 50% of their patients, while 27% reported it affecting more than 50%. The main consequences of this consumption are a deterioration in social context, poor adherence to methadone treatment, and health complications. Regarding cardiac risk, most risk factors for QT prolongation are known. However, drugs-induced bradycardia, as well as methadone metabolism inhibitors are less known. The prescription of an electrolyte balance test is rarely/never performed at the start of treatment (by 59% of doctors) and in the presence of QT prolongation risk factors (35%). The performance of an ECG is rarely/never carried out at the start of treatment (33%) and in the presence of risk factors (14%). Among alternatives, buprenorphine is infrequently used. Professionals expressed difficulties and requested informational support (drug interactions, cardiac effects…).

Discussion / Conclusion

This study confirms the significant presence of cocaine consumption among methadone users. Regular training and the dissemination of practical tools are essential among healthcare professionals and patients.

Keywords

methadone, cocaïne, QT prolongation, practice, addictovigilance

00136
Overview of Cannabinoid-Related Reports in Eastern France (2022–2024)

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Since the 2000s, synthetic cannabinoids (SCs) have emerged as novel psychoactive substances marketed as “legal” alternatives to cannabis but gradually added to the list of narcotics. These compounds, characterized by higher receptor affinity and longer duration of action than Δ9-tetrahydrocannabinol (THC), are associated with severe toxic effects. Their increasing recreational use, particularly through vaping, raises major public health concerns.[1]

Materials and methods

A retrospective descriptive study was conducted by the Addictovigilance Center (CEIP-A) of Nancy, covering the Eastern regions. Cases reported between 2022 and 2024 involving THC, cannabidiol (CBD) or SCs were analyzed. Accidental poisonings cases concerning children aged 0–10 years were excluded. Analyses focused on trends over time, user demographics, routes of administration, and severity.[1]

Results

An overall increase in cannabinoid-related reports was observed over the study period, with cannabinoids accounting for 29% of all cases received by the CEIP-A in

2024. THC remained the most frequently reported substance, with a median age of 29 years and predominantly inhaled forms (resin or herbal cannabis). CBD-related reports showed a transient increase in 2023, followed by a decline, with 29% of minors and increasing use of vaping and “edible” forms. Reports concerning SCs increased continuously during the study period. SCs users were significantly younger, with a median age of 19 years and 38% of minors. Vaping was the predominant route of administration, largely driven by e-liquids and disposable devices (“puffs”). The proportion of severe SC-related cases increased from 9% in 2022 to 24% in 2023 and remained high in 2024 (18%), including seizures, coma, respiratory distress, serotonin syndrome, which may require admission to intensive care.

Discussion / Conclusion

This regional analysis confirms an increase in recreational use of SCs among young people, encouraged by the attractive forms of the products marketed. These results highlight the need to strengthen prevention measures aimed at young people.

Reference(s)

[1]Vaping of psychoactive substances (excluding nicotine): riskier practices than commonly assumed. Saint-Denis: ANSM; 2025 Feb 6. Available from: https://ansm.sante.fr/actualites/vapotage-de-substances-psychoactives-hors-nicotine-des-pratiques-plus-risquees-quon-ne-le-pense

Keywords

synthetic cannabinoids, vaping, adolescents, addictovigilance, clinical toxicology

00141
Overview of reports of problems with the use of nefopam in eastern France from 2022 to 2025

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

In 2025, an increase in prescriptions for nefopam was reported in France(1). This could be linked to the launch of the tablet form in 2024 and to the introduction of secure prescriptions for other painkillers, restricting their prescription. Is the increase in sales associated with a change in the number of cases recorded by the Eastern Regional Addictovigilance Centre in recent years?

Materials and methods

We performed a descriptive observational study based on cases involving nefopam recorded from 2022 to 2025 in the eastern France. The objective was to analyse trends in reports, characterise the disorder of use, determine patient profiles and their patterns of consumption.

Results

A total of 20 cases were analysed. Almost half of the cases (45%) were reported in 2025, two-thirds of which involved the tablet form. The subjects were predominantly women (70%) and the mean age was 36. A history of mental illness was known in 55% of cases and nearly one-third of subjects had a history of substance abuse. Misuse was identified in 65% of cases, and abuse and/or dependence was found in 35% of cases. The desired effects were mainly analgesic, but three cases reported

reasons for taking the drug for anxiolytic purposes or to avoid cocaine withdrawal symptoms. The dosages for the tablet and ampoule forms ranged from 7 to 20 and 4 to 60 units per day, respectively. For 5 patients, the duration of use was at least 1 month with an average dosage of 32.5 units per day. Among the effects observed, neurological and digestive disorders were the most common (50% and 35%, respectively).

Discussion / Conclusion

This analysis shows a recent increase in nefopam misuse, in parallel with an increase in reimbursements. This highlights the need for increased vigilance regarding the risk of nefopam misuse, in a context of high prescription rate for the oral form.

Reference(s)

(1) APMNews - Pourquoi les prescriptions de l'antalgique néfopam augmentent. January 2026. https://www.sfmu.org/fr/actualites/actualites-de-l-urgences/pourquoi-les-prescriptions-de-l-antalgique-nefopam-augmentent/new_id/70823

Keywords

Addictovigilance, nefopam, misuse

00216
Contribution of Community Pharmacists to Addictovigilance in the Pays de la Loire Region (France)

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Community pharmacists play a central role in public health and are key contributors to French health vigilance systems. Within the national addictovigilance network, coordinated by regional Centres for Evaluation and Information on Pharmacodependence–Addictovigilance (CEIP-A), healthcare professionals report cases of abuse, misuse, and dependence involving psychoactive substances. In the Pays de la Loire region, community pharmacists regularly submit notifications. This study aimed to assess the quantitative and qualitative contribution of their reports to the regional addictovigilance system.

Materials and methods

We conducted a mixed-method study combining (1) a retrospective analysis of notifications submitted by community pharmacists to the CEIP-A of Pays de la Loire between 2013 and 2023, and (2) semi-structured interviews with community pharmacists to explore their motivations and perceived barriers to reporting.

Results

Between 2013 and 2023, 1,610 notifications were submitted by community pharmacists, representing 17.7% of all reports received by the regional CEIP-A. The

most frequently reported substances were zolpidem (10.19%) and zopiclone (8.99%), followed by paracetamol–codeine combinations (8.08%), tramadol (7.43%), and doxylamine (6.24%). Pharmacists notably contributed to the identification of misuse involving hypnotics, benzodiazepine-related drugs, and over-the-counter medications such as doxylamine, which are less frequently reported by other healthcare professionals. Interviews highlighted several barriers to reporting, including patients' reluctance to discuss misuse, lack of time, uncertainty about relevant clinical information, and insufficient training in addictovigilance procedures.

Discussion / Conclusion

Community pharmacists represent a significant source of addictovigilance data and play a crucial role in the early detection of medication misuse, particularly for widely dispensed drugs. Their reports have contributed to improve monitoring of opioid misuse and have partly supported regulatory changes. However, strengthening training and providing clearer guidance on reporting procedures appear essential to further enhance their contribution to the addictovigilance system.

Keywords

community pharmacists, drug misuse

00221
Lisdexamfetamine: Early Addictovigilance Data from Real-World Use

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Lisdexamfetamine is a psychostimulant prodrug and one of the first-line treatments for attention-deficit/hyperactivity disorder (ADHD). Long absent from the French market, it finally obtained marketing authorization in March 2025, with commercialization of the authorized product since July 2025. In September 2025, the French National Agency for the Safety of Medicines and Health Products (ANSM) requested the initiation of an addictovigilance survey to assess the potential for abuse, pharmacodependence, and misuse of lisdexamfetamine, given its amphetamine-related properties.
We report here the preliminary results of this first French addictovigilance survey.

Materials and methods

The French addictovigilance network is a unique system that enables signal detection through a multisource approach. For this national survey, the reporting addictovigilance center analyzed the following data over the period from July 3, 2025 to December 31, 2025: (i) utilization data provided by the company marketing the product holding a marketing authorization, (ii) addictovigilance cases involving lisdexamfetamine recorded in the French National Pharmacovigilance Database (BNPV), and (iii) data from addictovigilance pharmacoepidemiological surveys (DRAMES, OPPIDUM, OSIAP, drug-facilitated crimes) concerning misuse or diversion of lisdexamfetamine.

Results

During the study period, 412 person-years were exposed to the product holding a marketing authorization. No cases of abuse, misuse, or pharmacodependence involving lisdexamfetamine were reported in the BNPV. The OSIAP survey identified one falsified prescription mentioning lisdexamfetamine. These findings should be considered alongside addictovigilance cases reported in VigiLyze, the global pharmacovigilance database.

Discussion / Conclusion

The preliminary results did not reveal any specific addictovigilance signal; however, these findings must be interpreted in light of the low level of exposure to lisdexamfetamine in France, likely related to the lack of reimbursement for the treatment. Continued monitoring is warranted as commercialization progresses.

Keywords

Lisdexamfetamine ; psychostimulant ; misuse ; addictovigilance ; attention-deficit hyperactivity disorder

00284
Puffs: Rising Addictovigilance Reports in Pays de la Loire, but Persistent Data Gaps

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Introduced on the French market in the early 2020s, disposable e-cigarettes (“puffs”) have been banned from sale since 26 February 2025 in France. However, this measure has not curbed their use, particularly among adolescents. Their uncertain composition raises significant health concerns. In the Pays de la Loire region, the Addictovigilance Center (CEIP-A) observed an increase in reports of clinical complications associated with puff consumption in 2025.

Materials and methods

Reports (NOTS and DIVAS) recorded by the CEIP-A of Pays de la Loire were reviewed and compared across two periods: period 1 (14 months before the ban, from 1 January 2024 to 24 February 2025) and period 2 (from 25 February 2025 to 27 February 2026).

Results

Twenty reports were analyzed (16 NOTS, 4 DIVAS). The main symptom was dizziness, sometimes severe, requiring medical care and occasionally persisting for several days.

During period 1, five cases were recorded, including one minor. The presumed contents of the puffs were CBD (n=3), PTC/Buddha Blue (n=1), or unspecified (n=1). Two samples analyzed through the SINTES program revealed synthetic cannabinoids.

During period 2, 15 cases were reported, 11 involving minors. Presumed contents were THC (n=7), PTC/Buddha Blue (n=5), or unspecified (n=1). Two SINTES analyses were performed: one detected nicotine only, and the other remains pending.

Discussion / Conclusion

Data analysis highlights a significant increase in addiction monitoring reports for clinical complications related to puff use, despite the ban introduced in February 2025. Since that date, most reports have concerned minors. The clinical presentations cannot be explained by nicotine exposure alone.

Few SINTES analyses have been carried out due to the difficulty in collecting devices. When symptoms occur in a school setting, teenagers are reluctant to describe how they consume and obtain puffs for fear of punishment. In this sensitive context, the CEIP-A must develop alternative strategies to improve surveillance and data collection.

00298
National trends in tramadol use disorders in France from 2019 to 2024: An analysis of Addictovigilance data

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Following previous findings, continued monitoring is essential to assess tramadol misuse, abuse, and related harms [1]. This study aimed to analyse national trends in tramadol use disorders in France from 2019 to 2024, using Addictovigilance data and considering recent regulatory measures.

Materials and methods

This retrospective national study analysed French data from 2019 to 2024, including spontaneous Addictovigilance reports (NotS), suspect prescriptions (OSIAP), data from specialised addiction care structures (OPPIDUM), substance-related deaths (DTA, DRAMES: until 2023), and national sales expressed as defined daily doses

per 1,000 inhabitants per day (DID). High-dose use was defined as use exceeding 400 mg per day.

Results

NotS fluctuated between 215 and 237 cases annually from 2019 to 2023 before declining to 169 in 2024. The proportion of suspect prescriptions involving tramadol increased from 11.9% in 2019 to 16.0% in 2024 (a peak of 16.7% in 2021). In OPPIDUM, tramadol cases decreased from 1.2% in 2019 to 0.9% in 2023, and reached 1.2% again in 2024. Tramadol remained the leading opioid in analgesic-related deaths, peaking at 47.0% in 2020 and reaching 35.3% in 2022 (40.0% in 2023). In DRAMES, tramadol accounted for 3.2% of drug-related deaths in 2019, with a decreasing trend until it reached 1.1% in 2023. Monthly DID declined steadily from 8.2 in January 2019 to 5.0 in December 2024. In 2024, high-dose use represented 47.9% of cases, consistent with an increasing trend in previous years, and was associated with seizures, opioid overdoses, and serotonin syndrome. A fatal tramadol-induced hypoglycaemia in a recreational context was documented.

Discussion / Conclusion

Despite an overall decline in national exposure and a decrease in reports observed in 2024, tramadol-related high-risk use and serious complications persist in France. Starting March 1, 2025, tramadol and codeine require secure prescription forms, strengthening regulatory control. The impact of these measures will be assessed using 2025 nationwide Addictovigilance data.

Reference(s)

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Keywords

Tramadol; opioid; substance use disorders; abuse; addictovigilance; drug-related deaths; regulatory measures

00315
Health complications related to cocaine use in Nouvelle-Aquitaine 2021 – 2024 : regional specificities

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Spontaneous reports (SRs) involving cocaine collected by the French Addictovigilance Network are rising these last years with serious health consequences [1]. In Nouvelle-Aquitaine, hospitalizations related to cocaine have increased by 448% between 2010 and 2019, exceeding the national level (+300%) [2]. Thus, a regional analysis was carried out to describe complications related to cocaine use in Nouvelle-Aquitaine and to assess regional specificities.

Materials and methods

We analysed SRs involving cocaine use in Nouvelle-Aquitaine between 2021 and 2024.

Results

The number of SRs involving cocaine use increased 1.9-fold between 2021 (n=186, 17.5%) and 2024 (n=347, 32.6%), reaching 1063 SRs. Among them, 638 (60%) were serious. Users were mainly men (n=765, 72%) with an average age of 34.5 years and 42 (4%) were adolescents. The use of cocaine powder was reported in 873 (82.1%) SRs, crack in 173 (16.3%) SRs and both in 17 (1.6%) SRs. The main route of administration was nasal (19.5%), followed by inhalation (16.3%) and intravenous

(12.0%). Polyconsumption was reported in 661 (62.2%) cases, mainly with cannabis (24.8%), benzodiazepines and related drugs (13.0%) and opioid substitution medications (9.6%). The main complications were psychiatric disorders (especially substance use and behavioral disorders), followed by central nervous system disorders (particurlarly consciousness disorders). Regional specificities were observed : the injection route and concomitant use of cannabis were more common in Aquitaine, whereas concomitant use of benzodiazepines and related drugs was more common in Poitou-Charentes/Limousin. General disorders, administration site conditions and infections were more frequent in Aquitaine while injuries and poisoning were more frequent in Poitou-Charentes/Limousin.

Discussion / Conclusion

This analysis highlights regional specificities in health complications and patterns of cocaine use compared to national data [1] and within Nouvelle-Aquitaine, which require targeted measures to reduce risks.

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Keywords

Cocaine, Addictovigilance

00373
Semiology and Temporal Dynamics of Psychotic Manifestations Associated with Synthetic Cathinone Use in a Chemsex Context: acute substance-induced psychotic symptoms or emergence of persistent psychotic disorders ?

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Synthetic cathinones are closely monitored by addictovigilance system. Reports highlight that the use of synthetic cathinones in the context of chemsex is associated with a risk of psychiatric complications, particularly psychotic manifestations. However, differentiating acute substance-induced psychotic symptoms from prolonged psychotic disorders remains clinically challenging. This study aims to characterize the clinical features and temporal patterns of psychotic manifestations related to synthetic cathinone use in a chemsex context, based on cases reported to an addiction vigilance center.

Materials and methods

A retrospective descriptive analysis was conducted using reports collected between 2020 and 2025 by the Pays de la Loire Addictovigilance Centre, mentioning a chemsex context and involving cathinones. Reports describing clinical features consistent with psychotic manifestations were analyzed, focusing on the type of symptoms, their timing (during substance use, during the comedown phase, or delayed), and the need for specialized psychiatric care.

Results

Among the 99 cases involving cathinone use in a chemsex context, twenty-two (22%) described psychotic manifestations. Clinical presentations mainly included persecutory delusions, hallucinations, and marked suspiciousness, most often occurring immediately after substance use or during the withdrawal phase.
Two patients, with no prior history of psychotic disorder, experienced a psychotic episode requiring hospitalization and initiation of antipsychotic treatment. In these cases, symptoms persisted beyond the acute intoxication phase.

Discussion / Conclusion

Psychotic manifestations associated with cathinone use in a chemsex context occur predominantly in the setting of acute use; however, prolonged forms are observed. This observation leads us to question the potential triggering role that cathinones may have in the onset of genuine psychotic disorders. The distinction between acute intoxication and prolonged psychotic disorder requires careful clinical assessment and extended follow-up.

Keywords

Synthetic cathinones

Chemsex

Psychotic symptoms

Addictovigilance

00554
Digital tools in the context of the diversion of drugs from community pharmacies: current use, barriers and future directions

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The falsification of prescriptions represents growing public health issue due to its health, social, and economic consequences. While regulatory and organizational measures have been implemented to limit this phenomenon, they are not always sufficient to prevent diversions. In this context, digital tools emerge as complementary solutions, capable of enhancing traceability, improving the detection of fake prescriptions, and supporting pharmacy teams in their role as sentinels. This work aims to assess the current use of these digital tools (Pharmaceutical Record, Shared Medical Record, National Health Identity, e-prescriptions, teleconsultation platforms, Secure Health Messaging, ASAFO platform of French Health Insurance system, AI software (Ordosafe), pharmacy software and professional social networks) in community pharmacies, identify the barriers faced by professionals, and explore avenues for improvement.

Materials and methods

This is a descriptive study conducted via a questionnaire distributed from April to June 2025, to pharmacy teams, including pharmacists, pharmacy technicians, students, across France.

Results

The sample of 381 respondents, including 83% of pharmacists, shows a balanced distribution across age groups and practice areas. The results reveal varied use of digital tools depending on their nature and integration into common use. The Pharmaceutical Record and ASAFO service are widely adopted, with regular use by 87% and 50% of respondents respectively. Other tools are used irregularly, such as e-prescriptions, with 26% of respondents using them systematically versus 28% never using them. Conversely, some tools remain underused or unused, like the Shared Medical Record, which 41.5% of participants say they never use. Data also highlight the influence of age and practice area of professionals. Several barriers were identified: technical constraints, lack of interoperability between systems, insufficient training…

Discussion / Conclusion

These data support increased investment in digital solutions to balance patient safety and healthcare system efficiency, particularly the need for a single digital tool and widespread use of prescriptions.

Keywords

Prescription falsification, Digital tools, Medication diversion, Community pharmacy

00559
Substance use trends in French students: 2021–2025 PETRA study findings

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Psychoactive substance use among students is a public health concern that may evolve with new substances, usage patterns, and regulatory changes. The PETRA study, conducted in France in 2021 and repeated in 2023 and 2025 with additional universities, aims to describe trends in student substance use between 2021 and 2025.

Materials and methods

In this repeated cross-sectional study, conducted in distinct samples, an anonymous self-administered questionnaire was emailed between April and June to student enrolled at the following universities: (i) Lille in 2021; (ii) Lille, Bordeaux, Paris and Grenoble in 2023; and (iii) Lille, Bordeaux, Paris, and Lyon–Saint-Étienne in 2025. The questionnaire included sociodemographic characteristics, academic curriculum, and psychoactive substance use since university entry.

Results

4,431 students participated in 2021, 7,293 in 2023, and 8,159 in 2025, with a majority of women. In 2025, 77.6% of respondents reported having used alcohol since the first university year (2021: 80%; 2023: 82.5%), 38% tobacco (2021: 40.3%; 2023: 40.1%) 30.4% cannabis (2021: 34%; 2023: 35%), 26.3% poppers (2023: 26.3%), 18.6% opioid drugs (2021: 24% ; 2023: 14.7%), 16.4% benzodiazepines (2021: 15.4%; 2023: 16.9%), 8.3% MDMA (2021: 6.5%; 2023: 8%), 6.9% nitrous oxide (2021: 6.8% ; 2023: 9.3%), 4.7% mushrooms (2023: 5%), 3.6% amphetamines (2021: 5.7%; 2023: 5.5%), 4.4% cocaine (2021: 7.5%, 2023: 4.9%), 3.4% ketamine. Methylphenidate use increased from 0.7% in 2021 to 4% in 2025. For several substances, use varied according to field of study. In 2025, a substantial proportion of users reported having experienced a sense of dependence, particularly among benzodiazepine (33%) and cannabis users (24%), but also among alcohol, opioid, illicit psychostimulant and ketamine users.

Discussion / Conclusion

Overall, substance use among students remained high and largely stable between 2021 and 2025, with alcohol, tobacco and cannabis being the most prevalent, a notable rise in methylphenidate use, and a substantial proportion of users reporting perceived dependence.

Keywords

student, misuse, psychoactive substances, addictovigilance

00579
Doping behaviors of athletes candidates for competitions of the Ivorian Office of School and University Sports in Abidjan

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Doping is a global phenomenon against which the World Anti-Doping Agency fights continuously. University sports, being a melting pot of sporting success through the competitions of the Ivorian Office of School and University Sports (OISSU), are not spared. The aim of the study was to assess athletes' doping attitudes.

Materials and methods

It was a cross-sectional analytical study, involving athletes from different UFRs, during the month of May 2024. We studied the profile of the participants and the

substances consumed. The data was processed using R Studio and EPI-INFO 7 software.

Results

Out of 330 athletes who consulted, 256 agreed to participate in our survey (77%). The average age of participants was 22.81±3.34 years with a male predominance and a sex ratio of 5.4. The most practiced category of sport was football (51.17%). 32% of the athletes admitted to having consumed stimulants, the majority of whom were football players. Alcohol accounted for 68% of the products consumed, at the expense of energy drinks and other stimulants. In the bivariate analysis, athletes aged ≤ 20 years, the UFR of Criminology, ICA-SHS, and SJAP-SEG appeared to be associated with the consumption of doping products.

Discussion / Conclusion

This study made it possible to take stock of the consumption of doping substances by athletes in a university setting, and this, in preparation for competitions. It would be appropriate to raise awareness among athletes about the dangers associated with the use of these doping substances.

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Keywords

Doping, University sports, Athletes

6- Pharmaco-épidémiologie, Pharmacologie sociale et Pharmaco-économie

00023
Pharmacological interaction between abiraterone or enzalutamide and antithrombotic agents: is there a clinical impact?

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

In patients with prostate cancer, pharmacokinetic interactions between antithrombotic agents and ARPIs (in particular, abiraterone and enzalutamide) may lead to thrombotic events (myocardial infarction, ischaemic stroke, deep vein thrombosis) or severe haemorrhages when initiating the latter. This study aims to assess the clinical impact of these interactions.

Materials and methods

Using the SNDS, we selected prostate cancer patients who were exposed to antithrombotic drugs between 2016 and 2021. A case-crossover study design

evaluated a possible triggering effect of serious thrombotic or haemorrhagic events (defined as requiring hospitalisation and identified via ICD-10 codes) within 6 months of initiating abiraterone or enzalutamide in stable patients on antithrombotic therapy (VKA, DOAC or antiplatelets). Each patient was their own control. The frequency of events during the three months following initiation (risk period) was compared to that of the following three months (control period) and an odds ratio (with 95% CI) was estimated. These analyses were performed for each ‘event type - antithrombotic - ARPI initiated’ triplet (e.g. thrombosis - rivaroxaban - enzalutamide). Sensitivity analyses varied the case-crossover parameters (including the duration of the risk and control periods).

Results

Although initially including nearly 200,000 patients, fewer than 300 haemorrhagic or thrombotic events were identified in stable patients receiving various antithrombotic agents who had initiated abiraterone or enzalutamide within the previous six months.

Respectively, only 11 patients stable on fluindione initiated abiraterone or 11 on enzalutamide within six months prior to a thrombotic event. No statistically significant difference was identified for any ARPI initiated. Most of the other pairs evaluated included either none or fewer than 10 patients.

Discussion / Conclusion

Following the recent initiation of an ARPI, the low number of serious events identified in stable patients on antithrombotic therapy is a reassuring factor regarding the clinical impact of pharmacokinetic interactions between treatments frequently used in elderly patients with prostate cancer.

Keywords

drug-drug interaction, abiraterone, enzalutamide, VKA, DOAC, antiplatelet, thrombosis, bleeding

00031
Effectiveness of nirsevimab immunisation on invasive pneumococcal disease in children: an observational cohort study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Invasive pneumococcal diseases (IPD) remain a leading cause of morbidity and mortality in children worldwide, despite the widespread use of pneumococcal conjugate vaccines (PCVs). Respiratory syncytial virus (RSV) is suspected to trigger IPD.

The main objective was to assess whether immunization with nirsevimab, a monoclonal antibody targeting RSV, reduced the risk of IPD in children.

Materials and methods

We conducted a national population-based cohort study using data from the French National Health Data System. All live-born children in metropolitan France between February 6, 2023, and January 31, 2024 for whom nirsevimab immunization status was available were included.

The index date for immunized children was the date of nirsevimab dispensation. For non-immunized children, index date was randomly assigned during the enrolment period following the distribution of the index dates for the immunized subpopulation.

The primary outcome was hospitalization for IPD within six months after the inclusion among children immunized with nirsevimab vs non-immunized. Propensity score analysis using inverse probability of treatment weighting (IPTW) was conducted to adjust for baseline characteristics. Several sensitivity analyses were performed.

Results

Among 608,641 children born in France during the study period, 527,971 were included, of whom 119,435 (22.6%) received nirsevimab. During the six-month

follow-up period, 112 cases of IPD occurred: 17 (14.2/100,000) in the immunized group vs. 95 (23.3/100,000) in the non-immunized group. Six months after immunization, nirsevimab was associated with a 36% reduction in the odds of hospitalization for IPD (odds ratio [OR]: 0.64; 95% confidence interval [CI], 0.48 to 0.85). Nine months after immunization, effectiveness remained consistent with a 32% reduction (OR: 0.68; 95% CI, 0.53 to 0.87). Other secondary and sensitivity analyses provided similar results.

Discussion / Conclusion

This real-world cohort study indicated that nirsevimab immunization in children < 12 months of age was associated with a reduced risk of IPD.

Keywords

Invasive pneumococcal diseases, RSV, nirsevimab

00032
Safety of GLP-1 RA and other new generation anti-diabetic drugs for the management of type-2 diabetes in pregnancy: A French nationwide population-based study.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

GLP-1 RA and other non-insulin glucose-lowering medications are increasingly used in women of reproductive age with type 2 diabetes mellitus (T2DM). Data on the safety of these medications in pregnancy are limited. We aimed to assess the comparative safety of first-trimester exposure to non-insulin antidiabetic medications on the risk of organ-specific congenital malformations (MCMs) among pregnancies with T2DM.

Materials and methods

Population-based cohort study using the French SNDS including singleton pregnancies in women aged 18 to 50 years with pregestational T2DM from January 2011 to August 2024. First-trimester exposure to antidiabetics, defined as at least 1 prescription filled from 30 days before through 91 days after conception. All antidiabetics were considered. The primary reference group was nonuse of any antidiabetics; insulin use alone was also a comparator in additional analyses. MCM identified according to EUROCAT definitions within the first year of life. Adjusted risk ratios (aRRs) and 95% CIs were estimated using Poisson regressions with generalized estimating equations. Correction for multiple comparisons were made.

Results

Among 17,125 eligible pregnancies, 9.3% were unexposed to antidiabetics, 18.3% exposed to insulin alone, and 26.8% to at least one second-line antidiabetic. Compared with nonuse, first-trimester exposure to GLP-1 RA (aRR, 1.57; 95%CI, 1.17–2.11), DPP-4i (aRR, 1.43; 95%CI, 1.06–1.89), and sulfonylureas (aRR, 1.79; 95%CI, 1.37–2.34) were associated with increased MCM risk. GLP-1 RA and sulfonylureas were also associated with higher risks of cardiac and atrial septal defects, respectively, compared with insulin use alone; these findings became null when correcting for multiple comparisons. No increased risks were observed for other organ defects.

Discussion / Conclusion

In the largest study to date on newer generation antidiabetics in pregnancy, first-trimester exposure to GLP-1 RA and sulfonylureas were associated with increased risk of MCM, particularly cardiac defects, when compared to non-use, and to insulin use alone, but chance findings cannot be ruled-out.

Keywords

Antidiabetics, GLP-1 RA, Pregnancy, Malformations, Real-Wold French Data, Teratogenicity

00036
Trends of methylphenidate use in France: a population-based, monthly cross-sectional study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental condition affecting approximately 5% of children and 2.5% of adults worldwide[1]. Besides behavioral interventions, pharmacotherapy—particularly methylphenidate, the only medication approved for ADHD in France—plays a central role in ADHD management. In recent years, in France, regulatory changes and growing recognition of adult ADHD may have modified prescribing practices[2]. We aimed to describe national trends in methylphenidate use in France between 2015 and 2024.

Materials and methods

We conducted a population-based, monthly cross-sectional study using the French National Health Data System (SNDS), which covers over 99% of the population. All patients with dispensed methylphenidate between 01/2015 and 12/2024 were included. We constructed time-series analyses for the monthly number of patients receiving methylphenidate, new users (no dispensing in the previous 12 months),

prescribers, and dispensing pharmacists. Rates per 100,000 inhabitants were calculated using national census data.

Results

Between September 2015 and September 2024, the monthly prevalence of methylphenidate use increased from 58.4 to 181.3 patients per 100,000 inhabitants (+210%), and the incidence of new users rose from 3.1 to 11.6 (+280%). Increases were observed across all age groups, with the steepest growth among adults aged 18–39 years (18-29: +844%; 30-39:+728%). Use increased in both sexes, with a greater rise among women (+446%). The number of initiating prescribers increased, particularly in private practice (+749%). To a lesser extent, the number of pharmacists dispensing methylphenidate also increased (+28%).

Discussion / Conclusion

Methylphenidate use and accessibility rose sharply in France from 2015 to 2024, especially among young adults and women, coinciding with regulatory easing and improved structuring of ADHD care[3]. However, overall prescribing rates remain lower than in several neighboring European countries, suggesting persistent undertreatment[4]. Continued expansion of access, combined with careful prescribing and monitoring, appears warranted to meet unmet clinical needs while limiting misuse.

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Keywords

pharmacoepidemiology; methylphenidate; ADHD; prescribing

00045
Systemic therapy-free remission under dupilumab for atopic dermatitis: a nationwide cohort study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Advances in the understanding of atopic dermatitis (AD) pathophysiology have led to the development of new therapeutic options that reduce symptoms and may enable sustained, off-therapy remission. Recent studies suggest that extending the interval between dupilumab injections could be effective and safe; however, the effects of complete treatment discontinuation still require further investigation. Therefore, we aimed to evaluate the systemic therapy-free remission under dupilumab, on a large scale at population-level.

Materials and methods

We conducted a retrospective cohort study using the French nationwide database (SNDS). We included adults initiating dupilumab for AD between January 2021 and June 2023, with ≥6 months of treatment, with a follow-up until December 2024 or death. Patients who discontinued all systemic drugs for ≥1 year were identified and characterized as under “systemic therapy-free remission”. We estimated the

prevalence of discontinuation, described their characteristics, and analyzed factors associated with systemic therapy-free remission.

Results

A total of 7,297 adults exposed to dupilumab for ≥6 months were included, among them 154 (2.1%) patients were considered under systemic therapy free remission. Baseline characteristics suggested that these 154 patients were younger (32 vs 42 years, SMD=0.37) received more emollients (33% vs 27%, SMD=0.12), topical calcineurin inhibitors (35% vs 27%, SMD=0.18) and ciclosporin (22% vs 16%, SMD=0.18) compared to those who did not discontinue dupilumab. Following discontinuation, most patients in systemic therapy-free remission continued to use topical corticosteroids treatments (77%). Discontinuation may have been related to reasons other than remission; 8% of patients had conjunctivitis, 8% had head and neck dermatitis, and fewer than 11 were pregnant.

Discussion / Conclusion

Our study suggested that a systemic therapy free-remission may exists in real-world practice among patients treated with dupilumab, the first marketed biologic for AD, but appears to be uncommon. The de-escalation from systemic to topical treatment support a disease modification by reducing disease severity.

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Keywords

atopic dermatitis, disease modification, dupilumab, pharmacoepidemiology, therapy-free remission

00046
Pharmacological treatment patterns in patients with atopic dermatitis: a nationwide cohort study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The therapeutic landscape for atopic dermatitis (AD) has expanded rapidly with first the approval of dupilumab in 2017, then additional biologics and Janus kinase inhibitors (JAKi). While European guidelines do not establish a hierarchy among systemic therapies, safety concerns led the European medicines agency (EMA) to issue recommendations regarding JAKi use in patients with cardiovascular risk. This study assessed real-world prescribing patterns of systemic treatments for AD.

Materials and methods

We conducted a retrospective cohort study of adults exposed to newly approved systemic treatment of AD (dupilumab, tralokinumab, abrocitinib, baricitinib, upadacitinib) between 2018 and 2024, based on data from the French nationwide database (SNDS). We analysed temporal trends in prescriptions from treatment initiation up to December 2024 or death. After identifying clusters of similar

therapeutic pathways using state sequence analysis, we performed logistic regression to identify factors associated with each cluster.

Results

A total of 25,490 adults exposed to systemic drugs for AD were included. The median age was 43, and 49% were women. Dupilumab remained the most frequently prescribed throughout the study period. Among patients with at least one year of follow-up, 92% initiated dupilumab, and over two-thirds maintained treatment for the entire year. A subset of patients discontinued drug without switching, with 21% no longer receiving any systemic treatment one year after initiation. Given the high persistence observed with dupilumab, only a small proportion of patients (15%) progressed to second- or third-line drug. Cluster analysis further indicated that dupilumab use was associated with older age, a higher prevalence of asthma, and more cardiovascular comorbidities compared with JAKi users.

Discussion / Conclusion

Despite the expansion of the therapeutic arsenal, dupilumab remains the most commonly prescribed treatment for severe AD in real-world practice, with high persistence. As suggest by the EMA recommendations JAKi users were less comorbid than dupilumab users.

Keywords

atopic dermatitis, biologic drugs, Janus kinase inhibitors, pharmacoepidemiology, state sequence analysis

00051
The Drug-RElated Hospitalizations for Nursing HOme Residents (RENHO) study-Part two: A nationwide study in the French National Health data System (SNDS)

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Nursing home residents (NHRs) with advancing age are often exposed to polypharmacy, a well-known risk factor for adverse drug reactions (ADRs), increasing the risk of hospitalization. The RENHO-1 study performed at the Toulouse University Hospital has shown that one-quarter of ED admissions among NHRs were related to ADRs, and that 12% of which were assessed as avoidable. Based on these findings, four main categories of ADRs leading to ED admissions were identified : anemia; fall/fracture; bleeding/hemorrhagic event; constipation/fecaloma. This study aimed to identify at a national level, the occurrence of these events and associated factors, using the French National Health Data System (SNDS)

Materials and methods

We identified in the SNDS NHRs hospitalized via ED with a ICD-10 diagnosis code related to the four ADR categories in 2022-2023. These cases were matched (1:1) with controls (residents from the same NH facility, hospitalized via ED for any reason except the four events of interest). We considered drug exposure during the quarter preceding ED admission. For each of the four events, a multivariate conditional logistic regression model was performed with adjustment on sociodemographic variables, comorbidities and history of ED admission.

Results

We identified 17,335; 60,909; 17,037 and 32,737 matched case-control pairs for anemia, fall/fracture, bleeding/hemorrhagic event, constipation/fecaloma respectively. Overall, a high number of drugs was strongly associated with an increased risk of experiencing an event of interest. The results suggest that drug underuse may be associated with such events, such as the lack of laxatives in subjects exposed to opioids who present with constipation or fecaloma, or the lack of proton pump inhibitors in subjects exposed to platelet aggregation inhibitors who present hemorrhagic events.

Discussion / Conclusion

Polypharmacy is one of the strongest factor associated with the risk of ED admission of NHRs for some ADRs. Future studies should focus more specifically on the avoidability of these events.

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Keywords

Nursing Home residents, SNDS, drug-induced iatrogenic disease, Hospital admission

00062
Trends in psychotropic medication use among pregnant women in France: a nationwide cross-sectional study, 2010-2024

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The prevalence of psychotropic use during pregnancy varies worldwide (6-20%) and has increased in recent decades. However, trends in psychotropic polypharmacy remain insufficiently characterized. This study examined temporal trends in psychotropic medication use and polypharmacy during pregnancy in France (2010-2024).

Materials and methods

This cross-sectional study included all women aged 15-49 years with pregnancies lasting between 91 and 300 days regardless of the pregnancy outcome between January 1, 2010, and December 31, 2024, in the French National Health Data System. Prescription fills for antipsychotics, lithium, anxiolytics, hypnotics, antidepressants, and psychostimulants were identified during pregnancy based on dispensing dates in the outpatient pharmacy records. The annual prevalence of psychotropic medication use and psychotropic polypharmacy was calculated as the number of pregnant women who filled at least one, and at least two distinct psychotropic medications, respectively, divided by the total number of pregnancies in the same calendar year. Joinpoint (JP) regression was implemented to identify time segments with distinct outcome trends and an average yearly change over the study period. All analyses were stratified by psychotropic class.

Results

Among 10,043,224 eligible pregnancies, 596,458 (5.9%) filled at least one psychotropic medication, and 143,395 (1.4%) were defined as polypharmacy during pregnancy. JP analysis of the annual prevalence of psychotropic use in pregnancy identified three periods with distinct yearly trends: 2010–2016 (-1.1%; [95%CI, -1.5; -0.5%]), 2016–2019 (-5.9%; [-6.7; -4.5%]), and 2019–2024 (+2.9%; [+2.2; +3.7%]). Overall, prevalence decreased for anxiolytics and hypnotics, but increased for antidepressants, antipsychotics, lithium, and psychostimulants. JP analysis of the annual prevalence of psychotropic polypharmacy also identified three periods: 2010–2016 (-0.9% per year; [-1.3; -0.4%]), 2016–2020 (-3.9%; [-4.8; -3.3%]), and 2020–2024 (+6.6%; [+6.0; +7.2%]).

Discussion / Conclusion

Increasing use of certain psychotropic medications and polypharmacy during pregnancy may reflect improvements in screening and treatment of perinatal mental health disorders and/or worsening mental health.

Keywords

pregnancy, psychotropic medications, polypharmacy, pharmacoepidemiology

00063
Trends in continuation, discontinuation, and initiation of psychotropic medication use during pregnancy in France: a nationwide cohort study, 2010–2024

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Psychotropic use during pregnancy varies across countries (6-20%) and has increased in recent decades. However, contemporary patterns of use during pregnancy and their trends remain poorly described. This study examined temporal trends in continuation, discontinuation, and initiation of psychotropic medications during pregnancy in France (2010-2024).

Materials and methods

This cohort study included all women aged 15-49 years with pregnancies lasting between 91 and 300 days that resulted in birth or termination between January 2010 and December 2024 in French National Health Data System. Prescription fills for anxiolytics, hypnotics, antidepressants, antipsychotics, lithium, and psychostimulants were identified from pharmacy dispensing records in the six months before and during pregnancy. Medication use was classified into three groups: continuation (before and during pregnancy), discontinuation (before but not during), and initiation (during but not before). Annual group-specific rates were computed by dividing the number of pregnancies in each group by the total number of pregnancies that year. Joinpoint (JP) regression identified time segments with distinct outcome trends, stratified by psychotropic class.

Results

Among 10,043,224 eligible pregnancies, 664,004 (6.6%) discontinued, 272,834 (2.7%) continued, and 323,624 (3.2%) initiated psychotropic medication during pregnancy. JP analyses of psychotropic medication continuation rates showed three periods with distinct yearly trends: 2010–2015 (-0.2%; [95% CI, -0.8; +1.0%]), 2015–2020 (-2.9%; [-4.0; -2.2%]), and 2020–2024 (+5.3%; [+4.3; +6.2%]). Similar trends were observed for anxiolytics, hypnotics, and antidepressants, while antipsychotics, lithium, and psychostimulants exhibited steady increases throughout. JP analysis of initiation rates also showed three periods with distinct yearly trends: 2010–2016 (-1.9%; [-2.5; -0.6%]), 2016–2019 (-6.9%; [-8.3; -4.6%]), and 2019–2024 (+1.8%; [+0.7; +3.6%]). For discontinuation rates, there was a consistent annual decline of -2.4% [-2.6; -2.1%].

Discussion / Conclusion

Declining discontinuation rates along with rising continuation and initiation rates suggest substantial practice evolution, possibly reflecting improved understanding of psychotropic safety profiles and treatment of mental health disorders in pregnancy.

Keywords

pregnancy, psychotropic medications, polypharmacy, pharmacoepidemiology

00078
Age- and Sex-Related Disparities in French Population Exposure to Drug Shortages : A 2023 Nationwide Study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Drug shortages are an increasing public health concern. Patient populations differ in their drug use, both in terms of quantity and therapeutic class, yet the impact of these shortages on different age and sex groups remains poorly characterized. This study investigated the age and sex profiles of patients who consumed drugs reported in shortage in France in 2023.

Materials and methods

We conducted a nationwide retrospective study in 2023 based on secondary analysis of two administrative databases: the French drug shortage notification system and the national health insurance database for entire French population. Data were cross-referenced by drug presentation code to identify consumed drugs with reported shortages, and shortage exposure risk was estimated and stratified by age group and sex.

Results

In 2023, a total of 4,925 drug shortage reports were recorded in France. The most affected therapeutic classes were cardiovascular system, nervous system, and anti-infective agents, representing 64.9% of reports (n=3,196).

Among the 12,625 pharmaceutical presentations used in France, 3,356 were reported to be in shortage or at shortage risk at least once during the year (26.6%). This proportion reached 30.4% of pharmaceutical presentations used by the <20-year-olds population (n=7.091).

A total of 24.2% of drug consumption (n=699M) was exposed to shortage risk, with approximately half of this consumption occurring in ≥60-year-olds (11.9%). Women represented a greater proportion of this consumption exposed to shortage risk than men (13.7% vs. 10.5%; $p<0.001$).

Taking into account the global consumption of each population, ratio of the proportion of consumption exposed to reported shortages to the proportion of total consumption was higher for ≥60-year-olds (1.13 vs. 0.92 and 0.85 for 20–59-year-olds and <20-year-olds respectively, $p<0.001$). Ratio was higher for men (1.04 vs. 0.97 for women, $p<0.001$).

Discussion / Conclusion

A population-level approach is essential to understand how shortages affect different groups and exacerbate health inequalities.

Keywords

Drug shortage, Pharmaco-epidemiology, Regulatory science, Risk assessment, Therapeutic Uses, Public health

00099
Statins in Pregnant Women: A Study Based on the new MediCA Database

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Lipids play a crucial role in organogenesis, and their reduction during pregnancy may potentially have adverse effects on embryonic development. For this reason, and due to concerning findings from animal studies as well as limited human data, statins are contraindicated during pregnancy. The aim of this study was to evaluate the risks of pregnancy interruption and major congenital anomalies among pregnant women exposed to statins.

Materials and methods

We conducted a study using MediCA, a new database linking the SNDS with four French congenital malformation registries. To date, MediCA includes 1,043,520 women whose pregnancies ended between 2012 and 2020. MediCA contains data on dispensed medications before and during pregnancy, women's characteristics, pregnancy outcomes, and fetal or children health, including congenital anomalies. We compared women exposed to statins during pregnancy with unexposed women and with women exposed only before pregnancy.

Results

The study included 910 pregnant women (0.1%) exposed to a statin during pregnancy, 1,706 women exposed only before pregnancy, and 1,023,257 unexposed women. Exposure to statins during the first trimester was not associated with an increased risk of major congenital anomalies compared with fetuses/children of mothers exposed only before pregnancy (ORa=0.75[0.45-1.22]) or with those of

unexposed mothers (ORa=0.97[0.63-1.43]). An association was observed between statin exposure during pregnancy and the risk of pregnancy termination, when compared with unexposed women (HRa=1.31[1.07-1.61]). However, no significant increase risk was observed when compared with women exposed only before pregnancy (HRa=1.09[0.85-1.42]).

Discussion / Conclusion

Our study did not identify a higher risk of congenital anomalies in women exposed to statins during pregnancy. An increased risk of pregnancy termination among exposed women compared with the general population was observed, but this may be related to the underlying health conditions of the women exposed to statins. These findings raise questions about the French contraindication of statins mainly in women at high cardiovascular risk.

Keywords

Statins, pregnancy, congenital anomalies, MediCA

00113
Potentially inappropriate medication at polypharmacy initiation in adults aged ≥45 years : a nationwide cross-sectional study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Although polypharmacy and potentially inappropriate medication (PIM) have been well described, the transition to incident polypharmacy and the contribution of PIMs in this transition remain poorly documented. We aimed to describe new polypharmacy users and identify the medications contributing to this transition

Materials and methods

In this cross-sectional study, we identified all incident cases of polypharmacy in 2024 among individuals aged ≥45 years using the SNDS. Incident polypharmacy was defined as the overlap of five distinct ATC-5 medication on a day, with no polypharmacy in preceding five years. Dispensed medications at polypharmacy initiation were classified as PIMs or not according to the PROMPT criteria (45-64 years old) and the REMEDI[e]S criteria (≥65 years) excluding those based on treatment duration or dose.

Results

In 2024, of the 693,309 subjects initiating polypharmacy, 71.1% were aged < 65 years. At the time of polypharmacy initiation, 16.2% had at least one PIM newly dispensed. The most frequent PIMs were opioids without laxatives (75.6%) and first-generation antihistamines (22.3%). Among individuals aged ≥65 years, 13.0% had at least one PIM; the most frequent were statins and antiplatelet agents for primary prevention of cardiovascular events (40.4% and 19.6% respectively), and 30.4% had two or more PIMs. Compared with non-exposed individuals, those exposed to ≥1 PIM were more often male (54.1% vs 50.0%), younger (mean age 56.6 vs 60.5 years), and received more medications at polypharmacy initiation (mean 4.3 vs 3.4).

Discussion / Conclusion

Our findings suggest that initiation of polypharmacy is not solely the consequence of gradual therapeutic accumulation and may coincide with prescriptions that meet PIM criteria. The frequent prescription of PIM at the time polypharmacy is initiated highlights that this transition represents a strategic opportunity for medication review.

Keywords

Polypharmacy, Inappropriate medication, Pharmacoepidemiology, Database

00147
Colchicine after ischemic stroke: cardiovascular risk reduction without excess mortality — a nationwide target trial emulation study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Low-dose colchicine has demonstrated cardioprotective effects in coronary artery disease (1), but evidence remains limited in patients with ischemic stroke (2,3), and some studies suggested excess of non-cardiovascular mortality (4) or adverse events (5). We assessed the effectiveness of colchicine initiation after ischemic stroke on major cardiovascular events, with particular attention to mortality outcomes, using French nationwide real-world data.

Materials and methods

We emulated a target trial using the French National Health Data System (SNDS), including adults hospitalized for a first ischemic stroke between 2012 and 2023 who were eligible for colchicine initiation (prior gout therapy and no contraindications). Treatment strategies compared colchicine initiation within 6 months after discharge versus never initiation. The primary outcome was major adverse cardiovascular events (MACE). Secondary outcomes included individual components of MACE (recurrent ischemic stroke, myocardial infarction, cardiovascular death), non-cardiovascular and all-cause mortality. Five-year risks, risk differences, and risk

ratios with 95% confidence intervals (CIs) were estimated using cloning, censoring, weighting, and pooled logistic regression.

Results

Among 21,466 individuals (median age 79 years; 67.3% women; 86.7% non-cardioembolic stroke), 594 initiated colchicine within 6 months. The 5-year risk of MACE was 12.5% (95% CI 10.6–13.9) under colchicine initiation versus 18.4% (17.7–19.0) under no colchicine initiation (absolute risk difference −5.9%, 95% CI −7.9 to −4.4). Consistent risk reductions were estimated for each individual component of MACE. No increase in non-cardiovascular or all-cause mortality was estimated.

Discussion / Conclusion

In this nationwide study of patients with gout, colchicine use after ischemic stroke was associated with reduced cardiovascular risk without excess mortality, supporting a favorable benefit–risk profile in selected patients with high cardiovascular risk (6). These findings reinforce the rationale for anti-inflammatory drug repurposing in cerebrovascular disease and highlight the need for dedicated randomized trials to confirm efficacy and safety in post-stroke populations.

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Keywords

Colchicine, ischemic stroke, secondary prevention, mortality, SNDS, target trial emulation.

00152
Real-World Utilization of Acute Treatments for Cluster Headache: Insights from the French National Open Health Data

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The utilization of open health databases offers a unique opportunity to analyze the dispensing of healthcare products within real-world populations. A recent study by Van Obberghen et al. (2025) was the first to leverage the French national database to examine consumption volumes for cluster headache (CH) treatments, with a specific focus on the sex ratio. Nonetheless, further investigation into additional variables—such as seasonality and geographical distribution—is warranted, given the well-established role of chronobiology in the pathophysiology of CH.

Materials and methods

A retrospective analysis was conducted using the French national health database (2014–2024). We extracted dispensing records for subcutaneous sumatriptan (SS) and oxygen therapy (OT), the two validated acute treatments for CH. These patterns were analyzed across demographic groups and administrative regions, with statistical correlations performed against climatic (sunshine, rainfall), demographic, and economic variables.

Results

Between 2014 and 2024, the total expenditure for OT in CH tripled, while SS costs increased only 1.6-fold. A consistent decrease in the male-to-female sex ratio was observed across all age groups for both treatments. This decline was statistically significant in all three age groups over 20 years of age for OT delivery, and in the two age groups between 20 and 59 years for SS delivery. A distinct peak in SS dispensing was observed in July; however, no statistically significant associations were found between SS dispensing and sunshine or rainfall. Younger men exhibited significantly higher consumption than older men, and overall consumption remained higher in men than in women.

Discussion / Conclusion

Our findings highlight evolving treatment patterns and a shifting sex ratio in the delivery of CH therapies among treated patients. While no clear environmental drivers of treatment use were identified, the study underscores the value of open health data in monitoring prescribing trends and evaluating the economic impact of CH therapies.

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00159
Immune checkpoint inhibitors and cardiovascular adverse events - A real-world analysis of cardiovascular adverse events in cancer patients treated with immune checkpoint inhibitors

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Immune checkpoint inhibitors (ICIs) significantly improve survival in patients with lung cancer and melanoma but may present immune-related adverse cardiovascular events. To evaluate ICI-associated cardiovascular safety and mortality, we utilized real-world data from two distinct baseline cardiovascular risk models: lung cancer (high risk) and melanoma (lower risk).

Materials and methods

A retrospective cohort study was conducted using the TriNetX network. Patients (≥18 years) recently diagnosed of lung cancer or melanoma receiving ≥4 ICI doses were 1:1 propensity-score matched to a non-ICI chemotherapy control cohort across 15 variables, including cardiovascular comorbidities. The primary endpoints were all-cause mortality and major adverse cardiovascular events (MACE: myocardial

infarction, heart failure, or stroke) at 12 months, evaluated using Kaplan-Meier analyses and Cox proportional hazards models.

Results

Matched cohorts included 7,748 patient pairs with lung cancer and 1,010 pairs with melanoma. At 12 months, ICI therapy was associated with lower all-cause mortality in the lung cancer (hazard ratio [HR], 0.73; 95% confidence interval [CI], 0.68 to 0.79) and melanoma cohorts (HR, 0.50; 95% CI, 0.37 to 0.69). ICI use did not increase the MACE risk in lung cancer (HR, 0.94; 95% CI, 0.84 to 1.04) and was associated with a lower MACE risk in melanoma (HR, 0.59; 95% CI, 0.42 to 0.83). Compared with early discontinuation (<4 doses), receiving ≥4 ICI doses was associated with lower 6-month mortality (lung: HR, 0.10; 95% CI, 0.09 to 0.11; melanoma: HR, 0.04; 95% CI, 0.02 to 0.07) and MACE risk.

Discussion / Conclusion

In this real-world analysis, ICI therapy was associated with a survival benefit and no excess risk of MACE at 12 months, regardless of the underlying baseline cardiovascular risk model. Overall prognosis was closely dependent on early treatment continuation. These data support a biphasic cardiovascular risk hypothesis, characterized by an initial vulnerability phase to acute events, underscoring the necessity for sustained early clinical vigilance.

Keywords

Immune Checkpoint Inhibitors, Major Adverse Cardiovascular Events, Survival Analysis

00161
Clinical, sociodemographic, and socioeconomic factors determinants of Clomiphene Citrate Use and Prevalence Trends: A Scoping Review

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Infertility affects a significant proportion of the global population, and Clomiphene Citrate (CC) has been a cornerstone treatment for ovulation induction (OI) for decades, although its real-world use has evolved across settings. We aimed to review and characterize population-level trends in CC utilization, including clinical, sociodemographic, and socioeconomic profiles, and treatments used with or instead of CC in infertility care.

Materials and methods

We conducted a scoping review following JBI guidance and PRISMA-ScR recommendations. Eligibility was based on the Population, Concept, Context framework and included observational, population-based studies in women of reproductive age reporting CC use. Animal studies, clinical trials, narrative reviews, and papers not in English, French, or Spanish were excluded. We searched PubMed/MEDLINE and Embase, complemented with Google Scholar and grey literature . Data were extracted and synthesized narratively.

Results

The search identified 383 records, of which 28 were included. Most studies were conducted in the United States, France, and Australia . Three periods of CC use were identified: steady increase, stabilization, and decline with rising letrozole use, particularly for PCOS, alongside expansion of medically assisted reproduction. Despite this, CC remains widely used due to low cost and accessibility. Use patterns varied by age and socioeconomic context. CC was most frequent among women aged 30–34 years, while younger women predominated in low- to middle-income countries. PCOS was the main indication, often associated with higher BMI. Combination therapies were common, including CC plus metformin for PCOS and CC with gonadotrophins in resistance. In MAR, CC was often used prior to IUI or IVF. Transition to MAR was more frequent among nulliparous women and those with higher socioeconomic status, whereas financial barriers were linked to early discontinuation.

Discussion / Conclusion

CC utilization has evolved over time, reflecting infertility patterns and treatment availability, underscoring the importance of clinical and socioeconomic contexts in real-world infertility care

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Lisonkova S, Joseph KS. Temporal trends in clomiphene citrate use: a population-based study. Fertil Steril. 2012 Mar;97(3):639–44.

Keywords

Clomiphene citrate

Ovulation induction

Infertility

Trends

PCOS

00162
Adverse pregnancy outcomes after maternal exposure to Clomiphene citrate: Comparative study in a French population-based-cohort

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Clomiphene citrate (CC) is widely used for infertility, particularly in women with anovulatory disorders. Although generally considered safe, animal studies and clinical reports have raised concerns about potential adverse effects on pre- and postimplantation embryo development. Pharmacovigilance reports have also described congenital malformations in children exposed in utero following accidental intake of CC during early pregnancy. We aimed to (1) describe trends in CC and other fertility medication use over time and (2) evaluate the association between CC exposure and adverse pregnancy outcomes according to timing of exposure.

Materials and methods

We conducted a population-based cohort study using the French EFEMERIS database (Haute-Garonne, 2004–2023), including over 190 000 pregnancies with detailed records of dispensed medications. Pregnancies were classified into three groups: (1) exposure to CC during pregnancy (at least one dispensing after conception), (2) exposure to CC before pregnancy only, and (3) no exposure to fertility medications (reference group). Outcomes included multiple pregnancy, miscarriage, medical termination, major congenital malformations, preterm birth, and low birth weight. Crude and adjusted ORs with 95% CIs were estimated.

Results

CC dispensing decreased from 1.5% in 2005 to 0.75% recently. Among 2457 CC-exposed pregnancies (1.24%), 720 were exposed during pregnancy. Compared with unexposed pregnancies, exposure during pregnancy was associated with higher risks of multiple pregnancy (adjOR 2.53; 95% CI 1.72–3.73), preterm birth (adjOR 1.69; 95% CI 1.30–2.20), and low birth weight (adjOR 1.94; 95% CI 1.48–2.54). No significant differences were observed when comparing exposure during versus before pregnancy for miscarriage, multiple pregnancy, preterm birth, or low birth weight. No increased risk of major congenital malformations was observed in any group.

Discussion / Conclusion

CC use declined over time while gonadotrophin-based protocols increased. No increased risk of major congenital malformations was observed in any group. Higher odds of adverse outcomes may reflect underlying infertility rather than a direct drug effect.

Keywords

Clomiphene citrate

Infertility

Pregnancy outcomes

Congenital malformations

Preterm birth

Low birth weight

Multiple pregnancy

Fertility drugs

00165
TENS in chronic pain management: an 11-year nationwide analysis using the French National Health Data System

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Almost one in five people worldwide suffer from chronic pain, which frequently results in polypharmacy. Transcutaneous electrical nerve stimulation (TENS) is a non-pharmacological treatment that may lessen medication burden and improve outctomes. Despite being prescribed frequently, there is still a lack of population-level data on TENS's actual use.

Materials and methods

To characterize trends in TENS use for chronic pain between 2014 and 2024, we conducted a nationwide retrospective study using the French National Health Data System (Open LPP database). Outcomes included the number of patients renting and subsequently purchasing a TENS device following a maximum six-month rental period, associated expenditures, and the purchase-to-rental patient ratio (P/R ratio), used as a proxy for adherence. Analyses were stratified by age group and sex.

Results

Between 2014 and 2024, TENS was initiated, through rental, in 1.5 times more patients (from 91,709 to 158,947). The number of patients who purchased a TENS device after this rental period also increased 2.4-fold, from 17,362 to 41,784. The mean rental duration prior to purchase was 5.7 months. The majority of patients (approximately 50%) were aged 40–59 years. For both rentals and purchases, the male-to-female ratio declined steadily over time ($p < 0.05$), indicating a progressive feminization of use. The overall purchase-to-rental (P/R) ratio was 22.7%, consistently higher among women (23.3%) than men (21.3%, $p < 0.001$), and varied significantly across age groups (lowest in patients <19 years: 15.2%; highest in those aged 40–59 years: 25.4%). Over the study period, the P/R ratio increased from 18.9% in 2014 to 26.3% in 2024.

Discussion / Conclusion

This real-world data analysis demonstrates a favorable trend in the prescription and use of TENS. Adherence beyond the trial rental period remains low, particularly among patients under 20 years of age, but has shown continuous improvement over time, most notably among women.

00172
Causal Language used in Titles and Abstracts of Target Trial Emulation Studies

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Target trial emulation (TTE) aims to strengthen causal inference from observational data when randomized clinical trials are not feasible. However, recent work has highlighted the heterogeneity of the robustness of studies self-defined as TTE (1-2), resulting in varying degrees of certainty about causal relationships. This study aimed to evaluate the strength of causal language in a sample of self-defined TTEs, and its association with their risk of bias and with the statistical significance of study results.

Materials and methods

We evaluated the strength of causal language in the titles and abstract conclusions from a sample of TTE studies included in a previously published systematic review (3). Causal language was independently assessed by two reviewer groups using the CLAIMS tool and classified as strong, moderate, or weak, with discrepancies

resolved by consensus. The risk of bias was assessed with the ROBINS-I tool and obtained from the original review. Associations between strength of causal language and risk of bias and study statistical significance were assessed using Spearman correlation.

Results

Of the 100 studies included in the original systematic review, 89 were eligible for analysis. After consensus, causal language was classified as strong in 27 studies (30%), moderate in 26 (29%), and weak in 36 (41%). The weighted kappa coefficient for inter-reviewer agreement was 0.54 (0.37-0.71). The strength of causal language was not significantly associated with the risk of bias (ρ=0.075, p=0.487) or with study statistical significance (ρ=0.185, p=0.082).

Discussion / Conclusion

Although a majority of TTEs used moderate to strong causal language, we did not observe a statistically significant association between the strength of causal language and study rigor. These findings suggest that causal language may not systematically reflect methodological quality. Greater caution in the use of causal language and stricter adherence to the TTE framework (4) are warranted as real-world evidence increasingly informs clinical and regulatory decision-making (5).

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Keywords

causality, emulated target trial, review

00189
Neurodevelopmental disorders in infants treated with anti–VEGF agents vs. laser photocoagulation or cryotherapy for ROP

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Objective: To compare the incidence of early neurodevelopmental disorders in very preterm infants treated with intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents versus laser photocoagulation and/or cryotherapy for retinopathy of prematurity (ROP).

Materials and methods

Design: Nationwide population-based retrospective cohort study.

Participants: All very preterm newborns (gestational age <32 weeks) born in France between 2013 and 2023 who received treatment for ROP with anti-VEGF agents, laser photocoagulation, or cryotherapy within the first 8 weeks of life.

Methods: Using the French National Health Data System (SNDS), a medico-administrative database, we compared the incidence of early neurodevelopmental disorders between newborns treated with anti-VEGF agents and those treated with laser photocoagulation and/or cryotherapy, applying a propensity score-weighted logistic regression model with inverse probability of treatment weighting.

Main Outcome Measures: Incidence of early neurodevelopmental disorders within the first six years of life.

Results

The number of infants treated with anti-VEGF agents increased by 875% from 2013 to 2023. The primary comparative analysis was conducted on 101 newborns born between 2013 and 2018, for whom mother–infant linkage was available in the SNDS: 44 treated with anti-VEGF agents, and 57 with laser and/or cryotherapy. Early neurodevelopmental disorders within the first six years of life were observed more frequently in infants treated with anti-VEGF agents than in those treated with laser and/or cryotherapy (63.6% vs. 47.4%; odds ratio [OR] 1.8; 95% confidence interval [CI] 1.0–3.1; P = 0.046).

Discussion / Conclusion

Using intravitreal anti-VEGF agents in very preterm newborns may increase the risk of early neurodevelopmental disorders within the first six years of life. While a direct causal relationship cannot be confirmed, these results suggest the need for caution in clinical practice, particularly given the substantial increase in the use of anti-VEGF agents for the treatment of ROP in recent years.

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Keywords

Drug safety, newborns, retinopathy of prematurity, intravitreal drugs, anti-vascular endothelial growth factor (anti-VEGF), neurodevelopment.

00211
GLP-1 Receptor Agonists initiation in recent psychotropic users : a descriptive nationwide cohort study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Psychotropic medications, including antipsychotics and antidepressants, are frequently associated with weight gain and metabolic syndrome. GLP-1 receptor agonists (GLP-1RAs) have demonstrated efficacy in promoting weight loss and reducing cardiovascular risk. However, evidence regarding their efficacy and safety in patients with mental health disorders remain unclear, as these were largely excluded from pivotal clinical trials. This study aims to describe the real-world use of GLP-1RAs in psychotropic recent users in France.

Materials and methods

Using the French National Health Data System nationwide databases (SNDS), we identified prevalent users of psychotropic medications (defined as ≥3 dispensings over the year before index date) who initiated GLP-1RAs (index date) between January 1, 2017, and December 31, 2023. Patients were characterized according to their indication for GLP-1RA treatment (type 2 diabetes mellitus [T2DM], obesity, or neither) and to the therapeutic class of psychotropic they received. One-year

persistence trajectories of monthly GLP-1RA dispensings were analysed using Group-Based Trajectory Modelling (GBTM).

Results

In this nationwide cohort of more than 100,000 patients initiating GLP-1RAs and prevalent to psychotropic, T2DM was the most frequent indication identified (95%). Anxiolytics/hypnotics (> 66%), antidepressants (50%), and antipsychotics (> 15%) were the most frequently dispensed psychotropics. Less than 5% of patients had neither T2DM nor obesity identified. The predominant trajectory of GLP-1RA use over one year (>60% of patients) was reflecting both high-adherence and prolonged persistence. Early disruption concerned 11% of patients ; they were less likely to have T2DM (80%) and more likely to have used antiemetics (8%).

Discussion / Conclusion

In France, GLP-1RA use among prevalent psychotropic users was primarily related to T2DM, regardless of psychotropic class. Limited evidence was found supporting an off-label use for psychotropic-induced weight gain. The most represented trajectories suggested prolonged persistence, mostly with high adherence. These findings suggest a predominantly appropriate use of GLP-1RAs in patients treated for mental disorders.

Keywords

GLP-1 Receptor Agonists, Type 2 Diabetes Mellitus, Obesity, Psychiatry, Metabolic Syndrome

00225
Use and Potential Misuse of Glucagon-Like Peptide-1 Receptor Agonists Identified Through a Hospital Health Data Warehouse

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The rapid expansion of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) has raised concerns about appropriate prescribing[1]. Hospital Data Warehouses (HDWs), integrating structured data and clinical narratives, enable more accurate assessment of prescription indications [2]. We aimed to evaluate the use and potential misuse of GLP-1 RAs using the Clinical Data Warehouse (CDW) of Bordeaux University Hospital.

Materials and methods

We conducted a retrospective cohort study including all patients having a prescription of GLP-1 RAs or a mention of treatment by GLP-1 RAs recorded in the CDW between 2014 and 2023. An algorithm combining structured data (diagnosis codes, anthropometric measures) and information extracted from clinical notes using a large language model was developed to identify the approved indication of GLP-1 RAs: type 2 diabetes, obesity, and overweight with comorbidity. A random sample of 380 medical records was manually reviewed to establish a reference standard and evaluate the performance of this algorithm.

Results

A total of 11,354 patients, accounting for 32,615 GLP-1 RA–exposed visits, were included (52.5% hospital stays and 47.4% outpatient care). The algorithm demonstrated high performance in identifying type 2 diabetes (F1-score: 0.94) and obesity (0.92), but lower performance in identifying overweight individuals with comorbidities (0.48). Across visits, type 2 diabetes was identified in 94.1%, obesity in 75.2%, and overweight with comorbidity in 13.8%. No approved indication was identified in 1.3% of visits. This occurred more frequently in outpatient care than in hospital stays. Among those hospital stays without an approved indication, 37% were related to type 1 diabetes.

Discussion / Conclusion

In this hospital-based cohort, GLP-1 RA use was largely consistent with approved indications. The low proportion of visits without an identified indication does not suggest widespread misuse. However, the presence of type 1 diabetes among exposed patients warrants further investigation. HDWs combined with natural language processing provide a robust framework for real-world pharmacoepidemiological surveillance.

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Keywords

glucagon-like peptide 1 agonists, off-label use, hospital data warehouse

00227
Changes in renal function after initiation of ARNI: A multicenter retrospective study of concomitant diuretics, NSAIDs, and PPIs

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Few previous studies have examined renal function decline associated with angiotensin receptor neprilysin inhibitor (ARNI), including the “triple whammy” with diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs). Long-term use of proton pump inhibitors (PPIs) increases the risk of progressive chronic kidney disease. We conducted a multicenter retrospective study to investigate the effect of the concomitant use of ARNI, diuretics, NSAIDs, and PPIs on renal function decline.

Materials and methods

Patients were classified into the following groups: ARNI alone, ARNI + diuretics, ARNI + NSAIDs, and ARNI + diuretics + NSAIDs. Changes in estimated glomerular filtration rate indexed to body surface area (eGFR, mL/min/1.73 m²) and body surface area–adjusted eGFR (BSA-adjusted eGFR, mL/min) were assessed before and after ARNI initiation. Multivariable logistic regression was performed to identify factors associated with renal function decline.

Results

A total of 547 patients were included. No significant decrease in eGFR (mL/min/1.73 m²) was observed in any group. BSA-adjusted eGFR (mL/min) showed a V-shaped pattern across all groups, with the lowest values occurring within 30 days of ARNI initiation. No significant difference was observed in PPI use in the triple-whammy group. Pre-ARNI eGFR ≥ 60 mL/min/1.73 m² (adjusted odds ratio [aOR] 4.23, 95% confidence interval [CI] 1.71–10.46; $p = 0.002$) and concomitant diuretic use (aOR 3.15, 95% CI 1.15–8.64; $p = 0.026$) were associated with renal function decline.

Discussion / Conclusion

A transient decrease in BSA-adjusted eGFR was observed in the early phase after ARNI therapy initiation. Patients with pre-ARNI eGFR ≥ 60 mL/min/1.73 m² and those receiving concomitant diuretics were identified as significant associated factors, suggesting the need for careful renal monitoring after ARNI initiation.

Keywords

angiotensin receptor neprilysin inhibitor, diuretics, non-steroidal anti-inflammatory drugs, proton pomp inhibitor, triple whammy, chronic kidney disease

00251
Proton Pump Inhibitors Reduce Upper Gastrointestinal Bleeding in Hemodialysis Patients Initiating Oral Anticoagulation: A Target Trial Emulation

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Patients on hemodialysis are at high risk of upper gastrointestinal bleeding (UGIB), particularly when receiving oral anticoagulants. However, evidence supporting preventive strategies is scarce. Although proton pump inhibitors (PPIs) are widely used in this population, their effectiveness has not been confirmed. Using data from the French national REIN registry, we emulated a target trial to determine whether or not PPIs reduce the risk of UGIB events in chronic hemodialysis patients initiating both a PPI and an oral anticoagulant.

Materials and methods

Data on patients receiving dialysis were extracted from the REIN registry and linked to the French national health database. Adults on hemodialysis having initiated an oral anticoagulant between 2012 and 2023 were eligible. The primary outcome was the first UGIB event, using the relevant ICD-10 hospital discharge diagnosis codes. The risk of UGIB in PPI users versus non-PPI users was calculated using inverse

probability of treatment weighting (IPTW) and cause-specific Cox proportional hazards model.

Results

Of the 8,205 hemodialysis patients who initiated an oral anticoagulant and did not have a PPI reimbursement in the preceding 3 months, 7,503 were included in the study. Of these, 2,323 initiated PPI therapy on the same day as anticoagulant initiation. Over a median follow-up of 1 year, 145 patients had a first UGIB event. After IPTW, the risk of UGIB was significantly lower among PPI users than among non-PPI users (weighted hazard ratio = 0·62 [95% confidence interval, 0·41-0·95]). The results of subgroup/sensitivity analyses (albeit underpowered) were consistent with the main findings.

Discussion / Conclusion

Our results suggest that PPIs are associated with a lower risk of UGIB after initiation of oral anticoagulation for the first time in patients on hemodialysis. Although our findings support the protective gastrointestinal effect of PPIs in this high-risk population, the potential for serious adverse events should prompt clinicians to regularly re-evaluate PPI prescriptions.

Reference(s)

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Keywords

Chronic kidney disease, Dialysis, Pharmacoepidemiology, Proton pump inhibitors, anticoagulation, bleeding

00260
Antipsychotic treatment patterns in children within one year of initiation: a population-based study in France

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Antipsychotic use in children has increased substantially over recent decades despite limited evidence regarding safety and efficacy in pediatric populations. Understanding longitudinal patterns of antipsychotic use after treatment initiation is essential for benefit-risk assessment. This study aimed to characterize real-world patterns of antipsychotic use in children in France during the first year after treatment initiation.

Materials and methods

We included 357,018 children and adolescents aged 3-17 years with newly dispensed antipsychotic prescriptions (ATC: N05A) recorded in SNDS between 2010 and 2023, using a three-year wash-out period to identify incident users. For each patient, weekly treatment coverage status during the 52-week follow-up period was

derived from dispensation data and modeled using longitudinal k-means clustering (2-8 trajectories). The optimal number of trajectories was determined based on quality criteria, clinical relevance, and size. Analyses were performed separately by age group (3-5, 6-11, and 12-17 years). Factors associated with trajectory membership were identified via logistic regression with the continuation trajectory as reference.

Results

Across age groups, approximately 20% of patients continued treatment throughout the year, while 50% discontinued early after initiation. Approximately one in six patients aged 3-5 years and 6-11 years discontinued shortly after initiation but resumed treatment toward the end of the year, compared to one in ten patients aged 12-17 years. The remaining patients discontinued treatment within months after initiation. Factors strongly associated with different discontinuation trajectories included treatment initiation by general practitioner/pediatrician versus psychiatrist, mental healthcare use suggesting a less severe psychiatric illness (fewer antipsychotic classes prescribed, fewer concomitant psychotropics, no psychiatric hospitalization in the prior year), female sex, and low socioeconomic status.

Discussion / Conclusion

Antipsychotic discontinuation patterns in the first year after initiation are complex and age dependent. Several potentially modifiable factors are strongly associated with different discontinuation patterns, suggesting opportunities for targeted interventions to optimize treatment persistence and quality of care in pediatric populations.

Keywords

Antipsychotics, patterns of use, trajectories, children, adolescents

00264
Sex and Age Differences in Antipsychotic Use Among Children: A Nationwide Study in France

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Sex differences in antipsychotic (AP) use have been reported in adults, but data for children and adolescents are scarce.

Trends and patterns of AP use in children and adolescents by sex and age over a 15-year period in France.

Materials and methods

We included all children aged 3-17 years with at least one AP (ATC: N05A) dispensing recorded in the national health data system (SNDS) from 2010 to 2024. Incident users were defined after a three-year washout period. Per calendar year, we assessed AP users' sex, age, concomitant psychotropic treatment and psychiatric diagnoses from hospital discharge records. Joinpoint analysis estimated the average yearly change over the study period for each sex-age group.

Results

A total of 381,273 pediatric AP users were identified; 41% were girls and 59% were boys. Mean (SD) age of incident users was 13.7 (±3.2) years for girls and 11.6 (±3.9) years for boys.

In girls 3-5 years, prevalence of AP use increased by 3.0%/year [95%CI: 2;3.8%]) and incidence by 2.3% [0.6;3.9%]. In boys 3-5 years, prevalence rose by 4.0%/year [3.3;4.5%]) and incidence by 3.6% [2.8;4.4%]. Concomitant psychotropic use reached 19% in 2024. Main diagnosis remained autism over the years.

In girls 6-11 years, prevalence increased by 5%/year [4.7;5.4%] and incidence by 3.7% [3.2;4.4%]. In boys 6-11 years, prevalence rose by 4.8%/year [4.6;5%] and incidence by 3.6% [2.8;4.3%]. Concomitant psychotropic use reached 37.9-41.1%. Main diagnosis remained anxiety disorders in girls, in boys it shifted from autism to ADHD.

In girls 12-17 years, prevalence increased by 9%/year [8.2;9.6%] and by 7.6% [6;8.8%]. In boys 12-17 years, prevalence rose by 3.5%/year [3.2;3.7%] and incidence by 0.7% [-0.1;1.4%]. Concomitant psychotropic use in children reached 46.7-65.4%. Main diagnosis shifted from mood disorders to anxiety disorders.

Discussion / Conclusion

This study shows a substantial increase in antipsychotic prescribing and a shift in the AP prescription, particularly among adolescent girls.

Keywords

Antipsychotics, drug utilization study, children, adolescents

00266
Impact of the Initiation of Medical Cannabis on Healthcare Utilization in France

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

In 2021, the French Medicine Agency (ANSM) launched a nationwide pilot program on medical cannabis to evaluate access pathways and to collect real-world data on efficacy and safety. In this study, we aimed to evaluate, the early impact of medical cannabis initiation on healthcare utilization.

Materials and methods

We conducted a cohort study including participants enrolled in the French medical cannabis experiment registry (ReCann) between March 2021, and September 2023 matched to the French National Health Data System (SNDS). Monthly indicators were assessed during the year before and the six months after cannabis initiation,

focusing on the use of alternative medications and non-drug therapies according to indication. Interrupted time series analyses were performed to assess changes in healthcare utilization when sample sizes allowed.

Results

Among 1,971 patients (median age was 56 years (IQR: 47–67) ;54% women), most were treated for refractory neuropathic pain (56.1%); other indications included painful spasticity (17.6%), palliative situations (10.9%), refractory oncology symptoms (7.9%), and refractory epilepsy (7.6%). Persistence declined over time, with 54.8% remaining on cannabis treatment at six months, varying by indication. A small but statistically significant reduction in analgesic use was observed in patients treated for refractory neuropathic pain, palliative care situations, refractory oncology symptoms (respectively -40.2, -239.1 and -119.8 patients per 1,000 treated patients). A slight but significant decrease in benzodiazepine use was noted among patients with refractory neuropathic pain (-16.5 patients per 1,000 treated patients). Reductions in non-pharmacological care were not statistically significant.

Discussion / Conclusion

Initiation of medical cannabis in France was associated with modest changes in healthcare utilization, particularly reduced use of some concomitant medications. Given the limited sample size and modest effects size, findings should be interpreted cautiously but align the pilot program evaluations (1) and existing meta-analyses on medical cannabis (2-3).

Reference(s)

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Keywords

cannabis, experimentation, SNDS, heathcare utilization, impact

00271
PATHS - Pulmonary Arterial Hypertension Trajectory Study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Pulmonary Arterial Hypertension (PAH) is a rare and serious condition. Half of PAH cases are idiopathic, the others are hereditary, associated with diseases, or some drugs and toxins exposures. The median time between first symptoms and final diagnosis is around 2-3 years, due to non-specific symptoms. Descriptions using registries data have been published, particularly in France, but longitudinal data on drug exposure and healthcare consumption prior to diagnosis are not available.

Materials and methods

Our main objective was to describe patient characteristics, medical history and medication consumption prior to PAH diagnosis, based on data from the French National Healthcare Database. A cohort of French adults diagnosed with PAH after 2009 was established using a validated algorithm (1). Comorbidities, exposure to specific drugs, general and specialist medical care were documented. Data were extracted from 2006 to 2024.

Results

The final cohort included 9964 patients, 50,3% of whom were women. The median age at diagnosis was 67 years. Around 550 patients were exposed to at least one of the 12 identifiable drugs prior to diagnosis. Duration of exposure ranged from several days for mitomycin to several years for dasatinib. In the 3 years period prior to

diagnosis, the most frequently consulted physicians were general practitioners, followed by cardiologists. Only 50-55% of patients consulted a pulmonologist. Regarding the steps of diagnosis, 46% of patients underwent a RHC intervention at the same time as hospitalization. Among all patients, 68% appear to have consulted one of the 29 French center of expertise for the diagnosis steps.

Discussion / Conclusion

A description of medication use, the care pathway and the stages of diagnosis for patients with PAH is necessary to improve and reduce the time taken to treat them.

Keywords

PAH

Trajectory

SNDS

00273
Intermittent anti-HIV treatment combination, from the French National Healthcare Database.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Treatment simplification is an important field in HIV care. Studies have evaluated efficacy of antiretroviral therapy (ART) administered 4, 5, or 6 days per week. In 2024, the “4 days a week” treatment strategy featured in the French recommendations for people living with HIV (PLWH) with undetectable viral load. This approach has not yet been incorporated into other countries.

Materials and methods

We aimed to describe ART dispensation evolution over the years, from data of the French National Healthcare database. Treatment of interest were combination of three combined antiretroviral drugs. Patients, must have had at least 3 dispensations of the same tritherapy, within a rolling year. ART were searched on ambulatory and hospital dispensations . Patients were classified into three groups: >11, 7–11, and <7 dispensations. >11 corresponded to monthly delivery (likely 7 days/week), and 7–11 to a likely 4–6 days/week schedule. Selected patients were described at two timepoints: 31.12.2015 and 31.12.2023.

Results

In the database, 111,736 adults met the inclusion criteria. Proportion of patients in each category changed over the years. In 2023, most PLWH appeared to receive daily ART. However, this proportion declined since 2012 (99% to 55%), alongside an increase in the number of patients receiving fewer dispensing (1% to 40%). Between 2015 and 2023, the distribution of men shifted slightly, with a higher proportion receiving simplified ART recently. However, the proportion remained lower in the 7–11 group than in the >11 group. In 2015, 20% of patients in the reduced group were receiving other chronic medication, compared with 27% in the group with > 11 dispensations. Furthermore, the mean number of distinct medications per patient was lower in the first category than in the second. These differences remained stable in 2023.

Discussion / Conclusion

In France, over the years, there is a change in dispensation patterns of combined ART, towards a treatment simplification.

Keywords

HIV

treatment simplication

ART

SNDS

00290
Impact of secure prescription requirements for tramadol and codeine-based analgesics on prescribing patterns in primary care

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Since March 1, 2025, following a decision by the ANSM, tramadol- and codeine-containing analgesics have been subject to secure prescription requirements in France, aiming to curb the rising rates of misuse and dependence. We aimed to evaluate changes in outpatient prescribing patterns for these medications following the new regulation, and to assess potential substitution effects on other analgesics.

Materials and methods

Using the Medic'AM database from the French National Health Insurance, which publishes monthly dispensing and reimbursement data for all marketed drugs in community pharmacies, we extracted data from January 2024 to November 2025 for the main analgesics, identified by their ATC codes. Temporal trends were analysed through a comparison of pre- versus post-regulation prescribing.

Results

Tramadol-containing analgesics showed a marked decline after March 1, 2025, with mean monthly reimbursed boxes decreasing from 1,793,791 to 1,339,826 (-25.31%). Codeine-based products similarly decreased from 2,173,022 to 1,667,053 boxes/month (-23.28%). Conversely, analgesics combining opium powder with paracetamol (Izalgi®, Lamaline®) increased by 11.20% (1,854,196 vs. 2,061,851 boxes/month). Prescribed paracetamol decreased by 9.98% (30,582,519 vs. 27,530,097 boxes/month). Step 3 opioids (morphine, oxycodone, fentanyl) remained stable (+0.81%; 1,150,932 vs. 1,160,213 boxes/month). Nefopam injectable forms declined sharply with mean monthly reimbursed boxes falling from 861,452 to 422,978 (−50.9%). The oral form (introduced mid-2024) rose to 451,346 boxes/month. When expressed in grams of active substance delivered, total nefopam dispensing increased by +227% (137 kg vs. 449 kg/month).

Discussion / Conclusion

The implementation of secure prescription requirements for tramadol and codeine was associated with a substantial reduction in their community dispensing. This was accompanied by a partial prescribing shift toward opium powder-paracetamol combinations and oral nefopam, while step 3 opioid prescribing remained stable. The next step will be to conduct these comparisons using defined daily doses (DDDs) rather than box counts, allowing for a more precise interpretation of the magnitude of substitution effects.

Reference(s)

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00291
Trends and characteristics of opioids use during pregnancy between 2010 and 2023: a French nation-wide drug utilization study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

While opioid use during pregnancy has raised increasing concerns worldwide, population-based data in Europe remain limited. In France, little is known about opioids use in pregnancy setting.ttention and ongoing monitoring.

Materials and methods

We conducted a nationwide drug utilization study using the French EPI-MERES Registry, derived from the National Health Data System (SNDS), including all pregnancies ≥22 weeks from 2010 to 2023. Exposure to weak and strong opioids was assessed before, during, and after pregnancy. Exposure modalities (number of filled prescriptions, prescriber type, oral morphine equivalent doses) were examined. Maternal sociodemographic and clinical characteristics associated with exposure were analysed using multivariable logistic regression.016, the continuous rise in tramadol use warrants further a

Results

Among 9.9 million pregnancies, 548,881 (5.5%) were exposed to weak opioids and 12,501 (0.13%) to strong opioids. Weak opioid exposure increased sharply until 2016 (+120%) before stabilising, with diverging trends thereafter: codeine use declined while tramadol continued to rise (+170% during study period; 2.5% of exposure in 2023). Through pregnancy, exposure strongly decreased after conception, with most exposures during the first trimester, regardless of calendar year or opioid type,. Opioid exposure was positively associated with maternal socioeconomic deprivation, chronic somatic diseases, psychiatric disorders. Associations were stronger with strong opioids than those observed with weak opioids.

Discussion / Conclusion

In France, opioid use in pregnancy setting is not infrequent and almost exclusively driven by weak opioids. Use is largely short-term, and associated with maternal vulnerability and low-income status. Although overall exposure increased and stabilized since 2

Keywords

maternal health, opioid, codeine, tramadol, pregnancy, drug utilization study

00300
Changes in durations of psychotropic treatment in the French young: a further impact of the COVID-19 pandemic

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Mental health of children, adolescents, and young adults deteriorated during the COVID-19 pandemic. The corresponding changes in the use of antidepressants, anxiolytics, and hypnotics remain poorly documented. We aimed to examine trends in psychotropic treatment initiations and duration among young French people between 2013 and 2024.

Materials and methods

We conducted a nationwide cohort study using the French SNDS databases. All individuals aged 12–30 years initiating antidepressants, anxiolytics, or hypnotics between 2013 and 2024 were included. Monthly trends in initiations and durations were estimated using seasonal-trend decomposition and indexed to 2013 (baseline).

Treatments were categorized by duration (≤1 month, 1–3 months, 3–6 months, >6 months). Analyses were stratified by age, sex, and medication class.

Results

Overall, 6,912,898 psychotropic initiators were identified over the study period. Across classes, initiations were stable before 2020 and increased thereafter across most age and sex groups. Psychotropic treatment durations changed markedly and durably after the pandemic, particularly for antidepressants. Among adolescents aged 12–18y, the proportion of short treatment (<1 month) declined from ~50% in 2013–2018 to 35% in girls and 40% in boys by 2024; prolonged episodes (>6 months) concomitantly increased from 20% to 35% in girls aged 12–15, from 20% to 30% in those aged 16–18 (both sexes), and from 20% to 25% in 19-25. For hypnotics, short episodes declined over 2020–2024 (80% to 65% in ages 12–15; 75% to 70% in ages 16–18), with parallel increases in 3–6 and >6-month episodes (5% to 10–15%). Benzodiazepine anxiolytic use showed similar trends among girls aged 12–18 but remained stable in adults aged 26–30.

Discussion / Conclusion

The sustained rise in initiations through 2024, coupled with longer treatment episodes, likely reflects persisting increased treatment needs; it could also mark an improved alignment with clinical guidelines.

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Keywords

Mental health, COVID-19, Children and adolescents, Young adults, Antidepressants, Anxiolytics, Hypnotics, France

00349
Early impact of the March 2025 French regulatory measure on tramacol/codeine prescription: a nationwide SNDS interrupted time-series analysis

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

On 1 March 2025, the French medicines agency (ANSM) implemented secured prescription forms and a maximum 3-month supply for tramadol and codeine. We performed a 6-month evaluation of the impact of this measure on tramadol/codeine prescription.

Materials and methods

Using the French national health data system (SNDS), we built monthly series (01/01/2022-30/09/2025) of prevalent users and incident users (no dispensing in the previous 6 months) of tramadol, codeine and opium combinations. Segmented interrupted time-series regression estimated 6-month post-measure level and trend

changes, comparing observed values with counterfactuals extrapolated from pre-intervention trends. In a cohort of chronic tramadol/codeine users identified in February 2025, we described 0-3-month trajectories (persistence, discontinuation, or switch to other opioids or non-opioid analgesics, focusing on oral nefopam).

Results

Before the measure, tramadol prevalence was already decreasing (-0.5%/month), codeine was stable, and opium slightly increasing (+0.2%/month). In March 2025, level changes *vs* counterfactual were -25% (tramadol), -34% (codeine) and +18% (opium; all p<0.0001). Thereafter, tramadol and codeine declined faster (-3.8% and -2.6%/month), while opium continued to rise without significant slope change. By September 2025 *vs* September 2024, patients with ≥1 dispensing fell ≈53% for tramadol (814,415 to 383,226) and codeine (686,068 to 324,705). Incident use fell markedly: tramadol and codeine primoprescriptions decreased 71% and 58%, whereas opium initiations increased 73% in the first 6 months. Nefopam dispensings more than doubled (+103%) with an additional +20% immediate level increase. Among 733,173 chronic tramadol/codeine users, 80% maintained these opioids, 3.5% stopped analgesics, ≈7% switched to paracetamol, ≈3% to opium, and <1% to morphine.

Discussion / Conclusion

This 6-month evaluation shows a marked reduction in tramadol/codeine exposure and initiations after the March 2025 ANSM measure, with partial substitution towards opium and, more prominently, oral nefopam, and no signal of a shift towards strong opioids. Longer follow-up is needed to assess the durability and clinical consequences of these changes.

Keywords

opioid analgesics; tramadol; codeine; nefopam; SNDS; regulatory measure;

00366
Signal detection of adverse events associated with PCSK9 inhibitors: a sequence symmetry and disproportionality analysis

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Evolocumab and alirocumab are the two monoclonal antibodies targeting the Proprotein convertase subtilisin/kexin type 9 (PCSK9) used in the treatment of dyslipidemia and cardiovascular prevention marketed in France. The recency of their launch and the fast increase of their use are two strong arguments for evaluating their safety in real-world setting.

Materials and methods

A sequence symmetry analysis (SSA) was conducted using the French nationwide health system databases (SNDS); PCSK9 inhibitor (PCSK9i) initiators were matched to ezetimibe ones in order to control for temporal trends and potential remaining indication bias relating to drug initiation. Outcomes of interest included all Designated Medical Events (DMEs) by the European Medicines Agency and all drug classes grouped by Anatomical Therapeutic Chemical (ATC) classification levels III and IV[AH1] [AP2] . Asymmetry in the distribution of each investigated outcome occurring before and after the initiation of the studied therapy was used to detect potential

safety signals for PCSK9i. These were defined as the combination of both a crude and an ezetimibe-adjusted sequence ratios (SRc; SRa) with 95%CI lower limit exceeding 1. Disproportionality analyses were performed in the WHO pharmacovigilance database VigiBase® to complete the assessment.

Results

In total, sequence symmetries could be studied for 36,163 PCSK9i initiators and 34,269 ezetimibe ones. Over the 700 outcomes analyzed, two potential signals were identified via SSA, that related to inhaled glucocorticoids (SRa=1.19 [1.06–1.35]) and colony stimulating factors initiations (SRa=2.25 [1.37–4.17]); both signals were duplicated at the corresponding ATC levels III. No equivalent signal was detected in VigiBase®.

Discussion / Conclusion

In this large real-world assessment considering nearly 700 outcomes, no credible potential new safety signals were detected for PCSK9 inhibitors. The two potential signals identified were likely to relate to residual indication bias or confounding despite the use of an active comparator group, underlining the persistent challenge of constructing fully adequate reference groups for last-line treatments.

Keywords

PCSK9 inhibitors, sequence symmetry analyses, real-world data, pharmacoepidemiology

00378
OPIO-Trend : Impact of the 2022 guidelines from the French National Authority for Health on the appropriate use of opioid analgesics

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The opioid epidemic has emerged in the USA in the late 1990s. At the European level, several studies performed have highlighted that opioid analgesic use increased substantially, and several proxies for misuse show a parallel increasing trend. In France, addictovigilance information and other data (1-4) lead to national guidelines by health authorities in March 2022 in order to improve use of opioid analgesics and to prevent opioid use disorders and opioid overdoses. This study aimed to assess the impact of these guidelines on the use of opioid analgesics, opioid agonists and naloxone between 2014 and 2025.

Materials and methods

Monthly reimbursement data (Medic'AM database) were used to calculate the monthly number of defined daily dose per thousand inhabitants per day (DID) for all opioids in ambulatory setting, between January 2014 and June 2025. The impact of 2022 guidelines was investigated through interrupted time series analysis (ITS), using Autoregressive Integrated Moving Average (ARIMA) models involving weak and strong opioids, opioid agonist drugs, and naloxone.

Results

There was not significant change in use of weak opioids related to 2022 guidelines (p=0.1), even if there were changes with +16.4 % increase until 2022 (reaching 17.4 DID), then a decrease of 5.8% (13 DID). This trend is related to a decrease in codeine and tramadol use (-30.4% between 2021 and 2025), incompletely compensated by opium increase (+22.6% between 2021 and 2025). No significant change was observed for strong opioids (from 3 DID in January 2014 to 2.5 in June 2025), nor for opioid agonists (3 DID in January 2014 to 3.3 in June 2025). Concerning naloxone, its level of use has remained confidential since it became available.

Discussion / Conclusion

These findings do not suggest any changes in practices observable within three years of the guidelines' diffusion. Efforts still need to be made to promote the use of naloxone.

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Keywords

Opioid analgesic, Opioid agonist, Buprenorphine, Codeine, Fentanyl, Methadone, Morphine, Naloxone, Oxycodone, Opium, Tramadol

00385
Estimating the prevalence of drug poisoning in France: A Capture–Recapture study in a university hospital

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

In France, medication poisonings are not captured through a standardized, comprehensive surveillance system. Published estimates often rely on a single data source, potentially underestimating the true burden. We aimed to estimate the prevalence of medication poisonings (intentional and unintentional) managed at a French university hospital using capture–recapture methods.

Materials and methods

We conducted a retrospective study at Clermont-Ferrand University Hospital (France), 2018-2020, using three independent sources: (i) inpatient hospitalizations with a diagnosis of medication poisoning (ICD10-codes: T36-T50, X40-X44, X60-X64, Y10-Y14), (ii) emergency department visits for medication poisoning (same ICD10-codes), and (iii) laboratory toxicology screening results. Records were cross-matched across sources to quantify overlaps (“recaptures”). Population size was estimated using log-linear capture-recapture modeling; model selection relied on likelihood-based goodness-of-fit and information criteria (AIC/BIC), favoring parsimonious models. Data management and statistical analyses were performed using Python 3.14 and SAS 9.4.

Results

Across the three sources, 2,681 stays were observed. Patients were 60% female; median age was 43 years (IQR 28-56). The overlap structure suggested substantial under-ascertainment in single sources. Depending on the selected log-linear model, the estimated total number of cases over 2018-2020 ranged from 6,175 to 10,043 (model-based uncertainty bounds up to 12,075). Using the Clermont-Ferrand metropolitan population (N=289,817) as denominator, the estimated 3-year prevalence ranged from 2.1% to 3.5%. The most frequently involved drug classes were benzodiazepines (25.5%), Z-drugs (13.8%) and antidepressants (8.4%); Bromazepam (18.2%), diazepam (12.2%), zopiclone (11.5%) and alprazolam (8.4%) were the most frequently identified molecules on toxicological screening and together accounted for 50% of all cases.

Discussion / Conclusion

Capture–recapture using three routine hospital sources provided higher, and likely more realistic, burden estimates than single-source counts, highlighting underreporting/under-capture in routine data. This approach could support harmonized local surveillance in France and guide prevention efforts targeting high-impact psychotropics.

Keywords

drug poisoning; capture-recapture; overdose; toxicology screening; pharmacoepidemiology;

00408
Respiratory Medications and Adequacy of Inhalation Devices in Children Aged 0–12 Years: A Descriptive Longitudinal Study of the POMME Cohort

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Asthma management guidelines recommend using of a valved holding chamber (VHC) with pressurized metered-dose inhalers (pMDIs) in children to ensure optimal drug delivery. Dry powder inhalers (DPIs) and breath-actuated pMDIs are considered appropriate alternatives from the age of six years. This study assessed inhaled medication prescribing patterns and inhalation device adequacy among children aged 0–12 years in the POMME cohort (Haute-Garonne, France).

Materials and methods

We conducted a descriptive longitudinal pharmaco-epidemiological study using anonymized data from the population-based POMME birth cohort (children born between July 1, 2010, and June 30, 2011). Prescriptions for respiratory medications (ATC code R03) and associated inhalation devices were analyzed by inhalation system type and child age. A prescription was considered adequate when a conventional pMDI (without integrated VHC or breath-actuated mechanism) was prescribed concomitantly with a VHC. Adequacy was assessed within three timeframes: within one week (±7 days), within one year before pMDI prescription, and at any time prior to (or up to one week after) pMDI prescription.

Results

Among 8,372 children, 4,957 (59%) received at least one inhaled medication between ages 0 and 12, totaling 71,342 prescriptions. Of 43,766 pMDI prescriptions, VHC co-prescription rates were 20.5% within one week, 45.9% within one year, and 82.7% at least once prior. DPIs and breath-actuated pMDIs represented 2.4% of inhaled prescriptions, with a mean age at prescription of 8 years and 10 months (SD 2 years, 2 months). For first prescriptions, 67.3% included concomitant VHC use, with higher adequacy in preschool children (69.9%) than in school-aged children (32.9%).

Discussion / Conclusion

This study highlights frequent non-adherence to guideline recommendations regarding VHC co-prescription with pMDIs. While two-thirds of initial prescriptions were adequate, overall concomitant prescribing remains suboptimal. Enhanced prescriber education and clearer recommendations on VHC renewal may improve pediatric asthma management.

Keywords

Asthme

Dispositif d'inhalation

Pédiatrie

Prescription

00429
Assessment of safety profile of sclerosing agents: a series of cohort studies in the SNDS

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Venous sclerosing agents are widely used for the treatment of chronic venous insufficiency. In France, three active substances are marketed across four proprietary products, with polidocanol (Aetoxisclerol®) accounting for more than 90% of doses dispensed between 2017 and 2021. Although generally considered safe, sclerotherapy has been associated with rare but potentially serious adverse events, including venous and arterial thromboembolic events, anaphylactic shock, cardiac arrhythmias, neurological and visual disorders, and vasculitis. To date, risk estimates rely mainly on clinical trials and uncontrolled cohorts, and no nationwide real-world comparative study has been conducted.

Objective: To estimate the risk of serious adverse events associated with sclerotherapy for varicose veins in France and to identify associated risk factors.

Materials and methods

We are conducting a retrospective cohort study using reimbursement and hospitalization data from the French National Health Data System (SNDS). Adults (≥18 years) affiliated with the general health insurance scheme, with at least one year of prior data and a preceding venous mapping procedure, will be included at the date of first reimbursed sclerotherapy (CCAM codes). Each exposed patient will be matched to patients exposed to alternative treatments (laser or radiofrequency) using a propensity score. The primary outcome is hospitalization for serious adverse events identified through validated ICD-10 codes (venous and arterial

thromboembolism, anaphylactic shock, arrhythmias, non-ischemic neurological events, vasculitis). Cox proportional hazards models will estimate hazard ratios.

Results

Preliminary analysis showed that in 2023 341 757 different individuals were exposed to sclerosing agents and 47 104 to laser therapy in France. These figures confirm that the power necessary for conducting theses cohort studies will be satisfactory and analyses are ongoing.

Discussion / Conclusion

This large-scale study will provide robust real-world estimates of the relative risk of serious adverse events following sclerotherapy and identify patient- and procedure-related risk factors, thereby informing clinical practice and regulatory decision-making.

00442
Hemorrhagic risk associated with the co-prescription of oral anticoagulants and antidepressants (SSRI/SNRI): a retrospective cohort study using the French National Health Database

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) are widely prescribed antidepressants(1) that impair platelet function by reducing intraplatelet serotonin levels. When combined with oral anticoagulants, this mechanism may result in a synergistic pharmacodynamic interaction, potentially increasing the risk of bleeding(2,3). We aimed to compare the bleeding risk associated with SSRIs or SNRIs versus other antidepressants (i.e., non-SSRI/SNRI) in the French population.

Materials and methods

A retrospective cohort study was conducted using data from the French national health data system (SNDS). We included adults with a first claim of an oral anticoagulant (vitamin-K antagonist [VKA] or direct oral anticoagulant [DOAC]) who initiated an SSRI, SNRI or another class of antidepressant within a 7-day window, between June 30, 2013 and June 30, 2023. The primary outcome was the occurrence of a first major bleeding event. Patients were followed for 180 days. Propensity score-weighted cause-specific Cox regression model was used to

compare the risk of bleeding between SSRI/SNRI users and users of other antidepressants.

Results

A total of 120,593 patients were included (median age [IQR]: 80 [69-87], 41% men), of whom 76,413 initiated an SSRI/SNRI and 44,180 initiated another antidepressant. Overall, 2,100 major bleeding events occurred: 1,342 in the SSRI/SNRI group and 758 in the other antidepressant group. The most frequent bleeding sites were gastrointestinal (31%) and intracranial (18%). After propensity score weighting, bleeding risk was significantly lower among users of other antidepressants compared with SSRI/SNRI users (weighted HR [95% CI]: 0.90 [0.82-0.98]). Results were consistent across sensitivity analyses.

Discussion / Conclusion

Our study is the first to use an active comparator in this population. A propensity score-adjusted Cox model provides a robust methodological approach. Our findings suggest that, among patients initiating oral anticoagulant therapy, antidepressants other than SSRIs or SNRIs may represent a safer option in terms of bleeding risk compared with SSRIs or SNRIs.

Reference(s)

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Keywords

Antidepressants, bleeding risk, oral anticoagulants

00446
Effect of statin discontinuation for primary prevention in the elderly French population

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

In older adults, the benefit of continuing statins for primary prevention has been called into question. In the absence of evidence from randomized controlled trials, our objective was to estimate the causal effect of statin discontinuation on the risk of cardiovascular events in older adults treated in primary prevention using routinely collected data.

Materials and methods

We emulated a sequence of 12 consecutive target trials using the French National Health Data System (SNDS). Individuals aged ≥80 years who were receiving chronic statin treatment and who had no history of atherosclerotic cardiovascular disease, cancer or cognitive disorders were included if they were not hospitalized, institutionalized, or receiving palliative care at the time of cohort entry. Each cohort compared statin discontinuation (no statin dispensed during the baseline month of each emulated trial) to statin continuation (at least one statin dispensed during the baseline month). The outcome of interest was the occurrence of a major cardiovascular outcome (acute coronary syndrome, stroke or coronary revascularization) within two years. Inverse probability weighting was used to adjust

estimates for both confounding and informative censoring. In sensitivity analyses, the intervention was defined as statin discontinuation of at least 3 months.

Results

Among 1,916,746 eligible person-trials (median age 84 years; 68% women), 535,813 discontinued statins. The 2-year risk of major cardiovascular outcome was 3.3% (95% confidence interval: 3.1; 3.4) under statin discontinuation and 3.7% under statin continuation (3.7; 3.8), with an absolute risk difference of -0.5% (-0.7; -0.3). Under statin discontinuation for at least 3 months, the absolute risk difference for was 0.0% (-0.2; 0.2).

Discussion / Conclusion

In this nationwide study of individuals aged 80 years or older without a history of cardiovascular disease, our findings suggest that discontinuation of statins prescribed for primary prevention does not increase the risk of major cardiovascular events.

Keywords

Cardiovascular; Cholesterol; Pharmacoepidemiology; Target Trial Emulation; Database

00451
Drug-drug interactions between androgen receptor pathway inhibitors in prostate cancer and anticoagulants – A disproportionality analysis of the WHO pharmacovigilance database

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Androgen receptor pathway inhibitors (ARPIs) are widely prescribed in prostate cancer, affecting elder patients with frailty and polymedication. However, few data on possible drug-drug interactions (DDI) between ARPIs and anticoagulants are available. The aim of the study was to evaluate potential safety issues related to DDIs between ARPIs and anticoagulants using the real-world data of the World Health Organization (WHO) pharmacovigilance database, Vigibase®.

Materials and methods

Individual case safety reports (ICSRs) with prostate hormonotherapy drugs (ARPIs and/or androgen deprivation therapies) in men over 65 years old were extracted from Vigibase® from inception to March 1, 2025. Haemorrhagic, arterial and venous thromboembolism events were chosen to reflect potential DDIs between ARPIs and

anticoagulants linked to increasing or decreasing anticoagulants' concentrations. We computed information component (IC) for Bayesian method to quantify the disproportionality between groups with its lower end of the 95% credibility interval (IC0.25). The interaction was: adverse drug reaction (ADR) x ARPI x anticoagulant in the design, with control analyses of ADR x ARPI x CYP 3A4 or 2C9 or P-gp strong or moderate inhibitors or inducers.

Results

Bayesian disproportionality analyses did not reveal statistically significant signals. Non-significant trends were observed for arterial thromboembolic events with apalutamide and enzalutamide combined with anti-Xa apixaban or rivaroxaban, and for hemorrhages with darolutamide combined with these anti-Xa agents, and with enzalutamide-edoxaban.

Discussion / Conclusion

Bayesian analyses did not show statistically significant signals, although trends were consistent with known pharmacokinetic mechanisms. Findings are exploratory and underscores the need for careful clinical monitoring and further investigation, particularly in older prostate cancer patients at high risk of bleeding and thromboembolic events.

Keywords

Pharmacovigilance ; drug interactions ; anticoagulants ; prostatic neoplasms ;

00462
Metabolic Adverse Events During Antipsychotic Treatment in the Pediatric Population: A Nationwide Study in France

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Antipsychotic (AP) medications are associated with metabolic adverse effects [1]. This study aimed to identify factors associated with metabolic adverse effects in children.

Materials and methods

We included children aged 6–17 years with at least one AP medication fill after a three-year washout period (incident users) recorded in the French national health data system (SNDS) from 2013 to 2024 [2]. Patients with metabolic conditions before treatment initiation were excluded. The primary outcome was a composite of metabolic adverse effects (diabetes, dyslipidemia, obesity), identified through hospital diagnoses, long-term disease status, and medication fills. Follow-up continued until outcome occurrence, treatment discontinuation, censoring, or study end. Incidence rates were estimated using Kaplan–Meier methods, and risk factors were assessed using multivariable Cox models.

Results

We included 280,662 pediatric incident AP users (43.9% girls, 56.1% boys), with a mean age of 12.92 (±3.24) years. Overall, 1,507 children experienced a metabolic adverse effect, mostly obesity (n=1,003), followed by diabetes (n=340) and dyslipidemia (n=164). Analysis showed higher risk among adolescents (12–17 vs 6–11 years; HR = 1.70 [95% CI 1.23–2.34]; p = 0.001), girls (HR = 1.70 [1.30–2.23]; p < 0.001), those with low socioeconomic status (HR = 1.42 [1.03–1.95]; p = 0.03), and individuals living in socially deprived areas (HR = 1.60 [1.21–2.11]; p < 0.001). Psychiatric severity during follow-up was also associated with increased risk (hospitalization: HR = 1.50 [1.31–1.72]; p < 0.001; chronic condition: HR = 1.47 [1.18–1.83]; p < 0.001), as were treatment features (polypharmacy: HR = 1.48 [1.08–2.03]; p = 0.02; AP switching: HR = 1.44 [1.11–1.88]; p = 0.007).

Discussion / Conclusion

In children, this study shows increased risk of metabolic adverse events after AP prescription in adolescents, girls, socially deprived patients, and those with severe psychiatric conditions.

Reference(s)

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[2] Maillard et al. (2024). Use of the French National Health Data System (SNDS) in pharmacoepidemiology: A systematic review in its maturation phase. Therapie, 79(6):659-669.

Keywords

Antipsychotics; Child and adolescent psychiatry; Metabolic adverse events; Pharmacoepidemiology; SNDS

00498
Epidemiology and Risk Factors of Carbapenem Resistance Among Gram-Negative Pathogens: A Two-Phase Clinical and Microbiological Study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Carbapenem-resistant Gram-negative bacteria (CR-GNB) are a growing threat in hospitals, but data on species-specific resistance and antibiotic exposure patterns are limited.

Materials and methods

We analyzed 46,313 hospitalized patients at the Second Xiangya Hospital in a retrospective cohort study. Antibiotic exposure was quantified by defined daily doses (DDD), length of therapy (LOT), days of therapy (DOT), and days after carbapenem start (DASC). A second phase study (n = 622) used logistic regression and random forest to identify resistance risk factors. Kaplan–Meier curves assessed time to resistance across species.

Results

Of culture-positive patients, 79.4% had Gram-negative infections. Carbapenem-resistant cases were younger (57.6 vs. 65.2 years), more often male (65.5%), and had significantly higher carbapenem exposure ($P < 0.001$). Acinetobacter baumannii

and Klebsiella pneumoniae were more common in resistant cases; Escherichia coli was dominant in susceptible ones. Key resistance risk factors included respiratory infection (OR = 4.27), A. baumannii (OR = 7.13), and carbapenem use (OR = 6.52). Protective factors included E. coli infection (OR = 0.07) and bloodstream infection (OR = 0.36). Higher DDDs (OR = 3.83), LOT (OR = 1.05), DOT (OR = 1.05), and multiple antibiotic use (OR = 2.24) increased risk; exposure to non-carbapenem antibiotics was protective (OR = 0.86). Random forest modeling identified E. coli, A. baumannii, and carbapenem exposure as top predictors. A. baumannii showed earliest resistance onset.

Discussion / Conclusion

CR-GNB resistance is closely tied to pathogen type and antibiotic exposure. Quantitative metrics and predictive models can support early risk identification and antimicrobial stewardship.

00507
Development of a Real-World Derived Gold Standard for High-severity Drug-Drug Interactions and Its Application to the Validation of an Automated Detection Tool

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Identification of potential drug–drug interactions (pDDIs) remains a major challenge in hospital practice, particularly at discharge, where polypharmacy is common. Manual detection is time-consuming and prone to error, while automated tools may provide valuable support for rapid and systematic screening. A critical prerequisite for their development and validation is the availability of robust, expert-derived gold standards. This study aimed to assess the inter-rater reliability of an expert-derived gold standard for high-severity pDDIs based on the ANSM Thesaurus, estimate the prevalence of high-severity pDDIs at hospital discharge, and evaluate its suitability for validating a natural language processing (NLP)-based detection tool.

Materials and methods

A gold standard was constructed from more than 30,000 unique drug pairs extracted from hospital discharge prescriptions of 6,027 patients aged ≥65 years. All prescriptions containing ≥1 medication were included. Independent double annotation was performed by two experts using a standardized decision algorithm, with discordant classifications adjudicated by a third reviewer. Inter-rater agreement was quantified using Gwet's AC1 statistic. The gold standard was then applied to estimate the prevalence of high-severity pDDIs and their association with polypharmacy. Finally, it was used to evaluate the diagnostic performance of the first iteration of an NLP-based detection tool, focusing on sensitivity and negative predictive value (NPV) within a rule-out screening framework.

Results

Inter-rater agreement was very high (Gwet's AC1 = 0.94; 95% CI: 0.94–0.96), remaining robust after exclusion of single-drug prescriptions (0.93; 95% CI: 0.92–0.94). High-severity pDDIs were identified in 9.7% of patients and were significantly associated with the number of prescribed drugs. The NLP-based tool showed a sensitivity of 63.1% and NPV of 96.0%.

Discussion / Conclusion

A reliable expert-derived gold standard for high-severity pDDIs at hospital discharge was established. While NLP-based tools show potential for rule-out screening, their performance remains limited and requires further refinement before routine clinical implementation.

00517
Longitudinal patterns of treatments and comorbidities in Type 2 Diabetes: insights from integrated health data in France between 2015 and 2023

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Type 2 diabetes (T2D) is a chronic condition with multimorbidity. Therapeutic options and strategies evolving quickly. In France, new drugs such as GLP-1 receptor agonists (GLP-1 RAs) and SGLT-2 inhibitors have reshaped treatment guidelines. This study aimed to describe longitudinal treatments, comorbidities, and healthcare resource utilization (HCRU) among adults with T2D in France between 2015 and 2023.

Materials and methods

The OREOT cohort included T2D patients (2015-2018) identified in IQVIA Electronic Medical Records (EMR) and linked to the French National Health Data System (SNDS) [1]. Up to 9-years follow-up, baseline characteristics, longitudinal clinical and biomarkers data, treatment patterns, incident comorbidities, and HCRU were assessed. Treatment trajectories were summarized using state sequence analysis and visualized with index plot and chronogram.

Results

Among 236,305 patients, 57% were male with median age 67 years. At baseline, 77% of patients had hypertension, 62% dyslipidemia, and 57% cardiovascular disease. Over a median 8.7-year follow-up, body mass index and HbA1c remained stable, while renal markers worsened (eGFR -7 mL/min/1.73m²; UACR +32 mg/g). Incident comorbidities were frequent (*e.g.*, 21% cancer; 11% chronic kidney disease). Metformin use declined (from 73% to 65%), while GLP-1 RAs increased (from 5% to 18%), such as SGLT-2 inhibitors (from 0% to 17%), and insulin (from 16% to 22%). Regimen complexity rose slightly, with increases in bitherapy (from 29% to 31%), tritherapy (from 15% to 18%), and quadruple therapy (from 1% to 4%). Care was predominantly in primary care, with limited endocrinology and nephrology involvement. About 20% of patients died during follow-up.

Discussion / Conclusion

Therapeutic patterns shifted toward newer agents and greater combination therapy, yet multimorbidity and renal function decline persisted. Findings emphasize the need for coordinated management and for robust evaluation of the long-term outcomes associated with GLP-1 RAs and SGLT-2 inhibitors. This study illustrates the value of enriched-SNDS for real-world diabetes research in France.

Reference(s)

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Keywords

Type 2 Diabetes, SNDS, Electronic Medical Records, Care Pathways, Treatment patterns

00522
Therapeutic trajectories in type 2 diabetes in France: a cluster-based analysis

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Type 2 diabetes (T2D) management requires complex and evolving treatment strategies. Characterizing real-world therapeutic trajectories may inform personalized care. Using the OREOT cohort, we aimed to build longitudinal treatment pathways among patients with T2D in France between 2015 and 2023 using a cluster-based analysis of drug dispensing.

Materials and methods

The OREOT cohort included patients with T2D (2015-2018) from the IQVIA Electronic Medical Records (EMR) enriched with National Health Data System (SNDS) [1]. During up to 9 years of follow-up, dispensed diabetes drugs were aggregated into discrete 4-month state sequences using state sequence analysis. Pairwise dissimilarities were computed using Optimal Matching, and hierarchical clustering was applied to a representative sample of 10,000 patients. The number of clusters was selected based on Average Silhouette Width and clinical interpretability, and cluster stability was assessed. Baseline characteristics, treatment patterns, and incident outcomes were summarized for each cluster.

Results

Among 231,093 patients, ten clusters were identified, from persistent metformin monotherapy to complex insulin-based regimens. Two GLP-1 RA clusters comprised younger adults (median 60-61 years) with lower all-cause mortality (7.4-10.6%). Several clusters dominated by insulin or glinides and sulfonylureas monotherapies included older adults (median 72-73 years) and had higher mortality (27.1-42.7%). Clusters using combination regimens showed intermediate ages (~66 years) and mortality (15.1-20.3%). Initiation of SGLT-2 inhibitors was lower in clusters with higher CKD prevalence. A large subgroup exhibited prolonged absence of diabetes medication, minimal T2D-related consultations (median 0/year), low long-term disease (~20%), and discordant prescribing and dispensing patterns (75% vs. 33% of patients with ≥1 prescription vs ≥1 dispensation during follow-up).

Discussion / Conclusion

Nationwide clustering of drug dispensing sequences reveals high heterogeneity in T2D therapeutic pathways in France, encompassing older multimorbid patterns, GLP-1 RA–centered regimens in younger profiles, transitions to combination therapies, and a large disengaged subgroup. These findings highlight opportunities for more targeted pharmacological interventions and personalized T2D management.

Reference(s)

[1] Le Goff, R., Brice, S., Contini, A., Boussac, M., Souche, A., Belloc, F., Coulombel, N., Collin, C., Gouverneur, A., Molimard, M., 2025. Successful linkage of electronic medical records and national health data system in type 2 diabetes research: methodological insights and implications. Pharmacoepidemiol. Drug Saf. 34, e70095. https://doi.org/10.1002/pds.70095

Keywords

Type 2 Diabetes, SNDS, EMR, Therapeutic trajectories, State Sequence Analysis, Optimal Matching, Clustering

00524
Hematological Changes Associated with Vancomycin Therapy Duration: A Real-World Longitudinal Analysis Using Linear Mixed-Effects Models

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Vancomycin, a cornerstone glycopeptide antibiotic for serious gram-positive infections, is primarily monitored for nephrotoxicity in therapeutic drug monitoring (TDM) programs. The hematological effects associated with treatment duration remain poorly characterized in real-world clinical settings. We aimed to evaluate time-dependent changes in hematological parameters during vancomycin therapy using a longitudinal statistical approach.

Materials and methods

A retrospective cohort study was conducted using electronic health record data from Chonnam National University Hospital (2021–2025), including 2,855 patients receiving intravenous vancomycin (mean age 65.5 ± 15.7 years; 60.1% male). Serial measurements of white blood cell (WBC) count, hemoglobin, platelet, neutrophil, and eosinophil counts were analyzed alongside MDRD-estimated glomerular filtration rate (eGFR) as a nephrotoxicity reference. Linear mixed-effects models (LMM) were applied with treatment day as the fixed effect and patient as the random-effects

grouping variable, accounting for within-patient correlations across repeated measurements.

Results

Among 26,459 observations from 2,669 treatment episodes, significant time-dependent decreases were observed in WBC count (β = −124.6 cells/μL/day, $p < 0.001$), neutrophil count (β = −133.0 cells/μL/day, $p < 0.001$), and hemoglobin (β = −0.006 g/dL/day, $p < 0.001$). Eosinophil count (β = +3.6 cells/μL/day, $p < 0.001$) and platelet count (β = +687.6 /μL/day, $p < 0.001$) increased significantly. Notably, MDRD eGFR showed no significant change over treatment duration (β = −0.08, $p = 0.306$).

Discussion / Conclusion

Despite vancomycin's established nephrotoxic reputation, renal function was not significantly altered in this cohort, while clinically meaningful hematological changes were consistently observed. Significant leukopenia and neutropenia, alongside eosinophilia indicative of potential drug hypersensitivity, underscore an underappreciated hematotoxic profile of vancomycin. These findings advocate for the incorporation of routine complete blood count (CBC) with differential into vancomycin TDM protocols to enable timely detection and management of hematological adverse effects.

Keywords

vancomycin, hematotoxicity, therapeutic drug monitoring, linear mixed-effects model, leukopenia, pharmacovigilance

00525
Concordance of End-Stage Renal Disease identification between Electronic Medical Records and National Health Data System in patients with type 2 diabetes

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Type 2 diabetes (T2D) is a leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD). In France, approximately 29% of patients with T2D have CKD. In real-world studies, understanding how different data sources, such as Electronic Medical Records (EMR) and the National Health Data System (*Système National des Données de Santé*, SNDS), capture kidney disease severity is important for surveillance and research.

Materials and methods

The OREOT cohort included, from 2015 to 2018, adult patients with T2D in IQVIA EMR data linked to the SNDS [1]. In EMR, CKD stages (G3a to G5) were defined using estimated glomerular filtration rate (eGFR) and ESRD was considered if at least one eGFR were <15 mL/min/1.73m² value. In the SNDS, ESRD was identified using treatment-based criteria (chronic dialysis or renal transplantation reimbursement). The study aimed to compare ESRD identification between EMR and SNDS. Concordance between sources were assessed, and alternative eGFR thresholds were evaluated using ROC curve analysis.

Results

ESRD was identified in 0.6% of patients in EMR (n=1,431), and 0.5% in the SNDS (n=1,198), with low concordance between sources (88 overlapping cases; kappa=0.05). The median age was 68 years in both sources, and SNDS-identified ESRD patients were more often male (70.3% vs. 60.0%). Among SNDS-identified ESRD patients, 64.9% had no recorded eGFR values in EMR. Overall, 9.9% of patients (n=23,374) had at least one EMR-recorded eGFR corresponding to CKD stages G3a to G5. Lower eGFR thresholds improved sensitivity (true positive rate, TPR) for detecting SNDS-defined ESRD (*e.g.*, TPR 20% vs. 10% for <25 and <15 thresholds).

Discussion / Conclusion

EMR and SNDS identified complementary aspects of ESRD. EMR allows earlier biological identification, while the SNDS reflects treated ESRD pathway. Integrating both sources provides a more complete picture of CKD and ESRD in patients with T2D, highlighting the limitations of relying on EMR or SNDS data alone.

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Keywords

SNDS, Electronic Medical Records, Type 2 Diabetes, Chronic Kidney Disease, End-Stage Renal Disease, Concordance

00526
Predicting chronic kidney disease in patients with type 2 diabetes using machine learning: insights from the OREOT cohort

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Type 2 diabetes (T2D) is a prevalent metabolic disorder and a leading cause of chronic kidney disease (CKD). In France, approximately 29% of patients with T2D have CKD, which remains insufficiently diagnosed in routine care despite recommendations for annual screening. Machine learning (ML) models leveraging linked real-world data may improve CKD identification in the French National Health Data System (SNDS) beyond traditional coding approaches.

Materials and methods

The OREOT cohort included adults with T2D between 2015 and 2018 in IQVIA electronic medical records and linked to the SNDS, with follow up through 2023 [1]. For CKD patients, index date was defined as first occurrence of estimated glomerular filtration rate <45 mL/min/1.73 m² or claims-based CKD indicator (hospitalization, chronic dialysis, transplantation) during the study period. Index dates for non-CKD patients were randomly assigned to ensure comparable observation windows. Predictors included healthcare utilization in the year before index and comorbidities identified over the prior three years. Logistic regression with L2 regularization (PLR), Random Forest (RF), and LightGBM models were trained using cross-validation. Performance was assessed using discrimination and calibration metrics.

Results

Among 236,184 patients included in the analysis, CKD prevalence was 15.5%. LightGBM achieved the highest discrimination (PR-AUC 0.66; recall 0.74; precision 0.45) but poorer calibration (Brier score 0.13), whereas RF showed lower discrimination (PR-AUC 0.60) with higher precision (0.76; recall 0.34) and better calibration (Brier score 0.09). PLR demonstrated lower overall performance (PR-AUC 0.54; Brier score 0.17). Permutation feature importance ranked diabetes duration and age, cardiometabolic comorbidities (*e.g.*, hypertension, dyslipidemia, hyperuricemia), repeated renal testing, hospital stays, and medication exposures (biguanides, antihypertensive comedications) among the top contributors.

Discussion / Conclusion

Although ML models demonstrated moderate discrimination, performance metrics suggest persistent uncertainty in identifying individuals with less advanced CKD. These findings emphasize both the potential and the inherent limitations of ML-based CKD identification in administrative databases.

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Keywords

SNDS, Electronic Medical Records, Machine Learning, Type 2 Diabetes, Chronic Kidney Disease

00591
Opioid analgesics use and misuse in France: a retrospective cross-sectional cohort study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

About 3.3% of patient exposed to chronic opioid analgesic treatment develop opioid use disorder.[1] These patients may exhibit drug-seeking behaviors, such as consulting multiple prescribers to obtain overlapping opioid prescriptions.[2] Although the situation in Europe remains less severe than in the USA, opioid-related adverse consequences have increased. This study aims to describe new users of opioid analgesics from 2018 to 2022 and identify factors associated with overlapping prescriptions.

Materials and methods

We used the French National Health Data System. We included new users of opioid analgesics, aged 18 years and older, with at least three dispensings within 12 months from January 1, 2018 to December 31, 2022. We assigned patients to separate cohorts based on the opioid analgesics dispensed. We included patients exposed to several analgesic opioids in each corresponding cohort at the relevant time points. We used overlapping prescriptions from different prescribers as a proxy for potential opioid abuse and misuse. First, we described patient baseline characteristics in each cohort. Next, we described patterns of opioid analgesic use

during follow-up in each cohort. Finally, we identified factors associated with overlapping prescriptions in each cohort using negative binomial models.

Results

We included 2,321,970 new users of tramadol, 1,918,158 of opium, 1,837,941 of codeine, 326,264 of morphine, 289,113 of oxycodone, 271,835 of transdermal fentanyl, and 22,086 of transmucosal fentanyl. Overall, users of strong opioid analgesics were older and most patients were women. While most patients had no overlapping prescription, few patients had an extremely high number of overlapping prescriptions (from 268 for opium to 514 for codeine). Overall, the main factors associated with overlapping prescriptions were prior exposure to opioid agonist treatments, active cancers, and younger age.

Discussion / Conclusion

While most users of opioid analgesics did not exhibit misuse, a specific subpopulation exhibited use patterns suggesting abuse and/or trafficking.

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Keywords

opioid analgesics, drug utilization study, misuse, abuse, pharmacoepidemiology

Analytical

00005
Pharmacometabolomics reveals notable differences between real-world and expected drug metabolism and excretion patterns

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Knowledge of drug metabolism plays an important role in clinical pharmacokinetics, informing decisions on which compounds to monitor via therapeutic drug monitoring (TDM) and which metabolic conversions to investigate through pharmacogenetics (PGx). It is, however, often overlooked that much of this knowledge comes from small-scale (mass-balance) studies, typically including <10 healthy males receiving a single dose. Although informative, such data may have limited generalizability to real-world patient populations, which highlights a need for larger-scale drug metabolism and excretion studies.

Materials and methods

We established an untargeted pharmacometabolomics workflow, combining liquid chromatography and data-independent acquisition mass spectrometry. Our method was applied to 24-hour urine samples of 1,421 kidney transplant recipients and 283

(potential) living kidney donors from the TransplantLines studies (NCT03272841/02811835).[1,2] Data analysis assessed alignment of observed metabolite profiles with established metabolic patterns of various immunosuppressants (azathioprine, mycophenolate-mofetil)[1,2,3], cardiovascular drugs (clopidogrel, enalapril, hydrochlorothiazide, metoprolol)[4,5,6], and antibiotics (sulfamethoxazole, trimethoprim)[7].

Results

The real-world metabolic patterns obtained frequently diverged from consensus expectations, generally with more metabolites identified than expected.[1-7] For example, for metoprolol, 9 metabolites were anticipated, 7 were confirmed, and 10 previously-unreported metabolites were discovered.[4] Interestingly, several studied drugs are prodrugs requiring activation by carboxylesterases, assumed to enable rapid and full conversions. Our findings, however, contradicted this assumption, with prodrugs and glucuronide counterparts being detected in most users, suggesting impaired prodrug activation. To illustrate, we found substantial and highly variable urinary presences of mycophenolate-mofetil and its previously-unreported glucuronide.[3] Pharmacoepidemiologic analyses furthermore revealed a positive association with increasing drug dose and kidney function, and with the pharmaceutical excipient Kolliphor® EL, for example present in cyclosporine capsules.[8]

Discussion / Conclusion

Our findings reveal substantial divergence between real-world and expected drug metabolism, including incomplete prodrug activation. Additionally, our study suggests a role for untargeted pharmacometabolomics to support target selection for TDM and PGx testing.

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Keywords

Pharmacometabolomics

Drug metabolism

Therapeutic drug monitoring (TDM)

Pharmacogenetics (PGx)

Prodrugs

00014
Fragile Rings, Strong Buffers: Stabilizing β-Lactams for Reliable TDM

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Sepsis is a common, life-threatening condition associated with high mortality. A cornerstone of treatment is adequate therapy with correct dosed β-lactam antibiotics such as meropenem and piperacillin. Therapeutic drug monitoring (TDM) of plasma concentrations can guide dosing, but both compounds are chemically unstable, requiring rapid sample processing. As no commercial kits are currently available, analysis involves manual pre-analytical steps, limiting 24/7 availability and increasing the risk of degradation.

Materials and methods

Plasma samples from patients treated with meropenem or piperacillin (n=10) were tested for stability at room temperature (22°C) using a validated liquid-chromatography mass spectrometry method. The effect of different buffers (MOPS, HEPES, phosphate and citrate) on stability was evaluated. Stability was assessed by monitoring drug concentrations over time and quantifying degradation products, particularly the open-ring metabolite.

Results

Meropenem remained stable for 7 h at 22 °C, while piperacillin showed stability for 3 h. Phosphate and MOPS buffers (both maintaining their pH most effectively when added to plasma) increased stability to >10 h for meropenem and >6 h for piperacillin (measurements limited to these timepoints) at 22°C. Addition of phosphate or MOPS buffer also reduced the formation of the major degradation product.

Discussion / Conclusion

Plasma stability of meropenem and piperacillin is limited under routine conditions but can be significantly improved by adding phosphate (2.0 M, pH 6.5, 1:20 ratio) or MOPS buffer (1.0 M, pH 6.5, 1:10 ratio). Buffer addition not only prolongs stability but also decreases degradation product formation, supporting more reliable TDM in clinical practice.

Keywords

Meropenem, Piperacillin, Stability, Buffer, Beta-lactam, TDM

00054
Method validation optimization for sertraline, fluoxetine and clozapine on LC-MS/MS

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Currently, we run sertraline (λ = 205 nm) and clozapine (λ = 245 nm) on HPLC with UV and fluoxetine (excitation/emission = 235/315 nm) on HPLC with fluorescence detector. Our goal is to optimize the method for these three drugs using our liquid chromatography tandem mass spectrometry (LC-MS/MS).

Materials and methods

Forty µL of calibrator, quality control and patient samples were pipetted in the microcentrifuge tubes and 300 µL of working deuterated internal standards (IS) /precipitation mix was added. This mix was prepared by mixing IS with 70:30 methanol: 0.1M ZnSO4.

Results

The resulting run time was 5.0 minutes with the injection volume of 2 µL. We used the gradient elution with the initial LC conditions of 80% mobile phase A and 20% B, and then to 10% A and 90% B for 2 min. This was held until 3.25 min., after which it went back to initial conditions. The sample compartment was cooled to 10.0 °C, and the column was heated to 40 °C. The mass spectrometry settings were adjusted for electrospray ionization in positive mode. The source settings were used: capillary voltage - 1.00 kV, source temperature - 150°C, desolvation temperature - 600°C,

cone gas flow - 200 L/H and desolvation gas flow - 1000 L/H. The multiple reaction monitoring of these drugs for the precursor and product ions, which were for sertraline (306.0 > 159.0), clozapine (327.0 > 270.0) and fluoxetine (310.0 > 148.0). The IS transitions were: 309.0 > 159.0, 335.0 > 274.0, 315.0 > 153.0, for sertraline, clozapine and fluoxetine IS, respectively.

Discussion / Conclusion

The LC-MS/MS method is by far superior to HPLC-UV/FD for these drugs. The run time is shorter, enables inclusion of all three drugs, and avoids non-specific interferences, which plague HPLC methods.

Keywords

Liquid chromatography tandem mass spectrometry (LC-MS/MS), therapeutic drug monitoring (TDM), antipsychotic drugs, antidepressant drugs

00071
Determination of ciprofol in human plasma by UPLC-MS/MS and its application to therapeutic drug monitoring

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

To develop and validate an ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method for quantifying ciprofol in human plasma and to apply it to therapeutic drug monitoring (TDM) and pharmacokinetic research in critically ill patients.

Materials and methods

Plasma samples were spiked with propofol as the internal standard (IS) and processed by protein precipitation with methanol. Chromatographic separation was performed on a Waters ACQUITY UPLC BEH C18 column (2.1 mm × 100 mm, 1.7 μm) at 40 °C, using a mobile phase of 0.025% ammonia solution and acetonitrile (flow rate: 0.3 mL/min). Detection was carried out by negative-ion electrospray ionization with multiple reaction monitoring. The ion transitions were m/z 203.1 → 175.1 for ciprofol and m/z 176.9 → 160.9 for propofol.

Results

The assay was linear over 0.1–10 mg/L, with a lower limit of quantification of 0.1 mg/L. Intra- and inter-batch precision (RSD) were ≤ 10.33%, and accuracy ranged from 96.84% to 105.85%. Mean extraction recovery was 88.03–103.68%. The IS-normalized matrix effect showed a coefficient of variation < 15%. The method was successfully applied to determine ciprofol concentrations in plasma from critically ill patients.

Discussion / Conclusion

The developed UPLC-MS/MS method is simple, sensitive, and reliable for quantifying ciprofol in human plasma, supporting its application in TDM and pharmacokinetic research.

Keywords

Ciprofol; UPLC-MS/MS; therapeutic drug monitoring; plasma concentration

00074
Development and validation of a UPLC method for determination of methylene blue in plasma from septic shock patients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Methylene blue has shown promise in septic shock in sepsis by inhibiting nitric oxide-mediated vasodilation. However, the dosage of the drug varies greatly, and there is a lack of pharmacokinetic research on the drug in the early stage. Therapeutic drug monitoring may be a potential strategy for achieving personalized treatment. This study aimed to develop and validate a sensitive and accurate ultra-performance liquid chromatography (UPLC) method for quantifying methylene blue in plasma from septic patients.

Materials and methods

Plasma samples were pretreated by protein precipitation with acetonitrile using methyl violet 3RAX as internal standard. Chromatographic separation was performed on an Acquity UPLC BEH C18 column (2.1 mm × 100 mm, 1.7 μm) maintained with gradient elution using methanol and 0.2% glacial acetic acid in water as mobile phases.

Results

The method exhibited excellent linearity over the concentration range of 0.2–40 μg/mL ($R^2 > 0.999$). Intra- and inter-day precision (RSD) ranged from 1.5% to 2.5% and 2.1% to 2.6%, respectively. Extraction recovery was between 88.3% and 100.4%. Stability studies under freeze-thaw, room temperature, and long-term storage conditions met the acceptance criteria for bioanalytical method validation.

Discussion / Conclusion

A simple, sensitive, and accurate UPLC method was successfully developed and validated for the determination of methylene blue in human plasma. This method is suitable for therapeutic drug monitoring and pharmacokinetic studies in septic shock patients.

Keywords

methylene blue; septic shock; UPLC; method validation

00075
Development and validation of a UPLC method for determination of micafungin in human plasma

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

To develop and validate a rapid, sensitive, and accurate ultra-performance liquid chromatography (UPLC) method for quantifying micafungin in human plasma, supporting therapeutic drug monitoring (TDM) and individualized dosing in critically ill patients.

Materials and methods

Plasma samples were pretreated by protein precipitation with three volumes of methanol using posaconazole (2 μg/mL) as internal standard. Chromatographic separation was performed on an ACQUITY UPLC HSS T3 column (2.1 mm × 50 mm, 1.8 μm) maintained at 40 °C. The mobile phase consisted of methanol and 0.1% triethylamine + 15% glacial acetic acid in water (72:28, v/v) delivered at 0.35 mL/min. Detection wavelength was 273 nm, injection volume 5 μL, and total run time 5 min. The method was validated for specificity, linearity, precision, accuracy, recovery, and stability, and applied to clinical samples.

Results

The method showed excellent linearity over 0.5–40.0 μg/mL (r = 0.9986), with a lower limit of quantification of 0.5 μg/mL. Extraction recovery ranged from 90.51% to 96.89% for quality control samples (0.9, 3.0, and 30.0 μg/mL). Intra- and inter-day precision (RSD) were 1.45%–4.55% and 1.47%–5.53%, respectively. Micafungin remained stable under various storage and processing conditions (RE < ±15%). When applied to 15 critically ill patients, plasma concentrations ranged from 1.2 to 38.6 μg/mL, covering the routine therapeutic window.

Discussion / Conclusion

A simple, rapid, and reliable UPLC method was successfully developed and validated for micafungin quantification in human plasma. With straightforward sample preparation and no requirement for complex or expensive instrumentation, this method is well-suited for routine TDM and pharmacokinetic studies, particularly in primary care settings.

Keywords

micafungin; ultra-performance liquid chromatography; therapeutic drug monitoring; method validation; plasma concentration

00082
Therapeutic Drug Monitoring of Amikacin, Gentamicin and Carbamazepine And Their Potential Clinical Impact In Ghana

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic drug monitoring (TDM) optimises therapy for narrow therapeutic index drugs like amikacin, gentamicin (aminoglycosides for severe infections), and carbamazepine (antiepileptic) by measuring plasma levels to ensure efficacy while minimising toxicity such as nephrotoxicity or seizures. In sub-Saharan Africa, including Ghana, TDM is underutilised despite pharmacokinetic variability from factors like renal function, age, and drug interactions, leading to suboptimal dosing and risks. This study develops and validates Liquid Chromatography tandem Mass Spectrometry (LC-MS/MS) methods for simultaneous TDM, applied to patients at Kwame Nkrumah University of Science and Technology (KNUST) Hospital and Recovery Pathways Clinic (March-August 2025), to assess clinical impact in resource-limited settings.

Materials and methods

Pure analytes (amikacin sulfate, gentamicin sulfate, carbamazepine) and tobramycin (internal standard) underwent qualitative analysis (melting point, MS, FT-IR). LC-MS/MS methods used ExionLC 2.0 with Triple Quad 5500, formic acid-based mobile phases, gradient elution (0.3 mL/min), Electrospray Ionisation in positive (ESI+) mode; validated per ICH guidelines (linearity R^2>0.99, LOD/LOQ 0.05-0.1 µg/mL, accuracy 85-115%, precision <15% RSD). Twenty-two patients (5 amikacin, 7 gentamicin, 10 carbamazepine) provided plasma samples (peak/trough) with demographics; data were analysed via Spearman's correlation and dose-normalised concentrations.

Results

Methods exhibited excellent specificity, linearity (R^2>0.99), LOD/LOQ 0.05-0.1 µg/mL, matrix recovery 93-99%, accuracy 85-115%, and precision <15% RSD; method validation was conducted per ICH guidelines. Therapeutic targets met in 60% amikacin peaks (19.8-20.5 µg/mL), 71.4% gentamicin peaks, 60% carbamazepine troughs; 85.7% gentamicin troughs were toxic (>1 µg/mL). Dose-normalised variability: 2.5-fold amikacin, 1.8-fold gentamicin, 60-fold carbamazepine. These indicated weak dose-concentration correlations.

Discussion / Conclusion

Substantial PK variability confirms population dosing inadequacy; TDM enables individualised adjustments, preventing toxicity (e.g., gentamicin nephrotoxicity) and drug therapy failure. LC-MS/MS proves feasible in Ghana but needs infrastructure scaling. This study therefore recommends national TDM protocols, training, and policy integration for precision medicine in Ghana.

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Keywords

Therapeutic drug monitoring, LC-MS/MS, amikacin, gentamicin, carbamazepine, Ghana, clinical pharmacokinetics.

00091
From Microsomes to Cells: Upgrading a Multi-Isoform CYP Inhibition Assay using a Huh7 Cell Model

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Human liver microsomes are well established in drug metabolism and inhibition studies but they lack the complexity of cellular architecture. To overcome this limitation, we transferred a seven-isoform cytochrome P450 (CYP) inhibition assay from a cell-free microsomal system to a dynamic Huh7 hepatoma cell model. Applicability was tested using a dual-cocktail approach and the known CYP2D6 inhibitor 3,4-methylenedioxyphenmetrazine (MDPM) (Kroesen et al. 2025).

Materials and methods

Huh7 cells were matured over a 21-day differentiation period in Dulbecco's modified Eagle's medium supplemented with 2 % human serum (HS). Cells were then exposed in triplicates to two substrate cocktails for twelve hours: Cocktail A (phenacetin, CYP1A2; dextromethorphan, CYP2D6; diclofenac, CYP2C9; testosterone, CYP3A4) and Cocktail B (bupropion, CYP2B6; amodiaquine, CYP2C8; omeprazole, CYP2C19). Incubation was done in presence of specific CYP inhibitors (positive control), MDPM (test inhibitor), no cells (negative control), and no substrates (blank). Medium supernatants were precipitated with acetonitrile, centrifuged, and analyzed by reversed-phase liquid chromatography coupled to high-resolution tandem mass spectrometry.

Results

The Huh7 model allowed refined inhibition monitoring. When microsomal inhibition was >90 % (CYP1A2, CYP2D6) in the positive control, the Huh7-based system showed complete inhibition (undetectable metabolites). Other enzymes were inhibited with deviations <20 % from the microsome-based incubations, highlighting the impact of the cellular environment. MDPM as test inhibitor showed a strong CYP2D6 inhibition (80 %) and moderate but significant inhibition of CYP3A4 (30 %) and CYP2C9 (20 %) in line with microsomal results.

Discussion / Conclusion

Significant inhibition of the positive control and test inhibitor demonstrated applicability of the assay. The observed deviations in inhibition between Huh7 and microsomes are most likely attributable to the influence of cellular transport and membrane permeability. The Huh7 model thus provides a more sophisticated, physiologically more accurate tool for predicting human toxicokinetics.

Reference(s)

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Keywords

Huh7; human serum; toxicokinetics; HPLC-HRMS/MS; new psychoactive substances

00104
Validation of commercially available RECIPE Urine Calibrator and Controls for the simultaneous quantification of 12 Trace Elements on ICP-MS using the RECIPE complete kit for 29 trace elements in serum/plasma

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Exposure to toxic trace elements and deficiencies in essential elements are associated with a multitude of adverse health outcomes affecting multiple organ systems. Human exposure occurs mainly through environmental and occupational routes, including contaminated food and water, dust, dermal contact, cigarette smoke, clinical procedures (e.g., prostheses, teeth filling), and industrial activities. Consequently, the quantification of trace elements in biological matrices is a valuable approach for evaluating nutritional status and monitoring toxic exposure.

This study evaluated the validity and analytical performance of the commercially available RECIPE Urine Calibrator and Controls for the simultaneous ICP-MS quantification of 12 trace elements, in accordance with FDA and EMA guidelines: magnesium (Mg), manganese (Mn), molybdenum (Mo), selenium (Se), zinc (Zn), iron

(Fe), copper (Cu), cobalt (Co), arsenic (As), cadmium (Cd), palladium (Pd), and antimony (Sb).

Materials and methods

The RECIPE MS50000 kit is designed for the quantitative analysis of 29 trace elements in plasma/serum using ICP-MS system. The company also brought to market calibrator and quality controls for 30 trace elements in urine.

The 12 elements were chosen based on acceptable analytical precision, comparability of matrix effects between urine and plasma, and satisfactory performance in external quality assessment schemes.

Results

Method validation confirmed that inaccuracy and imprecision for all elements complied with FDA and EMA acceptance criteria (±15%). Calibration curves showed high reproducibility, enabling reliable determination of the lower limits of quantification for each analyte. Matrix effect evaluation revealed comparable behavior between plasma and urine for Mg, Mn, As, Mo, Pd, Cd, and Sb; Cu, Zn, Se, and Fe, showed stronger matrix influence in urine compared with plasma, whereas Co showed the opposite behavior.

Discussion / Conclusion

The robustness and reproducibility of the method achieve good performances in compliance with FDA and EMA guidelines. It ensures good accuracy and rapid analysis, suitable for the application in both clinical and toxicological settings.

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Keywords

Trace element, monitoring, ICP

00163
Statistically Driven Two-Point Calibration for LC–MS/MS Quantification of Amoxicillin in Plasma: Sequential Parameter Modeling (SPM) versus D-Optimal Linear Mixed-Effects Modeling (LME)

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

LC–MS/MS quantification of amoxicillin in plasma typically relies on multi-point calibration curves across the validated range (10–100 mg/L). Although analytically robust, full calibration increases laboratory workload. Data-driven two-point calibration strategies may provide a more efficient alternative if calibration parameters can be reliably predicted. This study compared two statistical approaches for predicting individual calibration parameters (intercept α and slope β) from selected calibration levels (C1–C6): Sequential Parameter Modeling (SPM) and linear mixed-effects modeling (LME) using D-optimal design.

Materials and methods

Eighty-eight calibration curves were used for model development. Analyses were performed on a LC–MS/MS (Sciex X500R QTOF detector). Analyte-to-internal standard peak area ratios (amoxicillin/IS) from six calibration levels spanning 10–100 mg/L were evaluated. In SPM, the optimal pair of calibration responses was identified through sequential variable selection. In LME, calibration levels were selected using a D-optimality criterion within a mixed-effects framework. Predicted parameters were

applied to recalculate concentrations from measured peak area ratios. Performance was assessed using an independent QC dataset (instrument-derived and theoretical concentrations, n = 191) and an independent patient dataset (n = 99). Metrics included R^2, RMSE, bias, and the proportion of results within ±10% of reference values (F10). Analyses were performed in R statistical environment.

Results

Both approaches showed excellent agreement with the reference method in QC samples (SPM: $R^2 = 0.996$, F10 = 96.2%; LME: $R^2 = 0.995$, F10 = 96.9%). Against theoretical concentrations, performance was comparable ($R^2 \approx 0.966$; F10 ≈ 69–71%). In patient samples, predictive accuracy remained high (SPM: $R^2 = 0.996$, F10 = 98.0%; LME: $R^2 = 0.993$, F10 = 98.0%).

Discussion / Conclusion

Two-point calibration strategies based on statistical modeling provided robust and comparable performance for LC–MS/MS amoxicillin quantification, supporting simplified calibration without compromising analytical reliability and improving efficiency in routine TDM workflows.

00182
Bridging the Gap Between Recommendations and Clinical Practice: Determinants of Antipsychotic Therapeutic Drug Monitoring Implementation

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Despite strong international recommendations, therapeutic drug monitoring (TDM) of antipsychotics remains inconsistently implemented in psychiatric practice [1,2]. This gap between evidence-based guidelines and routine care reflects not only clinical considerations, but also professional representations, organisational constraints and contextual factors [3]. Understanding how prescribers perceive and integrate TDM into their daily practice is a key prerequisite for improving its implementation. To explore the determinants of antipsychotic TDM implementation in hospital psychiatry, focusing on prescribers' practices, representations and perceived barriers and facilitators.

Materials and methods

A qualitative study was conducted at Nantes University Hospital using focus groups with psychiatrists and psychiatry residents. Participants were recruited on a voluntary basis. Three focus groups were organised, involving 14 participants. Discussions followed a semi-structured interview guide addressing knowledge of TDM, clinical indications, perceived usefulness, practical constraints and conditions required for

wider implementation. Audio recordings were transcribed verbatim and analysed using reflexive thematic analysis, following an inductive approach [4].

Results

TDM implementation was largely restricted to clozapine, which was perceived as inherently requiring biological monitoring and was conceptually grouped with mood stabilisers. For other antipsychotics, TDM was rarely integrated into routine care and often considered optional or marginal. Key barriers included insufficient initial and continuing training, limited access to practical guidance, organisational constraints related to blood sampling and result turnaround, and uncertainty regarding interpretation and clinical impact. Conversely, TDM was viewed as a potentially valuable tool in specific contexts, such as complex situations, suspected non-adherence or as a mediation tool in the therapeutic relationship.

Discussion / Conclusion

The limited use of antipsychotic TDM reflects an implementation gap driven by professional representations, organisational factors and lack of decision-support tools, rather than by insufficient scientific evidence. An implementation-oriented approach combining training, practical guidelines and strengthened collaboration between psychiatrists and pharmacologists may facilitate the integration of TDM into routine psychiatric care.

Reference(s)

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Keywords

therapeutic drug monitoring ; antipsychotics ; qualitative study ; focus groups

00194
Beyond the Parent Drug: Whole Blood Monitoring of Hydroxychloroquine and Metabolites Enhances Detection of Cumulative Toxicity Risk

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Hydroxychloroquine (HCQ) is commonly prescribed for the treatment of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and other inflammatory rheumatic diseases. HCQ is metabolized in the liver to form desethylhydroxychloroquine (DHCQ), desethylchloroquine (DCQ), and bisdesethylchloroquine (BDCQ) metabolites. Long-term use of HCQ has been linked to irreversible retinal toxicity and cardiotoxicity by a yet unknown mechanism. Therefore, therapeutic drug monitoring (TDM) of HCQ and its metabolites is necessary to address the tissue associated toxicity.

Materials and methods

We developed a simple and rapid ultrahigh performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) method for simultaneous quantitation of HCQ and its three metabolites in human blood and serum. Following protein precipitation, the samples were applied to a Kinetex (2.6 µm, 2.1 × 100mm) column that enabled detection of all four analytes. Data acquisition was performed in multiple reaction monitoring mode with an instrument analysis time of 1.5 minutes per sample. We evaluated the method's performance in patients on HCQ therapy.

Results

HCQ displayed linearity from 8.0 to 2000.0 ng/mL, and its metabolites from 4.0 to 2000.0 ng/mL, with a Pearson correlation of 0.995 across all analytes. In 48 clinical samples from patients on long-term HCQ therapy, HCQ concentrations in whole blood averaged 3.8 times higher than in serum and only BDCQ metabolite levels correlated between the two matrices. Therapeutic levels were observed in 10.4% of the patients in serum vs. 20.8% in whole blood samples, with most patients having sub-therapeutic concentrations (87.5% in serum, 68.8% in whole blood). While BDCQ was 18.8-fold lower than HCQ in serum in all patients, seven patient samples showed elevated BDCQ relative to HCQ in whole blood, suggesting a link between metabolite levels and potential toxicity.

Discussion / Conclusion

Monitoring of HCQ and its metabolites in whole blood, particularly BDCQ, may substantially improve identification of patients at risk for cumulative toxicity, which may be missed with serum based or parent-drug-only monitoring of HCQ.

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Keywords

therapeutic drug monitoring (TDM), LC-MS/MS, hydroxychloroquine (HCQ), systemic lupus erythematosus (SLE)

00204
Advancing TDM Standardization: Shifting Gentamicin and Vancomycin Measurement from Biological Activity to SI Units

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Gentamicin and vancomycin Therapeutic Drug Monitoring (TDM) is essential for patient safety, but global comparability is historically challenged. Currently, reference materials are often standardized based on biological activity, which inherently lacks robust traceability to the Système International d'Unités (SI units). This project aims to close this critical metrological gap by developing new Reference Measurement Procedures (RMPs) to establish full SI traceability for TDM assays of these critical antibiotics.

Materials and methods

An Isotope Dilution-Liquid Chromatography-Tandem Mass Spectrometry (ID-LC-MS/MS) method was developed as a candidate RMP, offering superior analytical performance for TDM applications. To establish metrological traceability, Quantitative Nuclear Magnetic Resonance (qNMR) spectroscopy was used to determine the absolute content (mass fraction; g/g) of the gentamicin and vancomycin primary reference materials. This approach ensures that all concentration values are directly linked to SI units. The RMP was rigorously validated for accuracy, precision, and matrix independence in both serum and plasma.

Results

For gentamicin, intermediate precision CVs ranged from 1.8% to 2.3%, with expanded measurement uncertainty (k=2) for target value assignment ranging from 2.0% to 2.4%. For vancomycin, intermediate precision CVs ranged from 2.5% to 3.0%, and expanded uncertainty (k=2) ranged from 2.1% to 3.1%. Method comparison studies with the currently listed biological activity-based RMPs revealed systematic bias, highlighting differences from the historical standardization approach.

Discussion / Conclusion

The candidate RMPs demonstrated robust analytical performance and high metrological quality. This work facilitates the crucial shift from biological activity to SI-traceable chemical concentration in TDM for vancomycin and gentamicin. The establishment of this RMP will significantly support laboratories, External Quality Assessment providers, and in vitro diagnostic manufacturers in achieving international standardization. This effort is a key step in advancing the consistency of patient results, which in turn will support patient safety and antibiotic stewardship across healthcare systems.

Keywords

Gentamicin, Vancomycin, Therapeutic Drug Monitoring (TDM), Standardization, SI Units, Reference Measurement Procedure (RMP), ID-LC-MS/MS, qNMR.

00206
Analytical Performance of an Automated liquid chromatography-tandem mass spectrometry (LC-MS/MS) Analyzer for Measurements of Linezolid and Meropenem

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Mass spectrometry plays a key role in therapeutic drug monitoring (TDM) by providing the high sensitivity and specificity to support dose optimization based on accurate results. Due to an interpatient variability in meropenem and linezolid exposure in critically ill patients, guidelines recommend TDM to balance efficacy and toxicity, particularly during prolonged therapy.

The Cobas® i 601 analyzer is a fully automated, random-access system designed for LC-MS/MS. A multicenter study evaluated the analytical performance of all assays, of which the Ionify® Linezolid and Meropenem assays are reported.

Materials and methods

Precision was evaluated by 5-day precision testing per CLSI EP05-A3, accuracy via inter-laboratory surveys, and comparability against laboratory-developed tests (LDTs).

Results

Ionify Linezolid was evaluated across three sites using three reagent lots. Repeatability CVs ranged from 0.9% to 4.6%, while intermediate precision CVs ranged from 0.9% to 5.4%. Site-to-site reproducibility CVs ranged between 1.8% and 4.5%, and lot-to-lot reproducibility CVs ranged between 1.3% and 4.0%.

Ionify Meropenem was evaluated using one reagent lot across three sites. Repeatability CVs ranged from 1.7% to 3.5%, and intermediate precision CVs ranged from 1.8% to 3.9%. Site-to-site reproducibility CVs ranged between 4.8% and 6.1%. Due to single lot testing, lot-to-lot reproducibility could not be performed.

Inter-laboratory surveys against target values and Reference Measurement Procedures (RMP) yielded results within 5% for Ionify Linezolid and within 11% for Meropenem across all standard materials.

Method comparison with the LDT showed strong agreement for Linezolid (n=106; r=0.978, slope=0.955) and Meropenem (n=114; r=0.980, slope=0.975).

Discussion / Conclusion

The Ionify Linezolid and Meropenem assays demonstrated high analytical precision and strong agreement with established methods. These results support the use of the Cobas i 601 analyzer for efficient antibiotic TDM in clinical laboratories.

Keywords

Therapeutic Drug Monitoring (TDM), Linezolid, Meropenem, LC-MS/MS, Mass Spectrometry, Cobas i 601, Ionify Assays, Analytical Performance.

00210
Clinical validation of the VAMS-LC-MS/MS method for methotrexate polyglutamates in patients with rheumatoid arthritis

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Methotrexate (MTX) is the anchor drug in rheumatoid arthritis (RA) therapy, and intracellular methotrexate polyglutamates (MTX-PGs) are key determinants of its pharmacological activity. Reliable quantification of MTX-PGs is essential for therapeutic drug monitoring and individualized treatment. Volumetric absorptive microsampling (VAMS) combined with liquid chromatography–tandem mass spectrometry (LC–MS/MS) offers a minimally invasive alternative to conventional venous blood sampling. This study aimed to clinically validate a VAMS–LC–MS/MS method for the quantification of MTX-PGs(1-5) in patients with RA.

Materials and methods

MTX-PGs(1-5) were quantified in VAMS whole-blood samples using a validated LC–MS/MS method. Analytical validation was performed in accordance with the international bioanalytical guidelines. Whole-blood concentrations were converted to RBC concentrations using individual hematocrit values. Clinical validation was performed using paired VAMS and conventional venous blood samples collected simultaneously from RA patients receiving stable MTX therapy. Statistical evaluation included Passing–Bablok regression, Pearson correlation, Bland–Altman analysis, and assessment of proportional and constant bias. The impact of hematocrit on conversion accuracy was evaluated using linear regression and residual analysis.

Results

The method showed excellent linearity ($r^2 \geq 0.99$), with intra- and inter-day accuracy and precision within ±15% for all MTX-PGs. Converted RBC concentrations from VAMS demonstrated a strong correlation with reference erythrocyte concentrations ($r = 0.89–0.96$). Passing–Bablok regression revealed slopes not significantly different from unity and intercepts not significantly different from zero. Bland–Altman analysis showed mean biases within ±10%, with over 95% of data points within the limits of agreement. No clinically relevant proportional bias related to hematocrit was observed.

Discussion / Conclusion

Statistically robust whole blood–to–RBC conversion enables clinically reliable MTX-PG quantification from VAMS samples. The validated VAMS–LC–MS/MS approach is equivalent to conventional erythrocyte-based methods and supports minimally invasive capillary blood sampling in therapeutic drug monitoring during RA treatment.

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2. D.N. Daraghmah, M. Moghaddami, L. Bobrovskaya, S.M. Proudman, M.D. Wiese. Quantitation of methotrexate polyglutamates in human whole blood, erythocytes and leucocytes collected via venepuncture and volumetric absorptive micro-sampling: a green LC-MS/MS-based method. Analytical and Bioanalytical Chemistry (2022) 414: 6029-6046.

Keywords

methotrexate polyglutamates; rheumatoid arthritis; VAMS; LC–MS/MS; therapeutic drug monitoring

00268
High Throughput Quantification of Immunosuppressant Drugs in Human Blood by multichannel LCMS using Shimadzu Nexera-MX and LCMS-8050RX

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Immunosuppressant drugs play a critical role in the treatment of transplanted patients. The most commonly used immunosuppressants are Cyclosporin A, Tacrolimus, Everolimus and Sirolimus. Blood concentrations of these compounds are monitored, and results should often be reported within a few hours.

Materials and methods

This work describes a LC-MS/MS method based on a multi-channel system, where two LC systems are operated in parallel. One channel is performing analysis while the other one is washing and equilibrating in order to prepare for the next injection. The software controls the full system and which channel is directed into the mass spectrometer.The time between each injection is less than one minute.

The method was tested using commercially available calibrators and controls (RECIPE Chemicals + Instruments GmbH) which were analyzed on a Nexera-MX system (Shimadzu Corporation) coupled to a Triple Quadrupole Mass Spectrometer model LCMS-8050RX (Shimadzu Corporation). Method performance was evaluated in terms of linearity of response within the calibration range, selectivity, intra- and inter-assay accuracy, intra- and inter-assay precision and carry-over for each analyte.

Results

Intra and inter assay accuracy and precision were evaluated on three different occasions using 6 replicates of QC-samples at 5 different levels. Intra-assay accuracy was between 85 and 115%, except Everolimus at LLOQ where it was 83.9%. Intra-assay Precision was better than 10% for all compounds at all levels. Inter-assay accuracy was between 87.9 and 108.9% and inter assay precision was 8 % for all compounds and at all levels, except for Sirolimus at LLOQ where it was 13.8%.

Carry-over was examined in blank samples immediately following a ULOQ sample. The carry over was in-line with CLSI guidelines.

Discussion / Conclusion

The presented method is fast, robust, accurate, precise and sensitive. The extra sensitivity of this method makes it especially suitable for clinical research studies. The investigated parameters comply with EMA guidelines for bioanalytical validation.

Reference(s)

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Keywords

immunosuppressants, LCMS, multiplexing

00274
From Clinical Validation to Nationwide Monitoring: Capillary Dried Blood Spots for 25-Hydroxyvitamin D Assessment in the Belgian National Food Consumption Survey 2022–2023

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Vitamin D deficiency has been associated with a wide range of chronic diseases, increasing the need for robust epidemiological data. Large-scale population monitoring requires minimally invasive and logistically feasible sampling strategies. Within the framework of the Belgian National Food Consumption Survey 2022-2023, capillary dried blood spot (cDBS) sampling was used to enable nationwide assessment of vitamin D status. Although the LC-MS/MS method for 25-hydroxyvitamin D (25-(OH)D) quantification had been previously analytically validated, clinical validation was required to assess the agreement between DBS and the reference matrix, plasma, prior to large-scale implementation.

Materials and methods

Venous plasma and whole blood, venous DBS (vDBS), and cDBS were collected from 44 healthy volunteers to evaluate agreement between matrices and sampling sites. A hematocrit (Hct)-dependent conversion factor was applied to transform cDBS

results to plasma-equivalent concentrations and assessed using four different Hct determination approaches. All samples were analysed using validated LC-MS/MS methods. Following successful clinical validation, the optimized approach was applied to 793 cDBS samples collected in the Belgian National Food Consumption Survey 2022-2023.

Results

No clinically relevant methodological (vDBS *vs.* whole blood) or sampling-site related (cDBS *vs*. vDBS) differences were observed. After Hct-dependent conversion, strong agreement between cDBS-derived and measured plasma concentrations was demonstrated, with 90% of results within 20% of the plasma value, independent of the Hct approach. Weighted Cohen's kappa values (0.83-0.85) indicated substantial to almost perfect agreement in vitamin D status classification. Application of the method to the survey samples revealed a considerable prevalence of vitamin D deficiency, with 45% of participants presenting 25-(OH)D3 concentrations below 20 ng/mL, underscoring the public health relevance of reliable nationwide monitoring.

Discussion / Conclusion

Capillary DBS, following Hct-dependent conversion, are a reliable and practical alternative to plasma for large-scale vitamin D assessment, as evidenced by successful implementation in a national survey context.

Keywords

25-Hydroxyvitamin D; Clinical Validation; Dried Blood Spots; LC-MS/MS; Hematocrit

00281
LC-MS/MS Determination of Gamma-hydroxybutyrate in Blood and Urine

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

This study developed a liquid chromatography–tandem mass spectrometry (LC-MS/MS) method for the selective determination of γ-hydroxybutyrate (GHB) in human post-mortem blood and urine at exogenous concentrations. GHB is commonly used as an illicit recreational drug and in drug-facilitated sexual assault.

Materials and methods

A 100-µL blood sample was extracted using organic mixture, and the supernatant after evaporation was reconstituted in an aqueous solution (H_2O/0.4% formic acid). GHB was extracted from 100 µL of urine by liquid–liquid extraction with H_2O/0.4% formic acid. Chromatographic separation was performed on a silica-based bonded reverse-phase LC column (Acquity HSS T3 Premium) using a Xevo TQ-XS instrument (Waters™). A 5-µL aliquot of the extract was injected, using a 4-minute gradient and a flow rate of 0.4 ml/min. The retention time of GHB was confirmed at 1.44 minutes. Multiple reaction monitoring (MRM) was used to detect the parent and product ions of GHB (105 m/z → 43 m/z and 105 m/z → 87 m/z) and GHB-D6 (111 m/z → 93 m/z).

Results

Validation results demonstrated that the method is selective, accurate, and precise, with acceptable linearity across the calibration range (1–200 mg/L). The lower limit of quantification was established at 1 mg/L in both blood and urine. Relative

reproducibility (RSD) and bias were below 6% and 4%, respectively, for blood, and below 14% and 7% for urine.

The validated method was successfully applied to twelve real post-mortem forensic case specimens (blood, n = 6; urine, n = 6). GHB concentrations in blood ranged widely (54–598 mg/L; median = 117 mg/L; mean = 220 mg/L), and similarly in urine (181–4093 mg/L; median = 952 mg/L; mean = 1569 mg/L).

Discussion / Conclusion

In conclusion, this simple and rapid LC-MS/MS method proved effective for forensic investigations and for the therapeutic drug monitoring of GHB in biological samples.

Keywords

GHB, drug, LC-MS/MS, whole blood, urine

00305
Designed for Real Life: A Weather-Resistant VAMS Method for TDM in Oncology

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic drug monitoring (TDM) of oral anticancer agents is increasingly used to support personalized and adaptive cancer treatment, in the context of marked inter- and intraindividual pharmacokinetic variability. However, trough sampling during hospital visits is often difficult due to suboptimal timing and organizational constraints. Volumetric absorptive microsampling (VAMS) enables patient self-sampling at home and may overcome these limitations, provided that robust and stable analytical methods are available, including under challenging transport and temperature conditions.

Materials and methods

An LC-MS/MS method was developed and validated for the quantification of palbociclib, ribociclib, abemaciclib, and abemaciclib metabolites (M2, M18, M20) from VAMS devices (30 µL Mitra®, Neoteryx). Samples were processed using a procedure involving rehydration with 150 µL of water (0.5% formic acid), incubation at 37°C for at least 30 minutes, followed by methanol extraction with internal standards. Method validation was performed according to IATDMCT and EMA bioanalytical guidelines, assessing selectivity, calibration model, accuracy, precision, and carry-over. Analyte stability on VAMS was evaluated over 14 days at 20°C and 37°C using low and high quality control samples (n = 5 per condition).

Results

The method demonstrated satisfactory analytical performance for all analytes. Calibration models were linear and reproducible, with acceptable precision, accuracy, and absence of significant carry-over. Stability studies showed that all analytes remained stable on VAMS for at least 14 days at both 20°C and 37°C with coefficients of variation ranging from 4.9% to 12.2%, and bias from -13.6% to 9.7%.

Discussion / Conclusion

This validated LC-MS/MS method provides a robust approach for TDM of CDK4/6 inhibitors using VAMS, with demonstrated stability under ambient and elevated temperature conditions, supporting applicability during summer periods. Ongoing investigations are assessing robustness after postal shipment. Clinical validation within the TDHOME study is currently pending regulatory approval and will further evaluate the feasibility of home-based TDM in routine oncology practice.

Keywords

VAMS ; oncology

00307
Can plasma calibration be used for tissue quantification? A cross-matrix validation approach for deruxtecan

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Quantification of drug concentrations in tissues is increasingly required to support pharmacokinetic–pharmacodynamic analyses and precision medicine strategies. However, full bioanalytical validation in each tissue matrix is resource-intensive and often impractical. Cross-matrix partial validation, using a single calibration model developed in plasma, may represent a robust alternative if linearity and accuracy are preserved across matrices.

Materials and methods

An LC-MS/MS method for deruxtecan (Dxd) quantification was developed and fully validated in plasma in accordance with ICH M10 guidelines. A cross-matrix partial validation was subsequently performed in five matrices: plasma (reference), tumor tissue, adipose tissue (fat pad), heart, and lung. Calibrators were prepared in each matrix over a concentration range of 0.5-500 ng/mL. Response ratios (analyte/internal standard) were measured and analyzed using weighted ($1/x^2$) analysis of covariance (ANCOVA) to assess linearity and equivalence of slopes across matrices. Intercept comparability and the absence of systematic bias were evaluated. Concentrations in tissue matrices were then back-calculated using the plasma calibration curve, and accuracy was assessed against nominal concentrations using predefined acceptance criteria (±15%, ±20% at LLOQ).

Results

ANCOVA demonstrated no statistically significant difference in slopes between matrices ($p = 0.057$). Slope ratios relative to plasma range between 0.98 and 1.07, all within the predefined analytical equivalence interval [0.85-1.15]. The global intercept was not significantly different from zero, indicating absence of systematic bias.

Back-calculated concentrations using the plasma calibration curve met accuracy criteria in all matrices from 1 to 500 ng/mL. Deviations observed at the lowest concentrations (≤1 ng/mL) in lung and adipose tissue were attributed to matrix-specific effects related to tissue composition.

Discussion / Conclusion

This study demonstrates that plasma calibration can be reliably applied to quantify deruxtecan concentrations in multiple tissue matrices following a rigorous cross-matrix partial validation, facilitating translational pharmacokinetic studies and precision medicine applications.

00314
Development and validation of a rapid LC-MS/MS method for the quantitation of 108 drugs of abuse in whole blood

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The analysis of drugs of abuse is essential in both forensic toxicology and clinical diagnostics. The aim of the present work is to develop and validate a targeted liquid chromatography–tandem mass spectrometry (LC-MS/MS) method for the detection and quantification of 108 drugs of abuse in whole blood. Given the large number of compounds involved, with diverse chemical structures and physicochemical properties, establishing a single unified method represents a significant analytical challenge.

Materials and methods

A protein-precipitation–based LC-MS/MS method was consequently developed and comprehensively validated for the quantification of the 108 targeted analytes, employing a 50-µL aliquot of whole blood. Chromatographic separation was achieved on a C18-bonded silica stationary phase LC column using a Xevo TQS-micro mass spectrometer (Waters™). A 10-µL aliquot of the processed extract was injected under a 15-minute gradient elution program, with a constant flow rate of 0.4 ml/min. The calibration curves were prepared using a Chromsystems “Drugs of Abuse” kit originally designed for urine analysis and subsequently adapted for quantification in whole-blood matrices.

Results

The method enabled the identification of 108 analytes, including 18 amphetamines, 10 barbiturates, 31 benzodiazepines and their metabolites, 31 opiates and opioids, 4 boosters, 1 cannabinoid, 4 cocaine-related compounds (cocaine and metabolites), 3 Z-drugs, and 6 additional drugs, along with 100 corresponding internal standards. Overall, all validation criteria were successfully met, confirming the reliability and suitability of the method for routine drug quantification in whole blood. The only exception was norbuprenorphine, for which accuracy and precision values exceeded the acceptable 20% threshold.

Discussion / Conclusion

The present methodology provides a rapid and broad-spectrum LC-MS/MS approach for the analysis of 108 drugs of abuse. Its robustness and analytical performance make it suitable for routine applications in both clinical toxicology and postmortem investigations.

Keywords

Drugs of abuse, quantitiation, whole blood, LC-MS/MS

00324
Simultaneous Quantification of Salivary Cortisol and Its Metabolites for the Development of a Non-Invasive CYP3A Phenotyping Method

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Cytochrome P450 3A (CYP3A) activity varies 5–20-fold among individuals, making its evaluation essential for personalized medicine. Previously, we identified the 6β-hydroxycortisol to cortisol plasma concentration ratio (6β-OHF/F) as a reliable CYP3A activity marker. In this study, we explored a non-invasive assessment method using saliva. Given that plasma cortisol (F) is rapidly converted to cortisone (E) by 11β-hydroxysteroid dehydrogenase type 2 in the parotid gland, a comprehensive evaluation of CYP3A activity must take into consideration both E and its metabolite, 6β-hydroxycortisone (6β-OHE). Here, we report a LC-MS/MS method for the simultaneous determination of F, E, 6β-OHF, and 6β-OHE in human saliva.

Materials and methods

Salivary samples were obtained from healthy adult volunteers using Oral Swab. The salivary levels of F, E, 6β-OHF, and 6β-OHE were measured by LC–MS/MS. Chromatographic separation was performed on a Kinetex C8 Column (75 × 3 mm I.D., 2.6 μm) at a flow rate of 0.35 mL/min. The analytes were eluted with a mobile phase gradient of (A) 0.0125% formic acid in methanol and (B) pure methanol. Detection was carried out using electrospray ionization in negative multiple reaction monitoring mode.

Results

The analytical recovery of the target analytes from saliva was over 90%. Both inter- and intra-day accuracy and precision were maintained under 13%. In a group of 24 healthy individuals, the concentrations of F, E, 6β-OHF, and 6β-OHE were found to be 1.67–8.02, 16.8–44.6, 0.051–0.656, and 0.0234–0.599 pmol/mL, respectively. The (6β-OHF + 6β-OHE)/(F + E) ratio was 0.00401–0.0412.

Discussion / Conclusion

An important advancement of this study is the successful quantification of all four analytes in saliva, allowing for comprehensive assessment of potential salivary biomarkers. In future studies, it will be necessary to determine which salivary metabolic ratio, such as 6β-OHF/(F+E) or (6β-OHF + 6β-OHE)/(F+E), best correlates with the plasma 6β-OHF/F ratio to establish the most appropriate non-invasive biomarker of CYP3A activity.

Reference(s)

R. Hirano, A. Yokokawa, T. Furihata, H. Shibasaki: Plasma 6β-hydroxycortisol to cortisol ratio as a less invasive cytochrome P450 3A phenotyping method. Br J Clin Pharmacol, 90, 1016-1026 (2024).

Keywords

biomarker, saliva, 6β-hydroxycortisol/cortisol ratio, CYP3A, phenotyping

00330
Stability of 5-fluorouracil in plasma post enzyme inactivation by freezing

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

5-fluorouracil (5FU) is highly active in many solid tumours with pharmacokinetic dose monitoring substantially improving efficacy and reducing toxicity. Despite this, 5FU analysis is not readily available as samples require cold chain, long-distance transportation to a laboratory equipped with an analytical method for drug measurement. This is often complex and costly.

Aims: Assess 5FU stability over 2-weeks in plasma at room temperature (RT) after enzyme inactivation by freezing.

Materials and methods

Patients (n=10) receiving IV-5FU underwent a venepuncture 18-40h post infusion start. Blood tubes were placed on ice immediately after collection before spinning (4°C, 2000 x g, 10min) to separate the plasma of the red cells and stored at -70°C (2 x~1.5mL). Analysis of one aliquot was performed post defrosting once. Second sample was defrosted and kept at RT (~23°C) and aliquots were taken at 0h, 4h, 24h, one and 2-weeks and stored at -20°C until analysis. Additionally, the duplicate aliquot of one sample was not placed at -70°C post centrifugation but instead kept at RT for a-week. Each time point was analysed in triplicates. Genotyping of the DPYD

gene was performed for the DPYD2A (c.1905+1G>A; rs3918290), DPYD13 (c.1679T>G; rs55886062), c.2846A>T (rs67376798; p.D949V) and c.1236G>A (HapB3; rs56038477; p.E412E) variants.

Results

5FU was stable for up to 2-weeks (mean degradation ≤11.6%, CV≤14.8%) in plasma when stored at RT provided the plasma was immediately frozen after centrifugation to arrest enzymatic activity. However, eliminating the freezing step resulted in analyte degradation by 40, 80 and 100% after 4h, 24h and 7 days, respectively. 5FU concentrations in patient samples ranged from 286-704 µg/L. Allelic variance of the DPYD gene did not influence stability.

Discussion / Conclusion

This study has demonstrated 5FU stability if plasma was immediately frozen. This eliminates the need for cold chain transport reducing the barrier to therapeutic drug monitoring of 5FU.

00332
Self-sampling by patients and clinical staff using three microsampling devices-data from 4 clinical studies

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Microsampling in patient care is increasing due to its minimally invasive nature, support for at-home collection, improved monitoring and compliance, and facilitation of remote diagnostics. However, successful implementation depends on sample adequacy especially for quantitative analysis.

Aims: Assess finger prick sampling success rate among patients and clinical staff from four clinical studies using three microsampling devices (Mitra®:2-sampler,10uL; Telimmune™DUO: ~65µL, 2x3µL dried plasma spot; HemaPEN™: 4x2.74µL blood spot).

Materials and methods

Patients with cancers (NBCF, n=110; FFTV, n=24; PREDICT, n=50) and adult kidney transplant patients (KHA, n=50) had samples collected by clinical staff and by

themselves (KHA) using Mitra® (NBCF, PREDICT), Telimmune™DUO (FFTV) and hemaPEN™ (KHA) devices. Sample quality was visually assessed by a trained scientist and deemed adequate if a) at least one polymer Mitra®tip was fully covered with blood without visible white mesh, no excess blood present on plastic holder or dark spots of dried coagulated blood was present on the tip, b) the paper membrane of Telimmune™DUO cards was covered with blood, the test spot turned red and at least one dried plasma spot was fully covered by a clear liquid smear without excess dried residue and c) 2/4 of the paper discs inside the HemaPEN™ device were fully covered with blood. Education on sample collection used commercial and in-house videos, face-to-face training, product guides and tailored instruction leaflets.

Results

Overall sampling success by clinical staff was 78% (86/110) for NBCF and 95% (63/66) for PREDICT study with Mitra® device; 71% (17/24) with Telimmune™DUO and 100% (50/50) with hemaPEN™. For patient collected samples with hemaPEN™ success rate was 67% (45/67).

Discussion / Conclusion

Sample quality was adequate for staff collection (≥71% across devices) but lower for patient collection (67%). Dedicated clinical staff (PREDICT/KHA) had higher success rate. Sample volume (Telimmune™ vs. Mitra®) and infrequent device use (i.e., long-term recruitment, NBCF) also influenced success rates.

00355
An updated LC-HRMS method for CFTR-modulators in plasma and breastmilk

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Since 2019 the treatment of cystic fibrosis has been revolutionised by the introduction of cystic fibrosis transmembrane conductance regulator (CFTR) modulators. Since 2022, Clinical Pharmacology at Karolinska University Hospital has offered TDM of all four approved CFTR-modulators elexacaftor, ivacaftor, lumacaftor and tezacaftor in human plasma and in breastmilk [1]. The aim has been to inform the clinician about individual exposure levels during assessment of therapeutic efficacy and/or possible adverse effects of CFTR-modulator therapy, and support potential decisions on individual dose adjustments.

The methodology has now been updated with regards to two new CFTR-modulators vanzacaftor, deutivacaftor (approved by FDA in December 2024, EMA in July 2025) plus the metabolites for ivacaftor and tezacaftor (ivacaftor-M1, ivacaftor-M6 and tezacaftor-M1).

Materials and methods

Plasma and breastmilk samples were subjected to protein precipitation and centrifugation. The supernatant was injected into a Thermo Vanquish Flex Binary UHPLC system coupled to Thermo Q Exactive (Thermo Fisher Scientific) high-resolution mass spectrometer (HRMS) operated in full scan mode (m/z 370-650).

Results

Using an HRMS and full scan method, the extraction of the new analytes was easily done by adding the exact mass of the analyte in the same range as previously used. In this case, all new analytes have an exact mass in the previously applied mass range, so no correction of the established MS instrument method was needed.

The method was validated for the new analytes and revalidated for the original analytes according to ICH guidelines. The quantitative matrix effect, recovery and process efficiency were carried out according to Matuszewski et al [2] for human plasma and breastmilk. The CV% were within 15% for both matrices.

Discussion / Conclusion

A simple and sensitive LC-HRMS method for the simultaneous quantification of six CFTR-modulators and three metabolites in human plasma samples and breastmilk has been validated. The method will be applied to routine TDM analysis of CFTR-modulators.

Reference(s)

1. Hansson AB, Wadstrom H, Eliasson E, Al Shakirchi M, de Monestrol I, Barclay V, Development and clinical implementation of an LC-HRMS method for ivacaftor, lumacaftor, tezacaftor and elexacaftor in human plasma and breast milk. Anal Bioanal Chem 2024, 416, 5565-5577.

2. Matuszewski BK, Constanzer ML, Chavez-Eng CM. Strategies for the assessment of matrix effect in quantitative bioanalytical methods based on HPLC-MS/MS. Anal Chem. 2003;75(13):3019-30

00360
Therapeutic Drug Monitoring of Colistin in Pediatric Liver Transplant Recipients with Multidrug-Resistant Infections: An UPLC-MS/MS Method and Its Clinical Application

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

When refractory multidrug-resistant gram-negative bacterial infections occur after pediatric liver transplantation, colistin is also used as a critical "salvage therapy" medication. colistin has a narrow therapeutic window, a high incidence of nephrotoxicity, and significant individual variability. Guidelines for the rational use of polymyxins recommend therapeutic drug monitoring (TDM). The rational clinical use of colistin is of great significance for improving efficacy, mitigating adverse reactions, and delaying the development of resistance.

Materials and methods

A sensitive UPLC-MS/MS method was developed and validated for quantifying colistin in human plasma using polymyxinB1 as internal standard. Plasma samples (100 μL) underwent protein precipitation with acetonitrile and separation on a C18 column with a mobile phase of water and acetonitrile containing 0.1% formic acid. The assay was successfully validated for accuracy, precision, LOQ, specificity, and short-term stability, conforming to US-FDA guidelines. The method fulfilled all acceptance criteria according to US-FDA guidelines and was successfully applied to quantify colistin concentrations in 6 plasma samples from pediatric liver transplant recipients.

Results

Quantification of colistin in human plasma was achieved within 3.5 min with excellent linearity ($R^2 > 0.99$) over the concentration range of 0.025-10.0 mg/L. Accuracy and precision were within ±15% across all quality control levels. The method was successfully applied to quantify colistin concentrations in 6 plasma samples from pediatric liver transplant recipients.

Discussion / Conclusion

A rapid and sensitive UPLC-MS/MS method for colistin therapeutic drug monitoring was developed and validated. Successfully applied to pediatric liver transplant recipients, this method enables precise dose individualization for refractory infections.

Keywords

Colistin; Therapeutic drug monitoring (TDM); UPLC-MS/MS; Pediatric liver transplantation

00361
Altered Serum Amino Acid Profiles in Recurrent Depressive Disorder: Insights from Targeted Metabolomics

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Recurrent Depressive Disorder (RDD) is characterized by high relapse rates and significant morbidity. While metabolic disturbances are implicated in major depressive disorder, the specific serum amino acid signatures associated with the recurrent phase of the illness remain poorly defined. This study aimed to characterize the serum amino acid profiles in patients with RDD using a targeted metabolomics approach and to evaluate their potential as diagnostic biomarkers.

Materials and methods

A total of 30 patients diagnosed with RDD and 30 age- and sex-matched healthy controls were enrolled in this study. Serum concentrations of thirty-nine amino acids were quantified using a fully automated amino acid analyzer. Multivariate statistical analyses, including principal component analysis (PCA) and orthogonal partial least squares-discriminant analysis (OPLS-DA), T tests, and receiver operating characteristic (ROC) curve analysis were performed to identify differential markers.

Results

The targeted metabolomics analysis revealed that 18 amino acid levels differed significantly between the RDD patients and healthy controls. Significant disturbances were observed in the metabolism of phenylalanine, tyrosine and tryptophan biosynthesis, one carbon pool by folate, cysteine and methionine metabolism, taurine and hypotaurine metabolism, and glycine, serine and threonine metabolism. The combination of these differential amino acids yielded an area under the curve (AUC) of 0.904 in distinguishing RDD patients from controls, indicating promising diagnostic value. Furthermore, levels of branched-chain amino acids (BCAAs)and β-aminoisobutyric acid were found to correlate with the severity of depressive symptoms as assessed by the Hamilton Depression Rating Scale (HAMD).

Discussion / Conclusion

Our study provides serum amino acid metabolic profiles of RDD patients and identifies potential biomarkers for this condition. These findings may offer clinicians an objective diagnostic method for early detection of RDD, as well as provide new insights into the pathophysiology of depressive recurrence.

Keywords

Recurrent Depressive Disorder, Amino acids, Biomarkers, Targeted metabolomics

00367
Impact of Preservative Type on Forensic Blood Alcohol Determination: analysis by HS-GC-FID

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

In the context of road traffic accident investigations, whole blood samples collected for ethanol determination are typically drawn into tubes containing a preservative, most commonly sodium fluoride in France. However, in routine forensic practice, ethanol measurements may also be performed on lithium heparin tubes used for drugs identification. The aim of this study was to evaluate, using headspace gas chromatography coupled with flame ionization detection (HS-GC-FID), the agreement between ethanol concentrations measured into 4-ml Vacutainer® sodium fluoride (NaF) tubes and into 9-ml Vacutainer® lithium heparin tubes. At present, no peer-reviewed publication has been identified that investigates this comparison.

Materials and methods

100 µL of whole blood and 100 µL of 1-butanol as internal standard were transferred into a 10 mL headspace vial, sealed, and vortex-mixed prior to analysis. Chromatographic separation (7.5 minutes) was performed on a mid-polarity Crossbond™ silarylene column (SH-I-624Sil-MS). A seven-point calibration curve (0.1–4 g/L) was prepared using ready-to-use LCG Standards.

Results

A total of 112 samples from 56 patients were analyzed (56 NaF tubes and 56 lithium heparin tubes). Ethanol concentrations were compared using a paired Student's t-test. No statistically significant difference was observed between the two tube types at the 0.05 significance level. Regardless of the storage duration at –20 °C (up to 18 months), ethanol concentrations remained consistent between the two types of preservatives tubes, with no significant differences observed.

Discussion / Conclusion

These findings indicate that, under the analytical conditions used, lithium heparin tubes provide ethanol concentrations comparable to those obtained from NaF tubes. Thus, lithium heparin tubes may serve as a reliable alternative for blood alcohol determination in forensic contexts when NaF tubes are not available.

Keywords

Preservative tubes, NaF, lithium heparinate, HS-GC-FID, whole blood, ethanol

00370
Preliminary application of novel dual-matrix volumetric microsampling device (InstaSep™) for quantification of five immunosuppressive drugs

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic drug monitoring (TDM) of immunosuppressive agents is essential for transplant recipients; however, conventional venous sampling restricts flexibility and may reduce patient adherence. Volumetric microsampling represents a promising alternative, contingent upon resolving analytical performance and matrix-related challenges. This study presents the preliminary application of a novel dual-matrix volumetric microsampling device (InstaSep™, SampleFacts, Uppsala, Sweden) for the simultaneous quantification of five immunosuppressive drugs using LC-MS/MS.

Materials and methods

Whole blood was collected using the InstaSep™ device, enabling volumetric sampling and physical separation into two distinct dried matrices following centrifugation. An LC-MS/MS method was developed on LC-MS/MS platform for tacrolimus, ciclosporin, sirolimus, everolimus, and mycophenolic acid (MPA, including glucuronide metabolite, MPAG). Method development involved systematic evaluation of approximately 30extraction scenarios, using three 3-mm punched discs per card. Analytical validation was conducted in accordance with international bioanalytical guidelines (ICH M10), including assessments of sensitivity, linearity, accuracy, precision, recovery, matrix effects, and stability.

Results

One 3-mm disc from each separated card was sufficient for quantification of all analytes with good sensitivity. The LLOQ was 0.5 ng/mL for ciclosporin, tacrolimus, sirolimus, and everolimus, and 0.1 mg/L for MPA and MPAG. A 2-hour drying time provided optimal recovery. Although the red blood cell membrane became fragile after drying, it was not compromised during punching. When hemolyzed blood was applied, visible hemolysis was observed in the plasma fraction, and immunosuppressive drugs were detected in plasma. Improved performance was achieved using freshly prepared calibration samples after 1 hour of equilibration at 36°C following spiking. The most suitable extraction involved reconstitution in acetonitrile or acetonitrile/methanol with an internal standard, followed by 45 minutes of sonication and liquid–liquid extraction with acidified tert-butyl methyl ether (MTBE).

Discussion / Conclusion

These results demonstrate the feasibility of the InstaSep™ dual-matrix microsampling device, combined with LC-MS/MS, for quantifying immunosuppressive drugs. The approach offers a robust, sensitive, and patient-centric decentralized TDM.

Keywords

InstaSep™; volumetric microsampling; immunosuppressive drugs; LC-MS/MS; therapeutic drug monitoring; analytical validation

00379
TDM of clonazepam and clobazam, the challenges of LC-MS/MS analysis

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The TDM Laboratory at Karolinska University Hospital analyzes over 100 pharmaceutical drugs, principally with LC-MS/MS. To meet the customer requests, an LC-MS/MS method for quantification of clonazepam (CZP), clobazam (CLB) and its active metabolite N-desmethylclobazam (N-CLB) in plasma was developed and validated, including selectivity in accordance with the ICH guidelines. Since the laboratory is accredited according to ISO15189, a proficiency testing (PT) program is required. After implementation of the analysis and evaluation of the PT samples, one of the LC-MS/MS systems was found to give slightly but systematically higher values for CZP, which lead to further investigations and the selection of a different analytical column.

Materials and methods

The analysis was performed on three identical LC-MS/MS systems to ensure the throughput of routine samples. The initial column used was a C18 which later was exchanged to a biphenyl. In both methods, plasma samples were precipitated with methanol containing isotope labelled internal standard (IS) for each analyte.

Results

Both methods were validated in the ranges of 5-500 nmol/L (CZP), 0.01-10 µmol/L (CLB) and 0.1-50 µmol/L (N-CLB). Accuracy and precision CVs were less than 15 % at all quality control levels. Investigation of the PT samples on the C18-column showed that carbamazepine partly co-eluted with the deuterated IS of CZP on one system, leading to ion suppression which caused the systematically higher concentrations. Changing the column to a biphenyl yielded better chromatographic separation and no ion suppression for CZP.

Discussion / Conclusion

When developing a new method, it is of great significance to investigate selectivity and interferences even when using an isotope labelled IS. PT samples are very important for the quantification accuracy and can help to discover methodological problems. After changing the column, the robust LC-MS/MS method is used to analyze patient samples 365 days a year with the possibility of reporting urgent samples within 24 hours.

00390
Point-of-Care Therapeutic Drug Monitoring Using Surface-Enhanced Raman Spectroscopy and Automated Microfluidics

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Timely drug concentration measurements are critical for dose optimization in oncology and intensive care units (ICU). However, current therapeutic drug monitoring workflows rely on centralized laboratories, resulting in turnaround times that may limit responsiveness in rapidly evolving clinical situations.[1] Point-of-care (POC) analytical systems capable of delivering reliable quantitative results directly at or near the bedside are therefore highly desirable.[2] Surface-enhanced Raman spectroscopy (SERS) offers molecular specificity and high analytical sensitivity, making it a promising candidate for decentralized drug quantification.[3]

Materials and methods

We developed an integrated analytical platform combining nanostructured silver nanopillar SERS substrates, centrifugal microfluidic discs for sample handling and detection, and a compact Raman reader.[4,5] The discs enable controlled fluid manipulation through centrifugal actuation and support on-disc SERS

measurements. The Raman reader regulates disc rotation, performs automated substrate scanning, and applies embedded multivariate regression models for quantitative analysis. Analytical evaluation was performed using methotrexate (MTX) and meropenem as relevant oncology and ICU drugs.

Results

For MTX, incorporation of solid-phase extraction (SPE) prior to SERS analysis reduced serum matrix interference and improved quantitative robustness. The µ-SPE to disc-based SERS approach achieved a limit of detection of 2.90 µM and a limit of quantification of 8.92 µM. Validation using patient samples demonstrated agreement with HPLC and immunoassay reference methods ($p < 0.05$) [4].

For meropenem, the centrifugal microfluidic SERS system achieved a limit of detection of 12.12 µM and a limit of quantification of 36.37 µM. Validation using ICU patient samples and comparison with HPLC reference analysis yielded $R^2 = 0.8$ ($p < 0.05$), with a mean positive bias of 14.3 µM. The integrated system enabled total sample analysis within approximately 30 minutes [5].

Discussion / Conclusion

These results demonstrate the analytical feasibility of a disc-based SERS platform for quantitative drug analysis in patient samples, supporting further development toward broader and more accessible point-of-care therapeutic drug monitoring.

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Keywords

Point-of-care testing

Surface-enhanced Raman spectroscopy

Oncology

Anti-infectives

Meropenem

Methotrexate

00417
Quantitation of Free Metanephrines using VAMS-collected (Mitra®) blood samples

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Metanephrine (MN), Normetanephrine (NMN) and 3-Methoxytyramine (3-MT), as stable metabolites of catecholamines are used as biomarkers of Pheochromocytomas tumors in clinical tests for diagnosis and treatment monitoring. Due to the risk of false positives, the patients should be supine, fasting, and at rest for at least 30 minutes before blood draw. In order to facilitate compliance with these restrictive conditions, Volumetric Absorptive Microsampling (VAMS) can be a helpful tool. The aim of the study was to adjust a ready-to-use kit (Chromsystems) for determination of Free Metanephrines (MN, NMN and 3-MT) in plasma for VAMS-collected (Mitra®) blood samples analysis.

Materials and methods

Blood samples/calibrators were collected on 30 µl Mitra® samplers and dried. Sample preparation included two stages: 1) hydration of the dried sample (addition of internal standards with extraction buffer, sonication, shaking) 2) SPE using 96 Well Plate according to the procedure provided with the kit (Chromsystems kit: 81000) with adjusted elution volume. Analysis were performed on QTRAP 5500+ LC-MS/MS system (SCIEX). Data processing and quantitation was done in SciexOS 3.3 software (SCIEX).

Results

Developed procedure met the validation criteria, including: reproducibility (%CV≤ 15% and accuracy 85-115%), LLOQ (S/N≥10) was established on calibrator 2 level (MN: 0.125 ng/ml; NMN: 0.181 ng/ml; 3-MT: 0.074 ng/ml), linearity (R≥0.995). Determined limits of detection (LOD) were: 0.0234 ng/ml for MN; 0.0222 ng/ml for NMN and 0.015 ng/ml for 3-MT.

Discussion / Conclusion

The procedure was successfully optimized enabling quantification of MN, NMN and 3-MT in VAMS-collected blood samples using ready-to-use kit with minimal method modification. Low LLOQ were achieved using only 30 µl of sample. Application of Mitra® samplers for blood collection enables patients collecting samples by themselves at home which is important especially for post-surgical tumor recurrence monitoring. Home sampling can help to meet sample collection restrictive requirements and will be more convenient for the patient.

Keywords

VAMS, metanephrines, quantification, LC-MS/MS

00419
Clinical validation of an improved method of simultaneous measurement of Tacrolimus, Cyclosporine, Sirolimus, and Creatinine using Dried Blood Spots.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Solid organ transplantation requires life-long immunosuppressive therapy, which needs to be monitored due to varying kinetics and a narrow therapeutic index. Therapeutic drug monitoring can be intensive on patients and healthcare resources. Patients and physicians could benefit from dried blood spot sampling. We validated a DBS method for the measurement of multiple immunosuppressive drugs and creatinine.

Materials and methods

Adults treated with immunosuppressives were included. DBS samples were collected using fingerprick and a Whatman 903 filter paper, which were compared to routine venipuncture samples. Bland-Altmann and Passing-Bablok analyses were used to assess agreement and bias between DBS samples and venipuncture samples.

Results

one hundred fifty-three patients were included for the clinical validation of the different analytes; Tacrolimus (36), Cyclosporine (39), Everolimus (38), Sirolimus (41), Creatinine (87). The mean bias for Tacrolimus was 0.1061 (95% limit of agreement -1.116 – 1.328) with 100% of the samples meeting the 20% acceptance limit. The mean bias for Cyclosporine was 1.730 (95% limit of agreement -68.47 - 71.93) with 85% of the samples meeting the 20% acceptance limit after correction. For Everolimus the mean bias was -0.03553 (95% limit of agreement -2.165 - 2.094) with 82% of the samples meeting the 20% acceptance limit. The mean bias for Sirolimus was -0.002162 (95% limit of agreement -2.962 - 2.957) with 63% of the samples meeting the 20% acceptance limit. The mean bias for Creatinine was -0.04425 (95% limit of agreement -45.16 - 45.08) with 86% of the samples meeting the 20% acceptance limit.

Discussion / Conclusion

We successfully validated a DBS method for the simultaneous measurement of Tacrolimus, Cyclosporine, Everolimus, Cyclosporine and Creatinine for convenient sampling after transplantation. This analytical method can help alleviate the burden of sampling for transplant patients and the hospitals.

Reference(s)

https://pubmed.ncbi.nlm.nih.gov/31268966/
https://pubmed.ncbi.nlm.nih.gov/35346637/

Keywords

Immunosuppressive therapy
Therapeutic Drug Monitoring
Dried Blood Spot
Transplantation

00426
Simple and robust analysis of alpelisib in breast cancer patient plasma samples using LC-DAD-FLD – a bioanalytical foundation for accessible TDM

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Alpelisib is used in the treatment of PIK3CA-mutated breast cancer. Its therapeutic drug monitoring (TDM) potential is exploratory [1], supported by evidence of a concentration-effect relationship [2]. Published analytical methods for determination of alpelisib in human plasma samples rely on mass spectrometry (MS) detection [2,3]. The aim of this work was to develop, validate and apply a liquid chromatography with diode array and fluorescence detection (LC-DAD-FLD) method for determination of alpelisib in human plasma samples.

Materials and methods

A Phenomenex Gemini C18 column (150 × 4.6 mm, 5 µm) was used, with water and methanol containing 0.1 % formic acid in gradient elution at 1 mL/min. Detection was carried out at 315 nm (DAD) and excitation/emission wavelengths 316/392 nm (FLD).

Plasma samples (100 µL) were prepared using simple protein precipitation with acetonitrile, followed by evaporation of the supernatant.

Results

The method was successfully validated in terms of linearity (range 300–3000 ng/mL, R > 0.996), precision (relative standard deviation 1.1–4.3 %), and accuracy (bias -1.8–11.3%). The matrix effects were negligible. Furthermore, two patient samples were analysed. Blood sampling was performed at steady state, 10 and 10.5 hours after the intake of a 300 mg dose of alpelisib, with quantified plasma concentrations of 783 and 1275 ng/mL, respectively. These results underline the feasibility of the method for clinical application as well as highlight potentially significant inter-individual variability, which may require further monitoring in the context of tolerability and effectiveness.

Discussion / Conclusion

The developed method represents a viable alternative to MS-based approaches due to its selectivity, robustness and cost-effectiveness, supported by its blue applicability grade index of 0.75 [4], as well as adequate sensitivity, accuracy and reproducibility.

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Keywords

alpelisib, HPLC, bioanalysis, analytical method, therapeutic drug monitoring

00441
Rapid and selective Methotrexate quantification in serum using a Lab-on-Disc SERS platform for clinical Therapeutic Drug Monitoring

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic drug monitoring (TDM) of methotrexate (MTX) is critical in oncology, particularly during high-dose therapy, where delayed clearance can cause severe toxicity. Timely and reliable MTX measurements are essential to guide leucovorin rescue and prevent adverse outcomes[1]. However, serum quantification remains challenging for immunoassays due to matrix complexity, structurally related metabolites (e.g.,DAMPA)[2], and co-administered medication such as 6-mercaptopurine (6-MP)[3]. While highly specific techniques like HPLC or LC-MS/MS address the issues, they require expensive instrumentation and centralized laboratory infrastructure. This limits accessibility in resource-constrained settings. We developed a centrifugal lab-on-disc (LoD) Surface-Enhanced Raman Spectroscopy (SERS) platform for rapid, selective, and cost-effective MTX quantification in serum samples[4].

Materials and methods

We evaluated multiple pretreatment methods: filtration and microextraction by packed sorbent (MEPS), for MTX extraction from human serum. The LoD integrates on-disc sample clean-up with silver-coated nanopillar SERS substrates, while

centrifugal microfluidics automates serum handling. This workflow streamlines and ultimately automates pretreatment, reducing manual steps and ensuring consistent sample processing. Extracted samples were analyzed using PCA, PLSR, ANN enebling selective discrimination and quantification of MTX in the presence of metabolites and 6-MP. Clinical performance was evaluated using patient samples against a reference assay.

Results

The integrated pretreatment step allowed reliable MTX quantification within the therapeutic range (20–200 µM) while minimizing matrix effects. The platform paired with data analysis enabled clear discrimination of MTX from its metabolites and from 6-MP in mixed-drug samples. MTX levels showed good agreement with immunoassay and total workflow was shorter than conventional laboratory-based assays.

Discussion / Conclusion

This integrated Lab-on-Disc SERS platform enables selective and accurate MTX quantification with reduced turnaround time. It shows strong potential for decentralized TDM in oncology, supporting faster clinical decisions, optimized rescue therapy, and improved patient safety, even in low-resource settings. Delivering timely, patient-specific measurements directly at the bedside translates the promise of personalized treatment into everyday clinical practice.

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Keywords

therapeutic drug monitoring

methotrexate

lab-on-disc

Surface-Enhanced Raman Spectroscopy

00444
General unknown screening of plasma proteins and their post-translational modifications using a LC-TOF-MS approach

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The identification of biomarkers able to detect diseases early and monitor their progression is an important part of precision medicine. Most pathophysiological processes induce changes in certain cell functions, that may translate in posttranslational modifications of proteins produced in this cell type, offering a large possibility of new biomarkers discovery. Our objective was to develop a new methodological approach to identify and quantify the highest possible number and diversity of plasma proteins and their associated post-translational modifications (PTMs), and confront these PTMs to different pathologies (1).

Materials and methods

After dilution of 20 µL of plasma in deionized water, proteins were separated, detected and identified using a 20-minute LC-TOF-MS method developed using a Bruker TIMS TOF Pro2 mass spectrometer. Separation was achieved on a Jupiter C4 column using a binary gradient of water and acetonitrile both containing 1% formic acid. Native protein high-resolution mass spectra were then obtained using appropriate deconvolution of multicharged spectra in the range of 5,000 to 100,000 Da. Samples from 30 healthy volunteers were screened.

Results

Deconvoluted spectra were exported in spreadsheet format and integrated in a processing pipeline developed in R. This processing tool integrates peaks, and tags the main proteins and their isoforms in a user-friendly manner. 37 PTMs were identified and quantified from 15 proteins including HSA and a majority of apolipoproteins.

Discussion / Conclusion

We have developed a “general unknown screening” procedure applicable to the identification of plasma proteins and their PTMs using a simple dilute and shoot approach, but highly selective in- high resolution mass spectrometry. This method can now be used in the search for plasma biomarkers of diseases, both in the study of variations in isoforms and in the relative abundance of proteins.

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Keywords

Biomarkers, Mass spectrometry, Proteins, Post-translational modifications

00484
Study on Factors Influencing Serum Concentration of Sodium Valproate in Patients with Bipolar Disorder

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

To analyze the influencing factors of valproic acid blood concentration in patients with bipolar disorder and provide reference for clinical individualized medication.

Materials and methods

A retrospective collection of 113 blood concentration monitoring data and clinical information from 101 bipolar disorder patients treated with valproic acid at Xijing Hospital from 2022 to 2025 was conducted, including body mass index (BMI), blood routine tests, liver and kidney function indicators, etc. Pearson correlation analysis was used for univariate analysis, and multivariate linear regression models were employed to screen for independent influencing factors of blood concentration.

Results

Univariate analysis showed that BMI (r=-0.303), white blood cell count (r=-0.378), hemoglobin (r=-0.404), hematocrit (r=-0.383), absolute lymphocyte count (r=-0.413), absolute basophil count (r=-0.324), alanine aminotransferase (r=-0.528), aspartate aminotransferase (r=-0.373), glutamyltransferase (r=-0.454), and albumin (r=-0.373) were negatively correlated with valproic acid blood concentration ($P<0.05$ or $P<0.01$), while AST/ALT (r=0.471) was positively correlated with valproic acid blood concentration ($P<0.01$). Multivariate linear regression analysis confirmed that the aspartate aminotransferase/alanine aminotransferase ratio (AST/ALT, β=0.386,

P<0.01) was an independent influencing factor of valproic acid blood concentration in bipolar disorder patients, with this model explaining 28.4% of the blood concentration variation (adjusted R^2=28.4%).

Discussion / Conclusion

Valproic acid blood concentration in bipolar disorder patients is influenced by blood routine tests and liver and kidney function. During clinical medication, the dosing regimen can be adjusted based on the monitoring results of the above indicators to achieve individualized and precise use of valproic acid, ensuring the blood concentration remains within the effective therapeutic range.

Keywords

Sodium Valproate; Therapeutic Drug Monitoring; Bipolar Disorder; Correlation

00485
Therapeutic drug monitoring of valproic acid in patients with epilepsy: a retrospective analysis of results and influencing factors

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Valproic acid (VPA) is a first-line antiepileptic drug with a narrow therapeutic window and considerable inter-individual pharmacokinetic variability. Although TDM is recommended to optimize efficacy and minimize toxicity, real-world data on factors influencing VPA concentrations remain limited. This study aimed to analyze VPA TDM results and identify clinical determinants of VPA exposure in epilepsy patients.

Materials and methods

Medical records of epilepsy patients who underwent steady-state trough VPA TDM between 2021 and 2025 at a Xijing Hospital were reviewed. Data collected included demographics, VPA daily dose, concomitant antiepileptic drugs, VPA trough concentrations, liver and renal function tests, and blood cell counts. Univariate and multivariate linear regression analyses were performed to examine associatiValproic acid.

Results

A total of 100 patients with TDM measurements were included. The mean age was 33.97 ± 18.57 years, and 82% were male. The mean VPA daily dose was 1080 ± 523

mg/day, and the mean trough concentration was 59.28 ± 23.29 μg/mL. Overall, 61% of concentrations were within the therapeutic range (50 - 100 μg/mL). Univariate analysis revealed that VPA concentration was positively correlated with daily dose ($r = 0.269$, $P < 0.01$) and negatively correlated with basophil percentage ($r = -0.215$, $P < 0.05$) and platelet count ($r = -0.342$, $P < 0.001$). In multivariate regression, daily dose ($\beta = 0.205$, $P < 0.05$) and platelet count ($\beta = -0.306$, $P < 0.05$) remained independent predictors of VPA concentration, together explaining 18.5% of the variability.

Discussion / Conclusion

This study demonstrates that VPA serum concentrations frequently fall outside the therapeutic range in clinical practice. Daily dose and platelet count were identified as independent predictors of VPA exposure, while basophil percentage showed a univariate association. These findings underscore the importance of routine TDM to guide individualized VPA dosing. Further prospective studies are warranted to validate these observations and explore underlying mechanisms.

Keywords

Valproic acid; Epilepsy; Therapeutic drug monitoring; Influencing factors; Platelet count

00494
Bridging the Gap Between Chemiluminescence Immunoassay and LC-MS/MS for Infliximab Monitoring: Method Validation and Clinical Comparability Study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Infliximab (IFX) is a cornerstone biologic for pediatric inflammatory bowel disease, where therapeutic drug monitoring (TDM) is essential but complicated by inter-platform variability. Systematic comparison of automated immunoassays with reference methods is therefore warranted. This study aimed to validate an in-house chemiluminescence immunoassay (CLIA) for IFX quantification and evaluate its agreement with liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Materials and methods

A CLIA kit was validated assessing limit of blank, specificity, linearity, accuracy, precision, matrix effects, and stability. IFX concentrations in 52 pediatric plasma samples were measured by CLIA and a reference LC-MS/MS method. Comparability was evaluated using linear regression, Passing-Bablok regression, and Bland-Altman analysis.

Results

CLIA showed excellent performance (LLOQ: 0.640 µg/mL; specificity < 10% interference; reportable range: 0.640 - 462 µg/mL). LC-MS/MS yielded higher concentrations than CLIA (median: 6.25 vs. 2.87 µg/mL). Strong correlation was observed (r = 0.9101) with no significant deviation from linearity (Passing-Bablok, p > 0.05). However, Bland-Altman revealed substantial mean relative bias (67.9%) and poor categorical agreement (52% concordance) within the therapeutic range (3 - 7 µg/mL), indicating non-interchangeability.

Discussion / Conclusion

We validated a rapid, automated CLIA suitable for high-throughput TDM. Despite strong correlation, significant quantitative differences preclude direct result substitution, underscoring the need for method-specific therapeutic thresholds.

Keywords

Chemiluminescence immunoassay; LC-MS/MS; Infliximab; Therapeutic drug monitoring; Children.

00505
Construction of AI assisted molecularly imprinted electrochemical sensor and its application in drug monitoring of levetiracetam therapy

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Levetiracetam (LEV), a first-line broad-spectrum antiepileptic drug, exhibits significant interindividual pharmacokinetic variability, particularly in pediatric populations, necessitating therapeutic drug monitoring (TDM) for dose optimization[1]. Conventional chromatographic-mass spectrometric methods, while accurate, suffer from prolonged turnaround times and limited point-of-care applicability[2]. Immunoassays remain susceptible to cross-reactivity[3]. Electrochemical sensing offers advantages of low cost, rapid response, and portability, making it promising for TDM point-of-care testing[4]. Molecularly imprinted polymers (MIPs), as artificial recognition materials with high selectivity and stability, can be integrated with electrochemical sensors for drug detection in complex matrices[5]. Therefore, this study proposes AI-assisted construction of a molecularly imprinted electrochemical sensor for point-of-care LEV monitoring.

Materials and methods

Gaussian and GROMACS simulations were employed to screen optimal functional monomers and template-to-monomer ratios for LEV.SPCE were sequentially modified with multi-walled carbon nanotubes, silver nanowires, and gold nanoparticles to construct a high-conductivity three-dimensional interface. MIP films were fabricated via electropolymerization, followed by template elution to create

recognition cavities. Key parameters including pH, polymerization conditions, elution and incubation time were systematically optimized. Methodological validation encompassed calibration curves, detection limit, specificity, reproducibility and stability. Serum samples from epilepsy patients were collected to evaluate sensor performance for LEV detection in authentic specimens.

Results

AI screening identified p-ABA as the optimal monomer with a 1:1 template-to-monomer ratio. Electrochemical characterization confirmed that the AgNWs/AuNPs/MWCNT/SPCE composite interface significantly enhanced electron transfer efficiency. Following MIP electropolymerization, peak current decreased markedly, while template elution effectively restored current response, confirming successful construction of imprinted cavities.

Discussion / Conclusion

This study achieved AI-assisted rational design for efficient screening of optimal LEV imprinting systems and successfully constructed a nanocomposite-enhanced MIP electrochemical sensor. Preliminary electrochemical results demonstrate high sensitivity and favorable interfacial conductivity, establishing a foundation for subsequent rapid and accurate LEV detection in authentic serum samples and clinical TDM applications.

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Keywords

Molecularly imprinted polymers; Therapeutic drug monitoring; Electrochemical sensor; Point-of-care testing

00542
Centrifugal Lab on Disc Surface Enhanced Raman Spectroscopy Platform for Rapid on-site Therapeutic Drug Monitoring of Meropenem

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Sepsis remain major cause of morbidity and mortality, particularly in intensive care units(ICUs), where timely administration and precise dosing of antibiotics are crucial. For β-lactam antibiotics such as meropenem(MER), therapeutic drug monitoring(TDM) is increasingly recommended due to pharmacokinetic variability in critically ill patients and the need to maintain effective and non-toxic levels[1]. Conventional analytical techniques, while accurate, require centralized laboratories which extend turnaround times, limiting timely dose adjustments, especially in limited resources healthcare settings[2][3]. We developed a centrifugal lab-on-disc(LoD) Surface-Enhanced Raman Spectroscopy(SERS) platform for rapid, selective, and cost-effective anti-infective quantification in serum samples. Our solution supports individualized anti-infective dosing.

Materials and methods

We developed a centrifugal microfluidic platform that integrates label-free SERS with automated sample handling for quantifying MER in serum. The system consists of a disposable microfluidic disc cartridge, spin motor, and embedded Raman spectrometer. A monospin solid-phase extraction(ms-SPE) column was coupled

upstream to enable off-disc serum cleanup. MER detection was performed on a silver nanopillar SERS substrate incorporated within the disc. Platform was paired with employed PLSR trained on large SERS datasets acquired across clinically relevant MER concentrations[1]. Performance was benchmarked against a commercial Raman setup and validated using serum from ICU patients analyzed by HPLC.

Results

Coupling ms-SPE with SERS platform significantly improved signal-to-noise ratios and analytical sensitivity. The PLSR model achieved limits of detection and quantification of 12.12 µM and 36.37 µM, respectively, suitable for TDM applications. Comparison to a commercial Raman system confirmed high analytical performance. Clinical validation against HPLC demonstrated a strong correlation($R^2 = 0.80$, $p < 0.05$), with a mean bias of 14.3 µM[1].

Discussion / Conclusion

This automated, compact platform enables MER quantification in 15–20 minutes, offering feasible solution for TDM of anti-infectives. Its integration of cleanup, label-free SERS detection, and chemometrics provides a promising solution toward rapid bedside monitoring of antibiotics and supports precision dosing in critical care.

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Keywords

Meropenem

Therapeutic Drug Monitoring

SERS

Lab-on-Disc

00546
Capillary Dried Plasma Microsampling for Lithium Therapeutic Drug Monitoring Using a Routine Colorimetric Assay

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic drug monitoring of lithium is essential due to its narrow therapeutic window and high interindividual variability. Capillary microsampling approaches such as dried plasma spots (DPS) offer advantages including minimal invasiveness, improved stability, and simplified logistics. This study aimed to develop and validate a simple method to estimate serum lithium concentrations using DPS generated from capillary blood collected with thr HealthID PSD plasma separation microsampling device and quantified using a routine colorimetric assay.

Materials and methods

DPS were obtained using the HealthID PSD capillary plasma separation device after finger-prick blood collection. Lithium was extracted with a bovine serum albumin solution and quantified using an automated colorimetric assay. A chloride-based correction factor was applied to compensate for variability in plasma volume within DPS extracts. Method validation included evaluation of linearity, extraction yield, precision, effects of hematocrit and applied volume, stability, and plasma migration uniformity. Clinical performance was assessed using paired serum and DPS samples from 40 patients undergoing lithium therapy. Agreement was evaluated using regression, Bland–Altman analysis, and predictive performance metrics.

Results

The method showed linearity from 0.1 to 2.5 mmol/L, extraction yields above 93%, and significant improvement in precision after chloride correction. Hematocrit (30–50%) and applied blood volume (160–240 µL) had minimal effects on corrected concentrations. Lithium remained stable for up to 21 days at room and elevated temperatures. In clinical samples, DPS-derived serum-equivalent concentrations demonstrated strong correlation with serum measurements (r = 0.984), minimal bias, and acceptable predictive error within clinical performance limits.

Discussion / Conclusion

Lithium can be reliably quantified in capillary DPS using a routine colorimetric assay combined with chloride normalization. The method provides accurate serum-equivalent estimates, shows robustness against preanalytical variability, and ensures extended analyte stability. This approach supports decentralized, minimally invasive therapeutic drug monitoring of lithium.

Keywords

Lithium; Dried plasma spots; Microsampling; Therapeutic drug monitoring; Capillary blood.

00567
Simultaneous Quantification of 17 Steroids Using a Semi Automated Tecan Kit on the Shimadzu Nexera X3/LCMS 8060NX

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Steroid hormones are essential regulators of metabolism, immune function, stress response, and reproduction. Accurate quantification of these hormones is critical for biomedical research, particularly in the investigation of endocrine disorders and metabolic diseases. To avoid the limitation of immunoassay (cross-reactivity and low multiplexing), the Tecan Steroid Panel LC-MS kit has been adapted to a Shimadzu Nexera X3 UHPLC coupled to an LCMS-8060NX.

Materials and methods

Samples were prepared using semi-automated solid-phase extraction on the Tecan Resolvex A200 to ensure optimal recovery and ionization efficiency for all target analytes. The data acquisition is done on 2 runs. Run 1 measured 14 steroids plus dexamethasone and run 2 measured Estrone and Estradiol. Chromatography used a C8 column with optimized gradients. The LCMS-8060NX operated in MRM mode with compound-specific transitions, collision energies, and stable isotope internal standards. Optimized chromatography and MRM transitions achieved robust separation of structurally similar and isobaric analytes (e.g., cortisol/cortisone; 11-deoxycortisol/21-deoxycortisol; 17-hydroxyprogesterone/11-deoxycorticosterone).

Results

Calibration was evaluated on 6 levels and employed linear models with 1/C or 1/C2 weighting. Calibration curves demonstrated excellent linearity (R2 >0.99 for most analytes; examples: 17-OHP4 0.998, testosterone 0.999, cortisol 0.999). Trueness was assessed on 3 QC sample levels (S1–S3) with an acceptance deviation at ±20%. The precision was done on high/low QC levels with 15 replicates. The acceptance was set on %CV <20% (e.g., 17-OHP4 3.9%/3.7%; testosterone 1.9%/3.2%; cortisol 4.5%/8.7%).

Discussion / Conclusion

The adapted Tecan kit on the Shimadzu Nexera X3/LCMS-8060NX provides a high-throughput, standardized workflow delivering strong linearity, accuracy, and precision suitable for clinical research. The semi-automated sample preparation reduces operator variability and improves reproducibility across large sample batches.

Reference(s)

Taylor AE et al., Eur J Endocrinol 2015; Vogeser M & Parhofer KG 2007.

Keywords

steroids; LC-MS/MS; multiplex; Tecan; Shimadzu

00585
Analytical and clinical performance comparison of the clozapine immunoassay with a liquid chromatography-tandem mass spectrometry assay

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic drug monitoring of clozapine, a first-line medication for treatment-resistant schizophrenia, is recommended for dose titration. Clozapine measurement is traditionally a send-out test with longer turnaround times. The MyCare Psychiatry Clozapine Assay is an immunoassay by automated clinical chemistry analyzers which can be implemented in-house to provide a faster turnaround time. This study evaluated the performance of the clozapine immunoassay and compared patients' results by the immunoassay to that of a LC-MS/MS assay.

Materials and methods

This study included a split-sample comparison between the clozapine immunoassay and an LC-MS/MS assay from a reference laboratory, and a recovery study using the immunoassay by spiking clozapine stock solution to blank serum samples. We also analyzed patient results before and after implementing the in-house clozapine immunoassay, including 659 clozapine results tested by the immunoassay in 15 months compared to 604 results measured by the LC-MS/MS assay in 19 months at the same hospital.

Results

Method comparison demonstrated a slope of 1.143 and a correlation coefficient of 0.9367 by Deming regression. The overall bias between the two methods is 4.6%. There were 56.5% (35/62) samples having a bias within ±20% between the two methods. The spiking study revealed an average recovery of 67.5% from the manufacturer's adjusted assay values. In the 604 results tested by LC-MS/MS at the same reference laboratory, the median (IQR) is 374 (217-539 ng/mL). There were 34.3% results falling with the listed therapeutic range (350-600 ng/mL). After the immunoassay implementation, 659 results were reported with a median of 339 (IQR 177-555 ng/mL, p=0.16) and 27.8% of results within the therapeutic range.

Discussion / Conclusion

The clozapine assay provides comparable results to the LC-MS/MS assay. The lower recovery from the spiking study was considered due to the solvent interference by methanol. Post implementation, the immunoassay produced similar long-term patient results statistics compared to the previous send-out LC-MS/MS assay.

Keywords

Therapeutic drug monitoring, clozapine, LC-MS/MS

00664
Impact of quadrupole time-of-flight mass resolution on quantitative reliability and discriminative performance of mid-regional proadrenomedullin

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Quantitative performance of biomarkers is critically influenced by analytical conditions, but the impact of instrumental parameter selection on downstream biomarker discrimination remains insufficiently investigated. Mid-regional proadrenomedullin (MR-proADM) is a clinically important peptide biomarker for the onset, progression, and mortality of various diseases including chronic kidney disease (CKD). Plasma MR-proADM is commonly quantified using immunoassays, while mass spectrometry approaches are increasingly being explored as alternative analytical platforms. In the present study, we systematically examined how mass resolution settings in quadrupole time-of-flight (QTOF) mass spectrometry influence MR-proADM quantification and the ability to discriminate renal dysfunction.

Materials and methods

We analyzed the data obtained from 211 randomly selected individuals with normal renal function and 89 individuals with CKD (eGFR < 60 mL/min/1.73 m2) enrolled in the Kyoto J-MICC Study. Plasma MR-proADM concentrations were quantified using micro-liquid chromatography coupled to QTOF mass spectrometry[1] operated at

multiple mass resolution settings (10, 20, 35, 50, 100, and 200 ppm), while all other analytical parameters were held constant. The mass spectrometry measurements were benchmarked against a time-resolved fluorescence immunoassay using the KRYPTOR platform. The discriminative performance of MR-proADM for CKD was evaluated using distribution analysis, effect size metrics, and receiver operating characteristic analysis.

Results

MR-proADM distributions and discriminative performance showed strong dependence on mass resolution. Lower resolution settings (10 and 20 ppm) were associated with broader quantitative distributions and reduced separation between individuals with and without CKD, whereas intermediate resolution settings (35–100 ppm) yielded tighter distributions, improved agreement with the reference immunoassay, and enhanced discriminative performance. Further increase in mass resolution did not provide additional benefit and was accompanied by renewed variability, indicating a non-monotonic relationship between mass resolution and biomarker performance.

Discussion / Conclusion

The results obtained using MR-proADM indicate that QTOF mass resolution is a critical determinant of quantitative reliability and downstream biomarker discrimination.

Reference(s)

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00673
Improving therapeutic monitoring of antibiotics: impact of lyophilised calibration standards on analytical robustness and laboratory workflow

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic drug monitoring (TDM) of antibiotics is essential for optimising treatment in various clinical contexts[1]. However, due to the limited stability of these compounds in solution, the weekly preparation of standard solutions for calibration ranges represents a significant workload for laboratories and a potential risk of reduced robustness[2]. Currently, our laboratory uses a multiparametric method for 15 antibiotics using liquid-chromatography coupled with triple-quadrupole-mass-spectrometer[3], for which the stability of standard solution is 5 days at 4°C. This study evaluates the evolution of our validated method to a lyophilised plasma calibration standard format to improve long-term robustness and laboratory workload.

Materials and methods

A standard solution containing 15 antibiotics (including meropenem, cefepime and levofloxine) at their upper limit of quantification (ULOQ), was prepared in a plasma matrix, aliquoted and lyophilised. Stability was evaluated at 6 months at -20°C for the lyophilised format and 10 days at 4°C after reconstitution . A calibration step (n=30) was performed using the conventional method to adjust the theoretical

concentrations to the real values after lyophilisation (e.g. amoxicillin was adjusted to 177.83 mg/L for a theoretical value of 200 mg/L). The method using lyophilised ULOQ was compared to the classic technique using 80 patient samples and internal quality controls over a two-month period.

Results

Stability after reconstitution showed satisfactory relative standard deviations ranging from 4.64% to 12.04%. Method comparisons for the 15 molecules demonstrated excellent linearity with R^2 ranging from 0.9051 to 0.9980. Regression slopes were highly consistent, ranging from 0.8585 to 1.0343 (e.g., amoxicillin: y=0.9412x+1.2756), with Bland-Altman-plots satisfying analytical requirements. External quality assessment confirmed the accuracy of the new method with z-scores< 2.

Discussion / Conclusion

Implementing lyophilised standards for antibiotic TDM enhances analytical robustness and streamlines workflow by reducing preparation from weekly to semi-annually. This strategy has been extended to quality control manufacturing and applied to other multiparametric methods, particularly antipsychotic drugs.

Reference(s)

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[2] Naicker S, Roberts JA, Cheng V, Parker SL, Seaton RA, Gilchrist M, Sime FB. A review of antimicrobial stability testing guidance for outpatient parenteral antimicrobial therapy programmes: is it time for global harmonization of testing frameworks? JAC Antimicrob Resist. 2024 Nov 28;6(6):dlae186. doi: 10.1093/jacamr/dlae186. PMID: 39619734

[3] Feliu C, Konecki C, Candau T, Vautier D, Haudecoeur C, Gozalo C, Cazaubon Y, Djerada Z. Quantification of 15 Antibiotics Widely Used in the Critical Care Unit with a LC-MS/MS System: An Easy Method to Perform a Daily Therapeutic Drug Monitoring. Pharmaceuticals (Basel). 2021 Nov 24;14(12):1214. doi: 10.3390/ph14121214. PMID: 34959617

Keywords

Therapeutic drug monitoring, antibiotics, lyophilised standards, robustness

00675
Analytical and Clinical Considerations in Schedule IV Drug Monitoring: Cross-Reactivity and Patient Outcome Analysis

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Solriamfetol is a Schedule IV medication approved for the treatment of excessive daytime sleepiness associated with narcolepsy and obstructive sleep apnea (OSA). Emerging reports suggest potential cross-reactivity with amphetamine urine immunoassays, which may result in unintended clinical consequences. Our objective is to evaluate the cross-reactivity of solriamfetol with amphetamine across four commonly used urine screening platforms and to determine the real-world frequency of false-positive amphetamine screens in patients prescribed solriamfetol.

Materials and methods

A dose-dependent interference study was performed by spiking drug-free urine samples with solriamfetol at concentrations ranging from 0.2 to 2000 µg/mL. Samples were analyzed on four immunoassay platforms: Beckman Coulter EMIT, Ortho Clinical Diagnostics Vitros 5600, Abbott Alinity c, and Roche Cobas c502. Liquid chromatography–tandem mass spectrometry (LC-MS/MS) served as the confirmatory method. A retrospective review was conducted exclusively in patients screened using the Beckman Coulter EMIT platform. Patients prescribed solriamfetol who underwent urine toxicology screening were identified, and positive amphetamine immunoassay results were evaluated, including confirmatory testing when available.

Results

Dose-dependent cross-reactivity was observed on three of four platforms. The Beckman EMIT, Abbott Alinity c, and Vitros assays produced false-positive amphetamine results at higher solriamfetol concentrations, whereas the Roche Cobas c502 demonstrated no cross-reactivity. All spiked samples were confirmed negative for amphetamines by LC-MS/MS. Among 41 patients prescribed solriamfetol (mean age 46 years; 78% female), 8 (19.5%) had at least one positive amphetamine screen. Five were concurrently receiving amphetamine–dextroamphetamine. Three patients (7.3%) had positive screens without documented amphetamine use; confirmatory testing in two cases was negative for amphetamines.

Discussion / Conclusion

Solriamfetol exhibits assay-dependent, dose-related cross-reactivity with certain amphetamine immunoassays. In this Beckman-screened cohort, 7% of patients experienced false-positive amphetamine screens without amphetamine exposure. Confirmatory mass spectrometry testing is essential when results are inconsistent with clinical history to minimize diagnostic errors and unintended patient impact.

Reference(s)

1. Gopal Kumar, Dennis Auckley, Troy Merrick, Michael Breckenridge, John C Carter, Mahesheema Ali. False positive urine amphetamine immunoassay due to solriamfetol. Sleep Medicine, 2023

Keywords

Schedule IV, Patient outcome, Cross reactivity

00702
Comparison between Roche's automated immunoassay (Cobas 8000) and LC-MS/MS (Cobas i601) methods for Therapeutic Drug Monitoring of carbamazepine, phenobarbital, phenytoin, and valproic acid

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

LC-MS/MS is considered the reference technique for therapeutic drug monitoring of antiseizure drugs due to its superior accuracy and selectivity compared to immunoassays. Our laboratory previously used KIMS immunoassays (Cobas 8000) for carbamazepine (CRB), phenytoin (PHN), phenobarbital (PHB), and valproic acid (VA). Recent introduction of a fully automated LC-MS/MS analyzer (Cobas i601) enabled round-the-clock testing in both routine and emergency settings. The objective of this study was to compare analytical performance of Roche Cobas i601 LC-MS/MS with Roche KIMS during method verification in a high-throughput laboratory.

Materials and methods

Verification followed Clinical and Laboratory Standards Institute (CLSI) guidelines EP06, EP15-A3, and EP17-A2 (1-3), assessing within- and between-run imprecision (5×4), limit of quantification, (LOQ), linearity (LIN), and bias on the Cobas i601 using

Roche QCs (2 levels). Method comparison using anonymized leftover patient samples was performed by Passing–Bablok regression.

Results

Table 1 summarizes results. Cobas i601 demonstrated high intra- and inter-assay precision, linear response across the therapeutic ranges and favorable trueness according to verification criteria. Manufacturer's linearity and LOQ data were confirmed. Method comparison showed strong agreement without statistically significant biases between the two techniques with Spearman's r ≥0.97.

Table 1	CRB KIMS	CRB LCMS/MS	PHB KIMS	PHB LCMS/MS	PHN KIMS	PHN LCMS/MS	VA KIMS	VA LCMS/MS
CV% within	≤1.5	≤1.5	≤2.1	≤3.4	≤2.8	≤2.3	≤4.4	≤1.8
CV% between	≤2.0	≤2.0	≤5.5	≤3.1	≤4.3	≤2.3	≤6.1	≤2.4
Bias%	≤6.6	≤1.8	≤(-)4.9	≤(-)1.7	≤1.9	≤1.8	≤2.0	≤(-)1.9
LOQ (mg/L)*	2.0	1.0	2.0	2.4	1.0	0.8	5.0	3.0
LIN (mg/L)*	2-20	1-15	2-60	2.4-60	1-40	0.8-40	5-150	3-120

*product insert Roche

Discussion / Conclusion

The fully automated Cobas i601 delivers highly reliable analyses for CRB, PHN, PHB and VA, enabling 24/7 routine and emergency testing without specialized LC-MS/MS expertise. With no clinically relevant differences from prior immunoassays but improved accuracy, implementation is technically and clinically justified.

Reference(s)

1. CLSI. Evaluation of Linearity of Quantitative Measurement Procedures EP06, 2nd edition [Internet]. 2020. Report No. Available from: https://clsi.org/shop/standards/ep06/

2. CLSI. User Verification of Precision and Estimation of Bias, 3rd edition. Wayne, PA, USA: Clinical and Laboratory Standards Institute; 2014. p. https://clsi.org/shop/standards/ep15/. Report Nos.: EP15-A3.

3. CLSI Evaluation of detection capability for clinical laboratory measurement procedures; Approved guideline — 2nd ed. 2012. CLSI document EP17-A2. Wayne, P, USA A: Clinical and Laboratory Standards Institute. https://clsi.org/shop/standards/ep17/

Keywords

LC-MS/MS, Cobas i601, therapeutic drug monitoring, carbamazepine, phenytoin, valproic acid, phenobarbital, immunoassay, method comparison

00707
Precision Dosing for Tuberculosis: Establishing the First Multiplex LC–MS/MS TDM Service for First-Line Anti-TB Drugs in New South Wales

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Subtherapeutic or toxic exposure to first-line anti-tuberculosis (TB) drugs contributes to treatment failure, adverse events and prolonged infectiousness. Despite increasing evidence supporting therapeutic drug monitoring (TDM), no laboratory in New South Wales currently offers monitoring of ethambutol, isoniazid, rifampicin or pyrazinamide. We developed and validated a multiplex LC–MS/MS assay to address this clinical gap.

Materials and methods

An in-house LC–MS/MS method for quantification of the four first-line anti-TB drugs in human plasma was validated according to NATA and NPAAC requirements. Validation included trueness, precision, linearity, limit of quantitation (LOQ), selectivity, matrix effects, carryover, dilution integrity, stability and measurement uncertainty.

Results

Ethambutol demonstrated trueness 99–104% and precision 3–6% over 0.3–8 µg/mL (LOQ 0.3 µg/mL). Pyrazinamide achieved trueness 98–100% and precision 5.6–5.9% (5–100 µg/mL; LOQ 4 µg/mL). Isoniazid showed trueness 97–100% and precision 4–

10% (0.5–15 µg/mL; LOQ 0.4 µg/mL). Rifampicin demonstrated trueness 98–100% and precision 5.6–5.9% (1–20 µg/mL; LOQ 0.8 µg/mL). Carryover was <20% of LOQ. Ion suppression was corrected using internal standards. Stability was acceptable at 4°C and after freeze–thaw cycles; isoniazid showed room temperature instability beyond 2 hours. Rifampicin autosampler degradation was mitigated by internal standard correction.

Discussion / Conclusion

This assay establishes the first local TDM capability for first-line TB therapy in NSW. The validated multiplex method enables precision dosing strategies to improve exposure, reduce toxicity and support public health management of tuberculosis.

Keywords

Therapeutic Drug Monitoring (TDM)

Tuberculosis Pharmacotherapy

LC–MS/MS

Multiplex Quantitation

Precision Dosing

Isoniazid

Rifampicin

Ethambutol

Pyrazinamide

Method Validation

00713
Determination of selected sartans in plasma on the LC-CN column using HPLC with fluorimetric detection

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Sartans are an important group of selective antihypertensive drugs that act by blocking the activation of angiotensin II AT1 receptors. A considerable percentage of ineffective treatment in resistant hypertension may be related to subtherapeutic dosage or non-adherence.

The aim of the study was to develop an analytical method suitable for monitoring primary sartanes: irbesartan (IRB) and telmisartan (TEL) in human plasma.

Materials and methods

An isocratic HPLC system with fluorescence detector was applied. The separation of IRB, TEL and internal standard bepridil (BEP) was performed at 25oC on Supelcosil LC-CN column (150 x 4.6 mm, 5 µm) which has not been used so far for the analysis of sartans. The mobile phase: CH3CN:H2O:0.5M KH2PO4:85% H3PO4 (270:227:3:0,05, v/v) was pumped at a flow rate of 1.5 mL/min. Ethyl acetate (4 mL) was used for 5-min liquid-liquid extraction from 0.2 mL plasma sample slightly acidified to pH=6 with 100 µL 0.5M KH2PO4. The analytical wavelength was 250 nm for excitation and 380 nm for emission.

Results

IRB, TEL and BEP were eluted at retention times of 3.0 min, 5.1 min and 6.6 min, respectively. Complete separation was achieved, with no significant interference from biological background. The extraction yield was: 87.8% for IRB, 93.4% for TEL and 92.1% for BEP. A linear signal-concentration relationship was demonstrated from 5 to 250 ng/mL (IRB) and from 0.5 to 30 ng/mL (TEL) when using 200 µL plasma sample and 50 µL injection volume. The target measurement range can be easily adjusted. Satisfactory intra-assay measurement precision (RSD <10%) was achieved for all compounds.

Discussion / Conclusion

Presented methodology may be applied as an analytical tool improving the pharmacotherapy in resistant hypertension.

Keywords

irbesartan, telmisartan, HPLC-Fluo, LC-CN column, bioanalysis

00720
Development and validation of a novel method for concomitant busulfan and treosulfan determination in plasma and Mitra™ microsampling device

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Busulfan and treosulfan are alkylating agents used in conditioning regimens prior to hematopoietic stem cell transplantation (HSCT). Busulfan requires therapeutic drug monitoring because of its narrow therapeutic window and high interindividual pharmacokinetic variability. Treosulfan pharmacokinetics are less studied but increasingly important, especially in pediatric patients. Volumetric absorptive microsampling (VAMS) using the Mitra™ device allows minimally invasive collection of small blood volumes (10 µL). This study aimed to develop and validate an LC–MS/MS method for the simultaneous determination of busulfan and treosulfan in VAMS samples and to assess its applicability in pediatric patients undergoing conditioning before bone marrow transplantation.

Materials and methods

An LC–MS/MS method for the simultaneous determination of busulfan and treosulfan in Mitra™ VAMS samples was developed. Analytes were extracted from VAMS tips using an organic solvent mixture containing an internal standard, followed by vortex mixing, sonication, and centrifugation. Chromatographic separation was performed on a reversed-phase (CN) LC column using gradient elution with water and acetonitrile containing formic acid, with MS detection using MRM pairs. Bu-d_8 was used as internal standard for both Bu and Tsu. Calibration ranges were 10–2000 ng/mL for busulfan and 0.5–100 µg/mL for treosulfan. Method validation followed international bioanalytical guidelines, evaluating selectivity, linearity, recovery, matrix effects, carryover, dilution integrity, and stability.

Results

The method demonstrated efficient extraction and chromatographic separation of both analytes within short run times. Calibration curves were linear ($r>0.99$). The lower limits of quantification met validation criteria, with intra- and inter-day precision <15% and accuracy within ±15% for quality control samples. Matrix effects were minimal, and stability studies confirmed analyte stability under all tested conditions.

Discussion / Conclusion

A novel LC–MS/MS method for the simultaneous determination of busulfan and treosulfan in Mitra™ samples was successfully developed and validated. The assay enables minimally invasive sampling and is suitable for pharmacokinetic studies and therapeutic drug monitoring in pediatric HSCT patients.

Keywords

busulfan; treosulfan; VAMS; LC–MS/MS; pediatric pharmacokinetics; hematopoietic stem cell transplantation.

00721
Assessing flaws in microsampling specimen : a pragmatic study in tacrolimus dried blood spots

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Volumetric absorptive microsampling (VAMS) are commonly used for the therapeutic drug monitoring (TDM) of tacrolimus in transplanted patients. However, VAMS are sometimes not filled correctly, particularly when patients self-sample at home. Thus, these samples are usually discarded. This work aimed to assess the clinical impact of wrong-filled VAMS.

Materials and methods

Tacrolimus quality control (Chromsystem^{TM}, theoretical concentration : 8.26ng/mL) was spiked onto VAMS tips (Neoteryx^{TM}, volume disclosed: 9.44µL) with controlled volumes to simulate underfilling (7µL/74%, 8µL/85%, 9µL/95%), overfilling (10µL/106%, 11µL/117%, 12µL/127%, 13µL/138%) and submerged-tips in liquid whole-blood samples. Experiments were performed in triplicate. Tacrolimus concentrations were measured using a validated UHPLC-MSMS. Visual inspection of tips was performed. The mean bias between the experimental and theoretical concentrations was calculated. A bias ≤± 15% was considered not clinically significant.

Results

Twenty-four samples were analysed. Due to the tips saturation capacity, filling tips above 12 µL was difficult. The underfilling was obvious for 7µL, 8µL and only slightly visible for 9µL. Overfillings were not obvious with the exception of an excessive thickness on the submerged-tips. The mean bias/range of concentration for each condition were : -28%/[5.83-6.2ng/mL] for 7µL, -17%/[6.58-7.37ng/mL] for 8µL, -7%/[7.03-8.53ng/mL] for 9µL, -9%/[7.26-7.70ng/mL] for 10µL, 6%/[8.63-8.87ng/mL] for 11µL, 23%/[8.50-13.29ng/mL] for 12µL, 19%/[8.34-12.39ng/mL] for 13µL and 61%/[12.36-14.26ng/mL] for submerged-tips. The concentration bias was ≤±15% between 9µL/95% and 11µL/117%.

Discussion / Conclusion

This study showed that, between 9µL/95% and 11µL/117%, the bias was not clinically significant which correlates with the visual aspect. Thus, those samples may be considered for TDM. We have developed a visual assessment grid that allows us to evaluate the use of VAMS or discuss a possible correction factor. The main problem remains the detection of overfilling. The quality of samples is crucial for TDM. Therefore, it is important to conduct an intensive training, especially if the sample collection is done by patients.

Keywords

immunosuppressive drug, transplantation, volumetric absorptive microsampling

00729
Assessing viability of dried blood spot-based analysis of epinephrine and norepinephrine: sensitivity gap analysis

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Catecholamines play a significant role in the central nervous system (CNS) and act as neurotransmitters or hormones, regulating various physiological functions. Due to their indispensable role, catecholamines are implicated in numerous diseases such as depression, anxiety, Parkinson and Alzheimer diseases, cancer, among others. Their instability and the need for quantification at low concentrations remain analytically challenging. Dried blood spot (DBS) microsampling can simplify logistics and improve pre-analytical handling in large clinical/toxicological and TDM-oriented studies; however, the low basal catecholamine levels combined with the small sample volume pose an analytical challenge.

Materials and methods

Preliminary liquid chromatography – tandem mass spectrometry (LC-MS/MS) conditions for epinephrine (E) and norepinephrine (NE) were evaluated using two setups: (i) HILIC chromatography coupled to an ACQUITY UPLC–Xevo TQ-MS and (ii) reversed-phase (RP) chromatography coupled to nanoLC–Xevo TQ-S micro.

Signal intensity and signal-to-noise ratio (S/N) were assessed from neat standards. In parallel, expected on-column mass from DBS punches was estimated considering typical 3–6 mm punch volumes combined with reported basal concentration ranges, to evaluate whether the current conditions are compatible with basal levels.

Results

In neat solutions (100 ng/mL), E and NE showed a signal intensity ranging from 4.9×10^{4} to 1.9×10^{6} and S/N >200 under microflow conditions, corresponding to 50 pg injected onto the column. However, mass calculations indicate that basal concentrations would translate into sub-pg amounts on-column when DBS punches are used, which may be limiting for direct DBS quantification at normal levels.

Discussion / Conclusion

These preliminary LC-MS/MS results show adequate response in neat solutions, but DBS application will require further optimization to reach the low on-column mass expected for basal catecholamines. Ongoing work will focus on increasing sensitivity by evaluating alternative MS instruments, reducing chromatographic dilution, and increasing sample volume, followed by matrix-based experiments.

Keywords

dried blood spot; catecholamines; epinephrine; norepinephrine; microsampling; LC–MS/MS

00730
Capillary Olanzapine Sampling Method validation Study (COSMOS)

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic drug monitoring is particularly valuable for antipsychotics, as measured concentrations provide critical insight into exposure–response relationships. Venous sampling is the current standard but is invasive and may cause distress in patients. Capillary microsampling, based on a simple finger prick, is a far less-invasive alternative that patients can perform at home, reducing hospital visits and lowering the threshold for monitoring. This study aims to validate capillary microsampling for olanzapine compared with venous sampling.

Materials and methods

This cross-sectional study compared capillary dried blood spot (DBS) with venous sampling for measuring olanzapine concentrations by quantification using a validated UPLC-MS/MS method. Agreement and bias between DBS and venous samples were evaluated with Deming regression and Bland–Altman analysis, using a predefined acceptance criterion of ±20% for at least 67% of ≥40 paired samples. The influence of hematocrit, albumin, and C-reactive protein (CRP) was assessed, with subgroup

analyses by sex, storage conditions, and concentration range. Different correction formulas were tested, and patient experiences with DBS versus venipuncture were descriptively assessed.

Results

In this interim-analysis thirty paired DBS–venous samples were included. Deming regression showed no constant or proportional bias, and Bland–Altman analysis indicated moderate agreement, with 50% of pairs within the predefined ±20% limits. Subgroup analyses showed no significant differences, and correction formulas did not improve agreement. Any correlation with hematocrit, albumin, and CRP will be assessed once the dataset is complete. Correlations with hematocrit, albumin, and CRP will be assessed in the final analysis once the inclusion target has been reached. Limited patient feedback indicated good tolerability of DBS sampling.

Discussion / Conclusion

In this interim analysis, capillary DBS showed moderate agreement with venous concentrations but did not meet formal clinical validation criteria. Additional research is needed to identify and address factors that may improve agreement.

Keywords

Dried blood spot, olanzapine, microsampling

00732
Quantification of tacrolimus and creatinine on Capitainer B50 cards – challenges and solutions for immunochemical and LC-MS/MS analysis

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

In transplant recipients, frequent therapeutic drug monitoring of immunosuppressants, e.g. Tacrolimus, and kidney function monitoring by creatinine is essential. Self-sampling potentially offers benefits for these patients. The aim of this study was to investigate the feasibility of the Capitainer B50 microsampling solution (Capitainer AB, Solna, Sweden) for quantification of Tacrolimus (B50-Tac) and creatinine (B50-Crea).

Materials and methods

Anonymized venous EDTA whole blood samples were pipetted onto B50-cards and dried overnight. Various elution protocols were evaluated for analysis of B50-Tac on Cobas Pro (Roche), B50-Crea on Atellica-CH (Siemens) and LC-MS/MS (Sciex) for both analytes.

In validations, the correlation between B50-results and routine method results was evaluated. Concentration re-calculation was done using linear regression equations. The total method coefficient of variation (CV) was calculated by using each B50-card double sample-disc results. Also, on-card analyte stability was studied at various storage conditions.

Results

B50-Tac could successfully be quantified (range 2-19 µg/L in blood) using Cobas Pro. A protocol applying elution with isotone NaCl followed by protein precipitation was used. The correlation of B50-Tac vs routine method showed R= 0.989 (n=101), and the CV was 4.2%. Applying the 4 and 6 µg/L decision limits for the recalculated B50-Tac concentrations resulted in diagnostic sensitivity and specificity of 94-100%. Tacrolimus was stable on B50-cards for at least 10 days.

For B50-Crea, Atellica-CH analysis was unsuccessful due to hemolytic interference. B50-Crea could however be quantified on LC-MS/MS after elution with a methanol:water mixture, showing promising correlation to routine method (R=0.995, n=15).

Lastly, B50-Tac and B50-Crea could be co-analysed in the same LC-MS/MS-assay, using the described elution protocol for Crea, and a hybrid retention mechanism LC-column.

Discussion / Conclusion

This study describes the first validated method enabling dried blood sampling for immunochemical analysis of Tacrolimus. Furthermore, promising results indicate that B50-Crea alone or along with B50-Tac may be quantified by LC-MS/MS. Validation studies are ongoing.

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Keywords

Dried blood spots

Microsampling

Tacrolimus

Creatinine

00736
Simulation-Based Training of Machine Learning Calibration Models for LC–MS/MS bioanalytical assays

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Calibration of LC–MS/MS assays in therapeutic drug monitoring typically relies on multiple calibration levels to estimate the slope and intercept of the calibration curve. Machine learning (ML) approaches may provide alternative strategies to estimate calibration parameters, but their performance depends on the availability and variability of training data. Simulation-based approaches could provide additional datasets reflecting realistic analytical variability and improve model development.

Materials and methods

Eighty-eight calibration curves were used for model development. Analyses were performed on an LC–MS/MS system equipped with a Sciex X500R QTOF detector. Analyte-to-internal standard peak area ratios (amoxicillin/IS) were measured across six calibration levels ranging from 10-100 mg/L.

XGBoost models were trained to estimate calibration slope and intercept using either all six calibration responses or two responses. Analytical performance was evaluated by back-calculating concentrations and identifying results exceeding ±10% deviation from reference back-calculated concentrations obtained using the instrument calibration.

Simulated calibration datasets (n=6000) were generated from a linear mixed-effects model fitted to experimental data, incorporating random effects on slope and intercept as well as heteroscedastic residual variability. ML models trained on simulated datasets were subsequently applied to experimental calibration datasets

for external validation. Statistical analyses were performed using the R statistical environment.

Results

When trained on experimental datasets, the six-point ML model resulted in 7 and 4 back-calculated concentrations exceeding ±10% deviation in the training and test datasets, respectively. The two-point model showed reduced robustness, producing 18 and 9 such deviations.

ML models trained on simulated datasets demonstrated good transferability to experimental data. In external validation, the six-point model produced one deviation beyond ±10%, while the two-point model produced two.

Discussion / Conclusion

Calibration datasets simulation based on mixed-effects models can generate realistic training data for ML calibration models. Models trained on simulated data can be successfully applied to experimental LC–MS/MS datasets and may support ML-assisted calibration strategies in analytical workflows.

00739
Determination of dasatinib, nilotinib, imatinib, and metabolite norimatinib in capillary dried plasma microsamples by LC-MS/MS

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Monitoring tyrosine kinase inhibitors (TKIs) in chronic myeloid leukemia (CML) enhances their efficacy, reduces adverse effects, and identifies issues related to patient adherence. Innovative sampling methods, such as dried plasma spots (DPS), improve the feasibility of therapeutic drug monitoring. This study aimed to develop and validate a bioanalytical method for quantifying dasatinib, nilotinib, imatinib, and norimatinib in DPS using the HealthID® plasma separation device and LC-MS/MS.

Materials and methods

Three 6 mm disks were incubated with 300 µL of 0.1% albumin at 45°C for 30 minutes, with 30 µL reserved for chloride analysis. The extract was subjected to liquid-liquid extraction with addition of Tris buffer pH 10, 20 µL of deuterated internal standards imatinib-D8, dasatinib-D8, nilotinib D3 and 1 mL of ethyl acetate:n-propanol (95:5, v/v). The organic layer was dried and the extracted recovered with mobile phase. Analysis was performed in a LC-MS/MS with positive electrospray ionization, using a C18 (100x2.1 mm, 1.7 µm) column and gradient elution with 0.1%

formic acid in water and acetonitrile. The method was validated according to ICH and applied to DPS samples from 33 patients with CML.

Results

Chromatographic run time was 6 minutes, with linearity (r > 0.99), CVs between 6.2–12.3%, and accuracy from 95.3-103.9%. Extraction yields ranged from 60.5%-70% and matrix effect was compensated by the internal standards, CV% 6.2-14.8%. There was no significative impact of hematocrit on accuracy -9-8% bias. The TKIs were stable for 31 days at 45 °C. DPS chloride corrected concentrations were within 1,106-4,461 ng/ml for nilotinib (n=6), 0.56-5.52 ng/mL for dasatinib, 100-2,190 ng/ml for imatinib, and 65-958 ng/mL for norimatinib. ITK concentrations in DPS represented 88.2%–124% of plasma levels, with correlation coefficients from 0.921 to 0.973.

Discussion / Conclusion

These results support the potential of DPS as a viable strategy for TKI monitoring, offering logistical advantages and sample stability without refrigeration.

Keywords

Imatinib, dasatinib, nilotinib, dried capillary plasma, CML

00741
Determination of Five Antihypertensives in Dried Capillary Plasma Spots by LC-MS/MS: A Novel Method for Monitoring Pharmacotherapy Adherence

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Adherence to hypertension treatment is critical for therapeutic success, as poor compliance negatively affects patients' quality of life and increases healthcare costs. Monitoring plasma drug concentrations offers a direct method to assess adherence, particularly for patients on complex regimens. This study aimed to develop and validate an LC-MS/MS method to quantify five antihypertensive drugs in dried capillary plasma collected via a microsampling device.

Materials and methods

Three 6 mm diameter discs were incubated with 150 µL of 0.1% albumin, after 45 minutes a 20 µL aliquot for chloride analysis. The remaining volume was precipitated with 25% trichloroacetic acid was added. After, 500 µL of methanol containing internal standards (losartan-D4 and atenolol-D7) was added. The extract was dried and reconstituted with 100 µL of methanol, and mixed with the supernatant from the protein precipitation. Analysis was performed using an octadecylsilic column with gradient elution of 0.1% formic acid in water and acetonitrile, while positive electrospray ionization was used for ionization, except for hydrochlorothiazide. The

method was validated according to ICH guidelines and applied to dried plasma spot (DPS) samples from 72 hypertensive patients.

Results

The run time was 8 minutes, demonstrating linearity from 0.5-500 ng/mL for amlodipine and losartan, and 1.5-1,500 ng/mL for atenolol, hydrochlorothiazide, and losartan ($r^2 > 0.99$). The method was precise an accurate with CV% 4.3-14.5% and bias -14-12%, with extraction yields between 75% and 101%. The analytes were stable at room temperature for 21 days. Concentrations of drugs in paired DPS and fresh plasma samples showed high correlation ($r = 0.93$ to 0.98) and represented, on average, 95.9-115% of plasma measurements. Notably, concentrations of amlodipine, hydrochlorothiazide, and losartan were lower in patients with adherence issues (n=21) compared to adherent patients (n=51) ($p < 0.05$).

Discussion / Conclusion

The bioanalytical method is promising for evaluating therapy and adherence to antihypertensives using dried plasma spot samples.

Keywords

Antihypertensive, therapeutic drug monitoring, LC-MS/MS, dried plasma spots.

00742
Evaluation of Creatinine Determination in Dried Plasma Samples from Pregnant Women Receiving Lithium Therapy

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Lithium is a cornerstone treatment for bipolar disorder but requires careful management due to its narrow therapeutic window. As pregnancy-induced increases in glomerular filtration can markedly affect lithium clearance, close monitoring of kidney function is essential. This can be achieved via assessment of plasma creatinine, to guide dosing and reduce maternal toxicity risk. Microsampling allows minimally invasive, frequent monitoring during pregnancy at home settings, and dried plasma spots (DPS) may eliminate the need to convert blood-based measurements to plasma, the reference matrix for creatinine.

Materials and methods

A previously developed and validated LC-MS/MS method for creatinine quantification in plasma and volumetric absorptive microsampling (VAMS) samples was employed. A newly developed DPS device, exploiting the KU Leuven (i)SIMPLE microfluidic technology (1), was evaluated: after applying 50 µL of whole blood, the device produces 2 DPS (5µl each) on 4-mm pre-cut paper discs. Analytical cross-validation was conducted using the DPS devices, assessing calibration, accuracy, precision, recovery, and robustness across varying blood hematocrit levels and

sample volumes. The clinical suitability of the DPS approach was examined by comparing creatinine measurements in DPS samples with those obtained from liquid plasma.

Results

Calibration curves were prepared by applying spiked liquid plasma calibrators onto 4-mm pre-punched filter paper discs identical to those used in the sampling device. Using a linear calibration model, all calibrators were within 15% of their nominal concentrations. Device precision was assessed by calculating the CV from duplicate spots, resulting in CVs below 8%. Recovery, assessed by comparing the results from device-generated DPS with DPS prepared by directly spotting the same plasma onto pre-punched filter paper discs, yielded a mean value of 99.6±9%.

Discussion / Conclusion

Our findings indicate that the new DPS device is fit-for-purpose:
the results meet predefined accuracy and precision
criteria, enabling reliable determination of creatinine concentrations in samples from pregnant women receiving lithium therapy.

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Keywords

Dried Plasma Microsampling, Creatinine, Lithium, Analytical Validation

00746
Microsampling-Based Quantification of Thiopurine Metabolites in Pediatric Solid Organ Transplant Recipients: LC–MS/MS Method Using VAMS, qDBS, and Conventional Blood Sampling

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Thiopurines, including azathioprine, are used as immunosuppressive agents in pediatric patients after kidney and liver transplantation. Therapeutic drug monitoring (TDM) of their metabolites, 6-thioguanine nucleotides (6-TGN) and 6-methylmercaptopurine nucleotides (6-MMPN), is essential to optimize efficacy and minimize toxicity. Conventional monitoring requires venous blood sampling, which may be challenging in pediatric patients due to repeated sampling and limited blood volume. Microsampling techniques such as volumetric absorptive microsampling (VAMS; Mitra™) and quantitative dried blood spots (qDBS; Capitainer B®) offer minimally invasive alternatives. This study aimed to develop and validate an LC–MS/MS method for quantifying thiopurine metabolites from microsamples and compare results with conventional whole blood.

Materials and methods

10 µL of whole blood samples were collected simultaneously using both Mitra™ VAMS and Capitainer B® devices and dried for 2 hours at room temperature. Analytes were extracted using a 45-min of ultrasound extraction in water (with internal standars and dithioeritol mixture). Next, protein precipitation and hydrolysis protocol followed by chromatographic separation on a C18-Kinetex-EVO column. Detection was performed using tandem mass spectrometry in positive electrospray ionization mode. Calibration curves ranged from 50–5000 pmol/8×10⁸ RBC for 6-TGN and 500–50,000 pmol/8×10⁸ RBC for 6-MMPN.

Results

The assay demonstrated good linearity ($R^2 \geq 0.995$) across the calibration ranges. Intra- and inter-day precision were ≤9.8% and ≤12.5%, respectively, while accuracy ranged from 92-108%. The lower limit of quantification (LLOQ) was estimated at 50 pmol/8×10⁸ RBC for 6-TGN and 500 pmol/8×10⁸ RBC for 6-MMPN. Extraction recovery averaged 82–95%, with matrix effects below 15%. Comparative analysis of paired venous blood and VAMS and qDBS microsamples (n=15) demonstrated strong correlation ($r \geq 0.94$) with minimal bias (<10%).

Discussion / Conclusion

These results suggest that microsampling combined with LC–MS/MS provides a reliable and patient-friendly alternative for monitoring thiopurine metabolites. The method may facilitate decentralized TDM and improve patient adherence to monitoring protocols.

Keywords

6-TGN; 6-MMP; VAMS; qDBS; azathioprine

00748
Determination of imatinib in oral fluid collected with quantisal® device by LC-MS/MS

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Imatinib (IM) is a first-line tyrosine kinase inhibitor for the treatment of chronic myeloid leukemia (CML). Therapeutic drug monitoring is recommended due to interindividual variations in pharmacokinetics and challenges in evaluating adherence. Oral fluid is a noninvasive alternative matrix with a detection window similar to that of blood and is being explored for therapeutic drug monitoring. This study aims to develop a bioanalytical method for the quantification of IM in oral fluid in LC-MS/MS

Materials and methods

Calibrators and quality controls were prepared in blank oral fluid and diluted (1:3 v/v) with the extraction buffer from Quantisal®. One mililiter of the oral fluid diluted with buffer was mixed with 50 µL of 1M NaOH, 2 mL of ethyl acetate, and 10 µL of the internal standard (IM D-8, 5 µg/mL). The organic layer was dried and resuspended in 100 µL of mobile phase. Analysis was performed on a UPLC-MS/MS Xevo® TQD-micro system using a C18 column, with gradient elution using water with 0.1% formic

acid (A) and acetonitrile with 0.1% formic acid (B) from 40% to 100% (B). Paired IM trough concentrations in oral fluid and plasma from 16 CML patients were compared.

Results

The chromatographic run time was 6 minutes, with IM retention time of 1.7 minutes.The calibration curve was linear between 10 and 1,500 ng/mL ($r = 0.999$). The method exhibited precision CV% 4.3-8.9% and accuracy 92-112%. The extraction yielded an average recovery of 70%, with no significant matrix effect. IM concentrations in oral fluid ranged from 15 to 1,200 ng/mL and were significantly correlated $r = 0.76$, $p < 0.05$ with plasma levels ranging from 100 to 2,210 ng/mL. Two patients were identified as nonadherent, with undetectable concentrations in both matrices.

Discussion / Conclusion

This method shows promise for saliva-based analysis due to its non-invasive collection and favorable preliminary results.

Keywords

Imatinib; Chronic myeloid leucemia; Therapeutic drug monitoring; oral fluid

00756
A Drop of Blood, a Full Panel: Therapeutic Drug Monitoring of Antiepileptic Drugs Using VAMS and LC–MS/MS

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic drug monitoring (TDM) is an essential tool in epilepsy pharmacotherapy, supporting dose individualisation, assessment of adherence, and prevention of toxicity—particularly for drugs with non-linear or complex pharmacokinetics and for active metabolites. Volumetric absorptive microsampling (VAMS) enables low-volume capillary blood collection and simplified logistics, which may improve access to TDM (e.g., paediatrics, remote sampling).

Materials and methods

We based the analytical workflow on the MassTox® TDM Series A "Antiepileptic Drugs XT2" LC-MS/MS All-in-One method (serum/plasma), covering 27 antiepileptic drugs and metabolites plus theophylline, using stable isotopically labelled internal standards and a rapid LC gradient (run time 4.9 min; injection ≤10 µL). Calibration is performed using analyte/ISTD peak-area ratios (y) versus calibrator concentration (x), with linear regression and $1/x^2$ weighting. For VAMS implementation, capillary blood is collected onto a VAMS device, dried, and extracted using an adapted protein-precipitation approach aligned with the kit principle (precipitation with ISTD,

centrifugation, dilution prior to injection), followed by LC-MS/MS acquisition in MRM mode (quantifier/qualifier transitions).

Results

The manufacturer’s analytical performance data in serum/plasma demonstrate broad quantitation ranges suitable for clinical TDM, e.g., LLOQ–ULOQ: levetiracetam 0,17–180 mg/L, valproic acid 88–250 mg/L, tiagabine 0.0067–0.500 mg/L (instrument-dependent). Prepared/diluted extracts are stable up to 14 days at +2 to +8 °C. These parameters provide a robust starting point for VAMS matrix-bridging and validation.

Discussion / Conclusion

A rapid, multiplex LC-MS/MS method for antiepileptic drugs can be conceptually extended to VAMS to reduce blood volume requirements and improve sampling flexibility. Implementation requires VAMS-specific validation (matrix effects, haematocrit influence, extraction efficiency, carryover, and—if clinically needed—conversion strategy between whole blood and serum/plasma equivalents) before routine reporting.

Keywords

VAMS, microsampling, LC-MS/MS, therapeutic drug monitoring, antiepileptic drugs, MRM

00758
Bridging the Gap: D-Penicillamine Measurement in VAMS with Parallel Whole Blood and Plasma Quantification

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

D-penicillamine (DPA) is a key chelator in Wilson's disease, but its measurement is analytically demanding because it can occur in different redox forms (e.g., monomeric and disulfide/dimeric species) and may undergo interconversion during handling. A microsampling approach using volumetric absorptive microsampling (VAMS) could facilitate outpatient and paediatric monitoring, provided that results can be robustly bridged to conventional matrices (whole blood and plasma).

Materials and methods

Capillary blood is collected onto Mitra™ VAMS tips (fixed volume) and dried under controlled conditions. In parallel, venous blood is collected into anticoagulant tubes; an aliquot is processed as whole blood, and the remainder is centrifuged to obtain plasma. Sample preparation controls DPA redox variability via stabilisation during extraction (e.g., chemical reduction and/or thiol derivatisation) to drive DPA into a defined measurable form prior to LC–MS/MS; internal standard is added early to correct for recovery and matrix effects. LC–MS/MS quantification is performed in MRM mode with matrix-matched calibration (VAMS extract, whole blood, and plasma as appropriate). Method validation follows fit-for-purpose bioanalytical principles with

VAMS-specific experiments: hematocrit bias assessment, extraction recovery, matrix effects, stability in dried VAMS, and incurred-sample reproducibility. Bridging between matrices uses paired samples to derive and verify conversion models.

Results

This approach is expected to yield: (1) selective and stabilised LC–MS/MS measurement of DPA across matrices by minimising redox interconversion; (2) paired-sample datasets enabling quantitative agreement assessment between VAMS, whole blood, and plasma (bias/limits of agreement and regression-based conversion); and (3) evidence-based pre-analytical recommendations for VAMS drying/storage that preserve DPA integrity.

Discussion / Conclusion

A three-matrix strategy (VAMS + whole blood + plasma) strengthens clinical implementability by allowing laboratories to report DPA in the matrix used in routine care while leveraging the logistical advantages of VAMS. Key success factors are rigorous stabilisation of thiol chemistry and robust matrix-bridging to ensure comparability and interpretability of results across sampling approaches.

Keywords

penicillamine, VAMS, microsampling, LC–MS/MS, whole blood, plasma, thiol derivatisation, matrix bridging, Wilson’s disease

00762
Development and Validation of a LC-MS/MS method for the quantification of atypical antipsychotics in dried capillary plasma samples

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Psychotic disorders such as schizophrenia require ongoing treatment with atypical antipsychotics. Adherence to treatment remains a challenge, making therapeutic drug monitoring (TDM) essential for individualizing therapy and ensuring efficacy. Micro sampling of dried capillary plasma (DPS) offers a less invasive alternative for blood collection, as well as logistical benefits for transport and storage. This study aimed to develop and validate a LC-MS/MS method for quantifying the atypical antipsychotics olanzapine, quetiapine, clozapine, and norclozapine in DPS obtained with Health ID device.

Materials and methods

Three 6 mm DPS disks were extracted with 300 ul 0.1% albumin, with 30 µL reserved for chloride analysis, followed by liquid-liquid extraction with 1 mL of ethyl acetate at pH 10. Analyses were performed via LC-MS/MS with electrospray ionization in positive mode, using a C18 column at 50°C. The analytes were eluted with 0.1 mM ammonium formate in water 0.1% formic acid in gradient from 10 to 90%

methanol at a flow rate of 0.4 mL/min over 6.0 minutes. The method was applied to 13 patients, with a chromatographic run time of 8 minutes.

Results

The method demonstrated precision (CV% of 4.5 to 15%), linearity (24 to 2,400 ng/mL for clozapine, norclozapine, and quetiapine; 4 to 400 ng/mL for olanzapine), and accuracy for olanzapine (84% to 98%). The matrix effect was compensated for by the internal standard, with values ranging from -16.7% to -1.87%. Average extraction yields were 65% for clozapine, 63% for quetiapine, and 43% for olanzapine. Clozapine and norclozapine chloride corrected concentrations ranged from 90% to 110%, quetiapine from 87% to 114%, and olanzapine from 103% to 138% compared to serum.

Discussion / Conclusion

The method presented adequate analytical performance for the quantification of the atypic antipsychotics in capillary dried plasma samples. A study with a larger patient cohort to establish correlations between DPS and venous serum measurements is ongoing.

Keywords

atypical antipsychotics, dried capillary plasma samples, LC-MS/MS.

00764
Analytical and Clinical validation of Dried Blood Spot (DBS)-Based Therapeutic Drug Monitoring of Mycophenolic Acid

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Traditional venous sampling poses logistical challenges for serial monitoring of mycophenolic acid (MPA), a key immunosuppressant in solid organ transplants and autoimmune disorders. This study developed and validated a robust LC-MS/MS method for MPA using Dried Blood Spot (DBS) sampling, with clinical validation against plasma analysis

Materials and methods

Venous plasma and DBS methods were optimized via LC-MS/MS. Analytical validation followed international guidelines, evaluating linearity, precision, accuracy, and hematocrit (Hct) effects (range: 19.3%–49.3%). A clinical study used 76 paired samples from 36 patients. Hct bias was corrected using C_pred=C_DBS/(1-Hct). Agreement was assessed via Pearson correlation, Intraclass Correlation Coefficient

(ICC), Passing-Bablok regression, and Bland-Altman analysis. Covariates (serum albumin, creatinine) were evaluated.

Results

The method showed excellent linearity ($r^2>0.99$) from 0.1–50 mcg/mL, with intra- and inter-day precision (CV%) <15%. Raw DBS underestimated MPA (6.85% within ±20% acceptance); Hct correction boosted pass rate to 79.45% (>67% regulatory threshold). ICC was 0.95; Pearson r=0.95. Passing-Bablok slope was 0.985 (95% CI: 0.953–1.022), indicating no proportional bias. Median Absolute Percentage Error (MdAPE) was 8.77%. No bias correlation with albumin (p=0.326) or creatinine (p=0.754).

Discussion / Conclusion

The Hct-corrected DBS method offers robust analytical performance and excellent plasma agreement, neutralizing volumetric biases across clinical profiles. It supports routine monitoring and remote care in transplant patients.

00765
Enhanced Ultra Sensitive Measurement of Serum Estrogens Using the Xevo TQ Absolute XR with UHPLC MS/MS for Clinical Research Applications

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Accurate quantification of estradiol (E2) and estrone (E1) at low pg/mL concentrations is essential for clinical research, yet immunoassays often lack adequate sensitivity and specificity. Many LC–MS/MS approaches require large sample volumes or derivatization. The Xevo™ TQ Absolute XR Mass Spectrometer, incorporating extended dynamic range and XR StepWave™ Ion Guide technology, may improve low-level estrogen measurement when paired with UHPLC separation and minimal sample preparation.

Materials and methods

Certified reference materials for E2 and E1 and their 13C3-labeled internal standards were prepared in stripped human serum. Calibration ranges were 2–1000 pg/mL (E2) and 1–1000 pg/mL (E1). QC samples were generated at 3, 10, and 700 pg/mL.
A 250-µL serum aliquot underwent liquid–liquid extraction with hexane:ethyl acetate (85:15), followed by evaporation and reconstitution. Chromatography used an ACQUITY™ UPLC™ I-Class FL IVD System with a CORTECS™ Phenyl Column and a water/methanol/ammonium-fluoride gradient.
The Xevo TQ Absolute XR operated in negative electrospray with MRM quantifier/qualifier transitions (0.7 FWHM). Precision, linearity, sensitivity, and matrix

effects were evaluated across multiple runs. Accuracy was assessed using UK NEQAS E2 materials.

Results

The UHPLC–MS/MS method achieved baseline separation of E1 and E2 in 4.75 minutes. Calibration ranges were linear ($r > 0.999$) and within-run and total precision were ≤3.2% CV. Quantification limits were 1.0 pg/mL (E1) and 3.0 pg/mL (E2), meeting criteria of ≤20% CV, ≤15% bias, and S/N ≥ 10. Matrix factor studies showed mild ion enhancement, effectively corrected by internal standards. Interference testing demonstrated 85–115% recovery. Comparison with UK NEQAS E2 samples showed strong agreement (Deming slope ~1.0; mean bias −2.5%).

Discussion / Conclusion

The Xevo TQ Absolute XR Mass Spectrometer enables sensitive, precise low-level estrogen quantification from small serum volumes without derivatization, supporting its suitability for clinical research.

For Research Use Only. Not for use in diagnostic procedures.

00766
Exploring the Capabilities of Intact Peptide LC MS/MS for Plasma Quantification of Amyloid β1 40 and Amyloid β1 42 for Clinical Research

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Amyloid-β (Aβ) peptides, including Aβ1-40 and Aβ1-42, are important molecular species for clinical research into amyloid biology and neurodegeneration. Their quantification in plasma is analytically challenging due to low endogenous concentrations, susceptibility to matrix effects, and the presence of multiple isoforms.

Materials and methods

A streamlined affinity-capture process was used to enrich Aβ peptides prior to LC-MS/MS analysis. Magnetic beads coupled to an Aβ 1-16 antibody enable broad capture of Aβ species. Samples (400 µL) were processed using only three reagents, with 15N-labelled internal standards added at the start of extraction. Chromatographic separation was performed on a peptide-optimized C18 column (2.1 x 50 mm, 1.7 µm, 300 Å) using a water/acetonitrile/ammonia mobile phase with a 10 minute cycle time.

A Xevo™ TQ Absolute Mass Spectrometer quanitfied intact Aβ peptides in the +4 charge state using MRM transitions for Aβ1-42, with corresponding stable-isotope internal standards.

Calibration ranges were 25–1600 pg/mL (Aβ1-40) and 5–320 pg/mL (Aβ1-42). Analytical performance was evaluated using diluted pooled plasma, depleted plasma supplemented with defined concentrations of Aβ peptides, and multiple-level QCs (low, medium and high).

Results

Calibration curves were highly linear across the full analytical range (Aβ1-40 R^2=0.9997; Aβ1-42 R^2=0.9994).

Precision studies conducted across multiple days showed %CV values typically 4.6–10.7% for Aβ1-40 and 8.1–13.2% for Aβ1-42 across the concentration range. Accuracy (recovery) across QC levels remained within ±15% for both peptides. At sub-quantifiable concentrations, Aβ1-42 demonstrated the expected increase in imprecision, while Aβ42/40 ratios remained stable within the low pg/mL research-use range.

Discussion / Conclusion

This simplified affinity-capture LC-MS/MS workflow enables sensitive, linear, and reproducible quantification of intact $A\beta_{1-40}$ and $A\beta_{1-42}$ in depleted plasma for clinical research applications.

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00768
Long run LC–MS/MS robustness in human plasma: a 30,000-injection evaluation of quantitative stability, carryover, and uptime on a triple quadrupole platform for clinical research.

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

High-throughput bioanalytical laboratories require LC–MS/MS systems that maintain quantitative stability in plasma matrices over long sequences with minimal maintenance. Protein-precipitation workflows are efficient but sometimes avoided due to concerns about ion-path contamination during extended runs. This study evaluated long-term robustness of a plasma-based LC–MS/MS workflow, focusing on signal stability, quantitative accuracy, carryover, and the sufficiency of simple user-level maintenance. Naltrexone and 6β-naltrexol were selected as model analytes due to their well-characterised metabolic variability and clinically relevant concentration ranges.

Materials and methods

Naltrexone and 6β-naltrexol were quantified in human plasma using a Xevo™ TQ Absolute XR tandem quadrupole mass spectrometer coupled to an ACQUITY™ Premier LC system. A 2.1-min reversed-phase method (5 µL injection, 0.8 mL/min, 60 °C column) was applied across 64 plates, each containing calibration standards (0.2–100 ng/mL) and five QC levels. Each plate was analysed five times, generating 30,720 injections over ~55 days. Bracketed calibration, and acceptance limits followed standard bioanalytical validation criteria (±15%, ±20% at LLOQ). Carryover was evaluated using bracketed blanks. Maintenance was limited to weekly cone cleaning without venting.

Results

Quantitative performance was stable across the entire 30,000-injection sequence, with no unscheduled downtime and >21 mL of plasma injected. All 320 plate runs met prespecified criteria for calibration linearity, QC accuracy/precision, and absence of carryover. At the LLOQ (0.2 ng/mL), %RSD was typically <3–3.5%, with 99.6% (naltrexone) and 99.8% (6β-naltrexol) of results within ±20%. Across all QC levels, 99.7% of values met acceptance criteria, with minimal drift in chromatographic or ion-path performance.

Discussion / Conclusion

The Xevo TQ Absolute XR Mass Spectrometer demonstrated consistent long-run quantitative robustness and low carryover under plasma-rich, high-throughput conditions. Simple weekly maintenance was sufficient to maintain sensitivity and uptime, supporting the platform’s suitability for sustained, productivity-focused LC–MS/MS workflows.

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Anti-Infective Drugs

00012
A multicentre, randomised controlled clinical trial to study the impact of bedside model-informed precision dosing of vancomycin in severely ill neonates and children– BENEFICIAL trial.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Whether model-informed precision dosing (MIPD) of vancomycin, compared with standard-of-care therapeutic drug monitoring (TDM), increases PK/PD target attainment, is safe and reduces vancomycin-associated acute kidney injury (AKI), is uncertain. This study compared PK/PD target attainment, safety and efficacy of Area-Under-the-concentration-time-Curve (AUC)-based MIPD in severely ill children.

Materials and methods

A multicentre, randomised controlled superiority trial was conducted across 14 intensive care and haematology–oncology units in seven Belgian hospitals. Patients aged <18 years initiating intravenous vancomycin for suspected or confirmed Gram-

positive infection were eligible. Exclusion criteria included extracorporeal support, severe AKI, chronic kidney disease, or imminent death. The intervention combined the use of an MIPD dosing calculator for starting and follow-up doses, as compared to standard-of-care TDM. The target 24-hour AUC was 400–600 mg·h/L. The primary outcome was the proportion of patients achieving this target between 24 and 48 hours after treatment initiation. Key secondary outcome was the proportion of patients with (worsening) AKI or death. Safety was evaluated in all patients receiving at least one dose.

Results

332 patients between 1 day and 18 years of age were randomised (165 standard-of-care; 167 intervention). PK/PD target attainment at 24–48 h was achieved in 82/156 (52·6%) patients in the standard-of-care group and 112/158 (70·9%) in the MIPD group (absolute difference: 18·3% [95% CI 2·0–33·9])). Proportion of patients with AKI or death favored the intervention group but was not statistically significant (absolute difference: -4·5% [95% CI: -11·6% to 3·5%]). Serious adverse events occurred in 8/156 (5·1%) patients in both groups.

Discussion / Conclusion

AUC-based MIPD improves early PK/PD target attainment and is safe. Given that elevated vancomycin AUC is a well-established driver of AKI, the lower cumulative exposure and numerically lower AKI incidence observed in this trial support the use of MIPD in severely ill children, particularly those requiring longer treatment durations or presenting with additional AKI risk factors.

Reference(s)

De Cock P. et al. A multicentre, randomised controlled clinical trial to study the impact of bedside model-informed precision dosing of vancomycin in severely ill neonates and children– BENEFICIAL trial., for the Beneficial study group. Accepted for publication in Lancet Child & Adolescent Health

Keywords

model-informed precision dosing; vancomycin; severily ill; neonates; children

00017
Impact of formulation and proton pump inhibitors on posaconazole target attainment and safety: a real-world study in patients with invasive pulmonary fungal infection

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Posaconazole is a broad-spectrum triazole antifungal used for the prophylaxis and treatment of invasive pulmonary fungal infections (IPFI). However, it exhibits significant pharmacokinetic variability, particularly with oral formulations, which can be influenced by gastrointestinal function and concomitant medications like proton pump inhibitors (PPIs). Real-world data regarding target attainment across different formulations and specific toxicity thresholds in Chinese patients remain limited. This real-world study, encompassing three posaconazole formulations, aimed to evaluate the target attainment rate of posaconazole in patients with IPFI, thoroughly analyses independent risk factors for inadequate exposure, and explore the potential plasma concentration threshold for hepatotoxicity in a Chinese population.

Materials and methods

This single-centre, retrospective observational study conducted between January 2023 and August 2025 enrolled 148 patients with IPFI. Posaconazole was administered for prophylaxis with a target trough concentration of ≥0.5 mg/L, or for treatment with a target of ≥1.0 mg/L. Multivariable logistic regression was utilised to identify independent predictors of subtherapeutic exposure.

Results

Subtherapeutic trough concentrations were observed in 24.0% of the prophylaxis group and 23.3% of the treatment group. Concomitant proton pump inhibitor (PPI) use was the dominant independent risk factor for subtherapeutic exposure in both prophylaxis (OR 17.97, 95% CI 4.22–76.53, P<0.001) and treatment (OR 3.60, 95% CI 1.10–11.75, P=0.034) groups. Regarding regimen optimisation, switching to the intravenous formulation proved more effective than oral dose escalation for correcting subtherapeutic levels. Furthermore, an exposure–safety analysis revealed that hepatotoxicity rates increased significantly when trough concentrations exceeded 1.95 mg/L (P=0.015).

Discussion / Conclusion

Subtherapeutic posaconazole exposure remains common. PPI use is a critical risk factor that may not be fully overcome by delayed-release or intravenous formulations. We propose a potential exposure–hepatotoxicity threshold of 1.95 mg/L for Chinese patients, highlighting the need for individualised therapeutic drug monitoring to balance efficacy and toxicity.

Keywords

Posaconazole, Therapeutic Drug Monitoring, Proton pump inhibitors, Hepatotoxicity

00021
Bone Penetration of Amoxicillin in Patients with Medication-Related Osteonecrosis of the Jaw: A Preliminary Study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Medication-related osteonecrosis of the jaw (MRONJ) is a complex clinical condition that appears to be associated with impaired bone perfusion and alterations in local drug distribution. These pathophysiological changes may affect the penetration of antimicrobial agents into bone tissue and potentially compromise treatment efficacy. The aim of this study was to compare amoxicillin exposure in both plasma and bone tissue between patients with MRONJ and control subjects undergoing oral surgery, in order to better characterize differences in systemic and local drug distribution.

Materials and methods

Twenty-seven patients treated with bisphosphonates or denosumab were enrolled between 2022 and 2024. Twelve patients with MRONJ were classified as cases, while fifteen were included as controls. Baseline characteristics, antibiotic regimens, and amoxicillin concentrations in plasma and bone tissue were collected. Drug concentrations were normalized to the administered dose.

Results

Cases and controls were well matched with respect to age, sex, body mass index, laboratory parameters, and duration of antibiotic therapy, indicating good baseline

comparability between the two groups. Median plasma amoxicillin concentrations did not differ significantly between patients with MRONJ and control subjects (p=0.533), suggesting comparable systemic drug exposure. In contrast, amoxicillin concentrations in bone tissue were significantly lower in MRONJ cases than in controls (p=0.004), highlighting a marked difference in local drug distribution. Consistently, the bone-to-plasma concentration ratio showed a trend toward lower values in patients with MRONJ compared with controls (49% vs 298%), although this difference did not reach statistical significance (p=0.133).

Discussion / Conclusion

Despite similar systemic exposure, bone amoxicillin concentrations were significantly reduced in patients with MRONJ, suggesting impaired local drug distribution, potentially related to necrosis and reduced vascularization. These findings highlight the need for personalized antibiotic strategies in the management of MRONJ and provide a rationale for the reduced effectiveness of beta-lactam antibiotics in this clinical setting.

Keywords

MRONJ; bone drug distribution; antibiotic; bisphosphonates; denosumab

00022
Proactive Intervention Model for Voriconazole TDM: Development and Efficacy

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Voriconazole (VCZ) exhibits nonlinear pharmacokinetics with marked variability and a narrow therapeutic index. Asian populations show heightened susceptibility to overexposure and hepatotoxicity, necessitating therapeutic drug monitoring (TDM) (Takesue et al. 2022). However, current data reveal that fewer than one-third of surveyed institutions in China have adopted VCZ TDM in routine practice (Liu et al. 2022), constrained by fragmented workflows spanning sampling to interpretation (Miyakis et al. 2010), and delays in achieving steady-state (Hanai et al. 2023). Transitioning from passive result-reporting to proactive integrated management is therefore warranted to advance TDM practice and enable precision therapy with VCZ.

Materials and methods

A proactive TDM intervention model for VCZ was established based on five strategies: standardized decision-making, preemptive risk interception, intelligent report facilitation, multi-dimensional education for healthcare professionals and patients, and multidisciplinary collaboration. A historical controlled study design was employed to compare proactive (2023) versus passive (2019) intervention, assessing changes in VCZ TDM coverage rate, target attainment rate (TAR), incidence of VCZ-related hepatotoxicity, discontinuation rate due to adverse drug effects, clinical adoption rate of pharmacists' recommendations, and overall treatment efficacy.

Results

Compared with the passive intervention period, the proactive intervention model demonstrated significant improvements across all measured outcomes. TDM coverage increased significantly (84.0% vs. 53.4%, P<0.001). The proportion of patients achieving the therapeutic window (1.0-5.0 mg/L) improved significantly (68.5% vs. 57.5%, P=0.001), whereas the supratherapeutic ratio decreased markedly (13.6% vs. 19.9%, P=0.01). Both VCZ-related hepatotoxicity and discontinuation due to adverse effects declined significantly (8.5% vs. 19.8%, P<0.001; 4.5% vs. 18.7%, P<0.001, respectively). Clinical adoption of pharmacists' recommendations increased considerably (87.3% vs. 63.7%, P<0.001), as did overall treatment efficacy (84.9% vs. 66.4%, P<0.001).

Discussion / Conclusion

This pharmacist-led proactive model enhances VCZ TDM coverage and precision, improving outcomes while reducing toxicity. It demonstrates pharmacists' evolution from data providers to therapeutic partners, offering a scalable framework for individualizing high-risk medication management.

Reference(s)

Hanai Y et al (2023) Mycoses 66: 1035-1044.

Liu XX et al (2022) Herald of Medicine 41: 1699-1710.

Miyakis S et al (2010) Ther Drug Monit 32: 661-664.

Takesue Y et al (2022) Clin Ther 44: 1604-1623.

Keywords

Voriconazole; Therapeutic drug monitoring; Proactive intervention; pharmacist led; Value-based healthcare

00039
An insufficient ceftazidime liquor penetration in PSAE associated brain ventriculitis with temporary external ventriculostomy

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Ceftazidime is commonly used in Pseudomonas aeruginosa (PSAE) infections. Although its penetration through the blood-brain barrier is limited and its cerebrospinal fluid/plasma distribution clearance is very low (approximately 0.03–0.12), ceftazidime is also sometimes used for brain infections. The primary objective of our study was to determine whether a patient with PSAE-associated ventriculitis and a dislocated ventriculo-peritoneal (VP) shunt, treated with ceftazidime, achieved adequate ceftazidime concentrations in the cerebrospinal fluid (CSF).

Materials and methods

Serum and CSF concentrations were assessed in a our patient admitted to the neurosurgery department with VP shunt-associated ventriculitis. An 83-year-old female (weight: 72 kg, height: 168 cm) was treated with ceftazidime at a dose of 3 g every 8 hours. Serum concentrations were measured three times daily for three consecutive days (trough level and two samples at 2 and 4 hours post-dose). CSF samples were taken randomly based on clinical need to relieve intracranial pressure via the ventriculostomy system (approximately 3–4 times/day). All concentrations were determined by high-performance liquid chromatography using mass spectrometry detection.

Results

Serum ceftazidime concentrations ranged from 11 to 233 mg/L, while CSF concentrations ranged from 0.56 to 2.56 mg/L. Only one isolated peak value was 4.79 mg/L. Two isolated strain of Pseudomonas aeruginosa had a minimum inhibitory concentration (MIC) for ceftazidime 12 and 16 mg/L, indicating increased exposure requirements (EUCAST reference values 9-16mg/L).

Discussion / Conclusion

The ceftazidime concentrations observed in the CSF were below the MICs for both isolated PSAE strains for the whole course of its treatment. We demonstrated that in this type of central nervous system infection, where the blood-CSF barrier remains largely intact, the standardly dosed ceftazidime treatment is suboptimal and even longer TDM of ceftazidime in serum and CFS would not provide any benefit. The patient was switched to local amikacin therapy administered via external ventriculostomy, monitored with TDM, and this treatment proved successful.

Reference(s)

Finazzi S, Antibiotics . 2022 Aug 29;11(9):1164

Keywords

ceftazidime, therapeutic drug monitoring, bacterial ventriculitis, Pseudomonas aeruginosa

00056
Optimising Avibactam Exposure: Clinical Impact and Challenges from Ceftazidime-Avibactam Therapeutic Drug Monitoring (TDM)

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Beta-lactamase inhibitor (BLI) TDM is uncommon; BLI TDM targets remain uncertain[1]. We performed a restropective study on ceftazidime-avibactam TDM to evaluate variability in ceftazidime-avibactam exposures and correlate them with clinical outcomes to justify the need for avibactam TDM and identify avibactam TDM target.

Materials and methods

Retrospective review of patients (≥16 years old) receiving ceftazidime-avibactam with TDM[2] at a quaternary hospital from Oct-2020 to Dec-2025. Ceftazidime-avibactam regimens ranged from 2.5g q4h to q48h. For avibactam, target concentrations of 1mg/L and 4mg/L were evaluated. Published tissue penetration data were used to estimate infection site concentrations. Univariate and logistic regression analyses were performed using SPSS.

Results

Fourty-nine patients with 86 TDM sessions- 240 plasma concentrations (62 peak, 70 trough) were included. Ceftazidime-avibactam concentrations were variable- ceftazidime median trough 49.8mg/L, IQR 26.9-77.7mg/L; avibactam median trough 7.9mg/L, IQR 3.2-14.3mg/L. Ceftazidime-avibactam ratios [median peak 5.8 (IQR: 4.5-6.5), median trough 7.6 (IQR: 4.8-9.0)] deviated from original formulation ratio of 4:1. Despite aggressive dosing [55 (64%) regimens exceeded labelled recommendations], only 57 (66%) and 40 (47%) of trough concentrations were deemed adequate at the infection site for ceftazidime and avibactam respectively. Neither ceftazidime nor avibactam plasma troughs were correlated with 30-day mortality. However, logistic regression revealed that SOFA score (OR 0.8, 95%CI: 0.6-0.9) and attaining avibactam trough > 4mg/L at infection site (OR 6.6, 95% CI: 1.3-32.2) were significant predictors for clinical response. Among 6 patients with adverse effects, free ceftazidime trough (median 51.4mg/L, IQR 38.4-127.2mg/L) was significantly higher than those without (median 31.3mg/L, IQR 18.4-50.2mg/L) (p=0.018) but not for avibactam (p=0.131).

Discussion / Conclusion

Avibactam exposure is highly variable and uncorrelated with ceftazidime exposure. Attaining avibactam exposure >4 mg/L at infection site is associated with clinical response, underscoring the need for BLI TDM. Up-titrating ceftazidime-avibactam regimens to achieve desired avibactam exposure is limited by unnecessary increase in ceftazidime exposure, risking ceftazidime-associated adverse effects.

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Keywords

betalactamase inhibitor, ceftazidime, avibactam, beta-lactam TDM, beta-lactam, antimicrobial resistance

00072
Population pharmacokinetic modeling and dose optimization of linezolid in plasma and cerebrospinal fluid of postoperative neurosurgical patients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Neurosurgical patients are at risk of linezolid underexposure with standard dosing. Limited data exist on its variable cerebrospinal fluid (CSF) penetration in this population, and no specific dosing recommendations for CSF targets are available. This study aimed to characterize plasma and CSF pharmacokinetics of linezolid in postoperative neurosurgical patients, identify influencing factors, and optimize dosing regimens.

Materials and methods

Patients receiving intravenous linezolid (600 mg q12h) after neurosurgery with external CSF drainage were prospectively enrolled. Plasma and CSF samples were collected for population pharmacokinetic (PPK) analysis using NONMEM. Monte Carlo simulations evaluated target attainment probability.

Results

Thirty-two patients were included (median age 55 years, weight 70 kg). A two-compartment model with body weight and external drainage volume (EDV) as covariates adequately described the data. Typical clearance and volume of distribution were 7.73 L/h and 32.6 L, respectively. By the fifth dose, plasma trough concentrations were significantly lower than CSF troughs (1.53±1.76 vs. 2.29±1.72 mg/L, P<0.05), while plasma AUC_{0-24h} remained higher than CSF AUC_{0-24h} (171.36±69.39 vs. 117.90±45.22 mg·h/L, P<0.05). Using AUC_{0-24h}/MIC ≥80 as target, probability of target attainment (PTA) in plasma/CSF decreased with increasing MIC, reaching 46.67%/21.43% at MIC=2 mg/L. For CSF at MIC=2 mg/L, T>MIC ≥85% achieved higher PTA than AUC/MIC target (78.5% vs. 21.43%, P<0.001). At MIC=1 mg/L, weight- and EDV-stratified dose adjustments (e.g., 800–1200 mg q12h) were required for CSF target attainment. At MIC≥2 mg/L, no regimen achieved the AUC-based target in CSF.

Discussion / Conclusion

Body weight and EDV significantly influence linezolid PK in neurosurgical patients. Standard dosing provides inadequate exposure at MIC≥2 mg/L for both plasma and CSF. The discrepancy between AUC/MIC and T>MIC targets in CSF suggests the need to reevaluate the optimal PK/PD index for linezolid in this compartment.

Keywords

linezolid; population pharmacokinetics; cerebrospinal fluid; dose optimization

00081
Does the model matter? Comparison of dosing recommendations provided by two cefepime population pharmacokinetic models as the Bayesian prior for a clinical precision dosing consult service

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Our institution recently launched a model-informed precision dosing service for cefepime.1 We utilize a population pharmacokinetic (popPK) model (Shoji)2 as the Bayesian prior to estimate individual PK parameters from measured concentrations and provide dosing recommendations for two targets: concentrations above 1x or 4x minimum inhibitory concentrations throughout the dosing interval (100%fT>1 or 4x MIC). We recently developed a popPK model from our institution's critically ill pediatric patients (Morales Junior)3, and investigated how dosing recommendations for previous consultations differ between models.

Materials and methods

We conducted consultations using the Shoji model on 17 patients. For patients on dialysis, whether hemodialysis (HD) (n=1), continuous renal replacement therapy (CRRT) (n=5), or peritoneal dialysis (PD) (n=2), we removed creatinine from the model. For HD and CRRT, we used modules accounting for dialysis prescriptions.4

When using the Morales Junior model, for dialysis patients, we set estimated glomerular filtration rate (eGFR) to 5 mL/min/1.73m2. We classified the recommendations generated by both models as concordant (identical), partially concordant (dose difference of ≤20% or infusion time different by one hour), or discordant.

Results

For most patients, the Morales Junior model estimated higher cefepime clearance (median: 19%, range -7% -36%). For non-dialysis patients and 100%fT>1x MIC, 4/8 (50%), 3/8 (38%) and 1/8 (12%) of recommendations were concordant, partially concordant, and discordant, respectively. For 100%fT>4xMIC, 4/7 (57%) were concordant; the rest discordant. For patients on HD/CRRT and 100%fT>1xMIC, 2/6 (33%) of recommendations were concordant, 3/6 (50%) partially concordant, and one discordant. For 100%fT>4xMIC, 1/5 (20%) was concordant, 3/5 (60%) partially concordant, and one discordant. For PD, concordance was 100%.

Discussion / Conclusion

Despite incorporating measured concentrations for Bayesian estimation, there were differences in dosing recommendations between the models. For HD/CRRT, handling of creatinine vs. eGFR likely contributed to decreased concordance. Further studies, including obtaining confirmatory concentrations after adjustments, can help identify the optimal model for specific populations.

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Keywords

*Model-informed precision dosing, antibiotics, pediatrics

00124
Impact of imparied renal function on voriconazole metabolism

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Chronic kidney disease (CKD) is known to alter drug pharmacokinetics beyond reduced renal clearance. Accumulation of uremic toxins may impair hepatic drug metabolism through inhibition and downregulation of CYP450 enzymes, particularly CYP2C19, CYP2C9, and CYP3A4[1]. Voriconazole, a triazole antifungal widely used in invasive fungal infections, undergoes extensive hepatic metabolism into voriconazole N-oxide (NOX). Our work aimed at evaluating the effect of renal impairement on the metabolic ratio of voriconazole in real life.

Materials and methods

We conducted a retrospective, monocentric observational study at Rennes University Hospital between 2022 and 2025. Adult patients receiving voriconazole with available therapeutic drug monitoring (TDM) data and renal function assessment were included. Voriconazole trough concentrations, NOX concentrations, dosing data, glomerular filtration rate (eGFR) and C-reactive protein (CRP) were collected. The metabolic ratio (MR = NOX/voriconazole) was used as a surrogate marker of CYP450 metabolic activity. Patients were stratified according to eGFR (GFR ≤60 mL/min vs >60 mL/min). Group comparisons were performed using appropriate statistical tests.

Results

Considering the first measurement of voriconazole concentration, a total of 179 samples were analyzed, including 57 patients with impaired renal function (GFR ≤60 mL/min) and 122 with preserved renal function (GFR >60 mL/min). The mean metabolic ratio was significantly lower in patients with impaired renal function compared to those with normal to mildly renal function (1.17 vs 2.16, p=0.03), indicating reduced metabolic conversion of voriconazole to NOX. No significant difference was observed in concentration-to-dose ratios between groups (p=0.42), and inflammatory status did not differ significantly.

Discussion / Conclusion

As suggested by the enzyme inhibitory effects of uremic toxins accumulated in kidney disease, impaired renal function seems to be associated with reduced voriconazole metabolic activity, likely reflecting CYP450 inhibition. These findings highlight the importance of therapeutic drug monitoring and individualized dosing of voriconazole in patients with impaired renal function to optimize efficacy and minimize toxicity.

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Keywords

voriconazole, metabolic ratio, impaired renal function

00128
Outcomes of Beta-lactam Therapeutic Drug Monitoring and Factors Influencing Therapeutic Target Achievement in Critical Care Settings

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Beta-lactam therapeutic drug monitoring (TDM) is increasingly utilised to personalise dosing in critically ill patients. However, it has not consistently demonstrated clinical benefits and there is limited experience in Singapore. This study aimed to correlate beta-lactam TDM with clinical outcomes and identify factors associated with failure to achieve therapeutic target.

Materials and methods

A retrospective, observational study was conducted at Tan Tock Seng Hospital from May 2023 to August 2024. Critically ill patients (≥ 21 years) eligible for TDM of beta-lactam (Ampicillin-sulbactam, Ceftazidime, Ceftazidime-avibactam, Cefepime, Meropenem, Piperacillin-tazobactam) were included. Clinical outcomes were the change in Acute Physiology and Chronic Health Evaluation II (APACHE II) score on day 5 of beta-lactam and mortality. Therapeutic target was an unbound trough concentration exceeding the plasma-to-tissue distribution adjusted minimum inhibitory concentration (fCmin > MIC × plasma/tissue ratio). Inverse probability of treatment weighting was performed to control for differences between TDM and non-TDM groups.

Results

Ninety-seven beta-lactam episodes were included (TDM, n = 76; non-TDM, n = 21). TDM group had higher odds of reduced APACHE II score (adjusted odds ratio [aOR], 2.435; 95% confidence interval [CI] [1.332, 4.451]; P = 0.004), with a beta coefficient of -12.866 points (95% CI [-17.186, -8.546]; P < 0.001). TDM group had more frequent individualised dosing regimens during the beta-lactam course (26/76 [34.2%] versus 1/21 [4.8%]; P = 0.008). However, there were no significant differences in 14- and 30-day mortality between both groups. In TDM group, 88.2% of beta-lactam episodes achieved therapeutic target. Increased urine output (≥ 0.2 mL/kg/hour over 24 hours) was more common in those who did not achieve therapeutic target compared to those who did (4/9 [44.4%] versus 14/67 [20.9%]).

Discussion / Conclusion

Beta-lactam TDM facilitated individualised dosing and may positively impact clinical outcomes. Patients with increased urine output should be particularly considered for beta-lactam TDM.

Keywords

Beta-lactam, Therapeutic drug monitoring

00129
Enhancing the reliability and accessibility of antibiotics therapeutic drug monitoring in critically ill patients through standardized protocols

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic drug monitoring (TDM) is essential for optimizing the efficacy and safety of pharmacotherapy in critically ill patients. However, the reliability of TDM results in this population is often compromised by multiple confounding factors—including patient-specific pathophysiology, pre-analytical processes, and drug characteristics—underscoring the urgent need for standardized protocols to ensure result accuracy.TDM is essential for optimizing the efficacy and safety of pharmacotherapy in critically ill patients. However, the reliability of TDM results in this population is often compromised by multiple confounding factors—including patient-specific pathophysiology, pre-analytical processes, and drug characteristics—underscoring the urgent need for standardized protocols to ensure result accuracy.

Materials and methods

A modified Delphi method was employed by an expert panel to establish consensus on the indications for TDM and to prioritize the target drug list for critically ill patients. For each prioritized drug, the maximum allowable turnaround time for sample delivery from the ICU to the laboratory and the therapeutic reference range were determined by integrating findings from a systematic literature review with

institutional stability study data. Concurrently, the information system was enhanced to automatically generate pop-up reminders for medications requiring TDM at the time of electronic order entry. This functionality triggered proactive pharmaceutical services, enabling clinical pharmacists to intervene promptly for dose optimization.

Results

Implementation of the standardized protocol significantly reduced the turnaround time for TDM samples from the ICU to the laboratory and expanded the scope of monitoring to include several high-risk drugs that were previously overlooked. The incidence of unqualified specimens, particularly unstable samples such as those containing beta-lactam antibiotics, declined substantially. Furthermore, the number of pharmaceutical consultations provided by clinical pharmacists for ICU patients increased markedly.

Discussion / Conclusion

Standardizing TDM protocols enhances the clinical utility of therapeutic monitoring for critically ill patients by improving the accessibility of reliable testing and minimizing the confounding effect of erroneous samples on therapeutic decision-making.

Keywords

therapeutic drug monitoring, critically ill patients, standardized protocols

00135
Evaluation of the Efficacy, Safety, and Economy of Nemonoxacin Injection versus Moxifloxacin Injection in the Treatment of Community-Acquired Pneumonia

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

To evaluate the clinical efficacy, safety, and cost-effectiveness of nemonoxacin injection versus moxifloxacin injection in patients with community-acquired pneumonia (CAP), providing an evidence-based reference for clinical decision-making.

Materials and methods

A retrospective cohort study was conducted, enrolling 196 patients hospitalized with CAP between January 2024 and March 2025. Based on the treatment received, patients were allocated to a nemonoxacin group (n=103) or a moxifloxacin group (n=93). Clinical efficacy, inflammatory markers before and after treatment, and safety outcomes were compared between the groups. A cost-minimization analysis was used for the economic evaluation.

Results

Baseline characteristics did not differ significantly between groups (P>0.05). Clinical efficacy was 100.0% in the nemonoxacin group versus 97.8% in the moxifloxacin group (P=0.135). Adverse reaction rates were 1.9% and 1.1% for nemonoxacin and moxifloxacin, respectively (P=0.622). Inflammatory markers decreased significantly after treatment in both groups, but the intergroup difference post-treatment was not statistically significant (P>0.05). The total hospitalization cost was significantly lower in the nemonoxacin group (¥6,726.31±1,849.50) than in the moxifloxacin group (¥7,354.12±2,477.16) (P<0.05), indicating superior cost-effectiveness for nemonoxacin. Sensitivity analysis supported the robustness of the economic finding.

Discussion / Conclusion

Nemonoxacin malate injection demonstrates clinical efficacy and safety comparable to moxifloxacin hydrochloride injection for CAP, while incurring significantly lower treatment costs, resulting in a more favorable economic profile.

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Keywords

nemonoxacin; moxifloxacin; community-acquired pneumonia; economic evaluation; cost-minimization analysis

00151
Pharmacologist-Guided Meropenem Therapeutic Drug Monitoring and PK/PD Target Attainment in Critically Ill Patients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Achieving meropenem pharmacokinetic/pharmacodynamic (PK/PD) targets in critically ill patients is challenging*. We evaluated whether pharmacologist-guided therapeutic drug monitoring (TDM) improves PK/PD target attainment in ICU practice and assessed the impact of prescriber implementation.

Materials and methods

We conducted a retrospective single-center cohort study (2020–2025) in adult ICU patients receiving meropenem. Eligible patients had ≥2 consecutive TDM measurements (T1 and T2, 24–96h apart) and a documented pharmacologist recommendation after T1. PK/PD target was defined as Cmin or Css/MIC ≥4 and <16mg/L; concentrations below the limit of quantification were classified as non-attainment. Implementation was defined as prescriber execution of the pharmacologist recommendation before T2. Paired changes in target attainment were assessed using McNemar's test. Adjusted analyses used logistic generalized estimating equations with a time (T2 vs T1)-by-implementation interaction.

Results

Among 247 patients screened, 104 were included. Meropenem PK/PD target attainment increased from 39.4% (41/104) at T1 to 57.7% (60/104) at T2 (Δ+18.3%; matched OR, 2.58; 95%CI, 1.33–5.03; p=0.005). Pharmacologist recommendations were implemented in 74.0% of cases (77/104). In implemented cases, target attainment improved from 42.9% (33/77) to 68.8% (53/77), whereas no improvement was observed in non-implemented cases (29.6% [8/27] to 25.9% [7/27]). In adjusted analyses, the overall increase in PK/PD target attainment remained significant (aOR, 2.18; 95%CI, 1.30–3.67). A significant time-by-implementation interaction was observed (aOR, 3.78; 95%CI, 1.03–13.84), with improvement in implemented cases (aOR, 3.13; 95%CI, 1.66–5.88) but not in non-implemented cases (aOR, 0.83; 95%CI, 0.27–2.55). Prolonged/continuous infusion increased from 11.5% at T1 to 30.8% at T2 (p<0.001), while the median daily dose remained 4 g (p=0.832).

Discussion / Conclusion

Pharmacologist-guided meropenem TDM was associated with improved PK/PD target attainment in ICU patients, with effectiveness strongly dependent on prescriber implementation and driven in part by infusion optimization. Future prospective studies should evaluate patient-centered outcomes and interventions to improve implementation.

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Keywords

Meropenem; Therapeutic drug monitoring; Intensive care unit; Pharmacokinetic/pharmacodynamic; Target attainment; Prescriber implementation.

00153
Review of teicoplanin pharmacokinetic population models for therapeutic drug monitoring

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Teicoplanin therapeutic drug monitoring (TDM) relies on validated population pharmacokinetic models (PPM) to optimize exposure in severe Gram-positive infections, especially in critically ill patients, this review aims to describe the available PPM in adults.

Materials and methods

A bibliographic research was conducted using the terms: teicoplanin, PPM and TDM. Models based on paediatric or healthy populations were excluded. The following variables were collected from the selected models: study design, population characteristics (size, age, sex, weight), clinical variables (ICU status, haemodialysis (HD), creatinine clearance) and model structure (compartments, covariates).

Results

Eight PPM analysed teicoplanin pharmacokinetics across diverse patients, most applying a two-compartment models, described below:

1. Cazaubon et al.2017 combine two European cohorts (geriatric and ICU) with wide variability in weight and renal clearance, being the only study to include subcutaneous administration.

2. Soy et al.2006 studied 79 European patients, initially 20% of them with ClCr <20 ml/min. The study carried out an internal validation in a one-compartment model.

3. Byrne et al.2017 analysed 30 haematological patients, excluding patients in the ICU or on HD, using a three-compartment model.

4. Ogami et al.2019: study of 237 patients, including HD and ICU patients, with a wide range of weights, ClCr and ages. Covariates include fat-free mass and ClCr.

5. Zhang et al.2023: study of 115 non-complicated patients with HD exclusion criteria. The model is one-compartment with covariates: albumin, ClCr, and weight.

6. Wang et al.2023: studied 108 ICU patients and applied an internal validation sample of 43 patients.

7. Chen et al.2023: analyses 59 septic ICU and HD patients.

8. Kang et al.2023: evaluates 15 ICU patients admitted for pneumonia.

Discussion / Conclusion

A thorough literature review and data analysis are essential for selecting the most appropriate PPM. Sample size, patient characteristics and covariates must be considered, and external validation is essential for ensuring predictive performance.

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Keywords

Teicoplanin, TDM, PPM , Review

00185
Accuracy of Diagnostic Coding for Acute Kidney Injury in Japan: A Foundational Assessment for Data-Driven Therapeutic Drug Monitoring Research

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Data-driven therapeutic drug monitoring (TDM) research using medical big data has rapidly expanded in recent years. However, a major methodological concern remains regarding the validity of diagnostic codes recorded in claims data. In particular, it is unclear whether assigned diagnosis codes accurately reflect true clinical diagnoses, which may affect the reliability of pharmacoepidemiologic and TDM-related research. We evaluated the accuracy of diagnostic coding for acute kidney injury (AKI) in Japan, which is a typical side effect of TDM-targeted drugs such as vancomycin and aminoglycosides.

Materials and methods

Data from a Japanese hospital-based administrative claims database were analyzed, including patients registered from April 2014 through August 2022. Eligibility was restricted to patients with serum creatinine measured at least twice, with the two tests performed ≤7 days apart. AKI was identified using International Classification of Diseases, 10th Revision (ICD-10) codes N14 and N17. Diagnostic-code accuracy was evaluated against AKI defined by the Kidney Disease: Improving Global

Outcomes (KDIGO) criteria. The protocol was approved by the ethics committee of the Keio University Faculty of Pharmacy (approval no. 240408-1).

Results

Overall, 467,019 patients met the inclusion criteria. Of these, 1,849 (0.4%) were assigned ICD-10 codes for AKI. Among these patients, the code was assigned within 7 days of the occurrence of AKI (as defined by the KDIGO criteria) in 212 patients, within 14 days in 294 patients, and within 30 days in 386 patients. The positive predictive value (PPV; 95% confidence interval) of the AKI code was 11.5% (10.1–13.0) for the 7-day window, 15.9% (14.3–17.6) for the 14-day window, and 20.9% (19.1–22.8) for the 30-day window.

Discussion / Conclusion

The ICD-10 codes showed poor positive predictive values, suggesting that it may be difficult to identify AKI. Identifying robust algorithms to detect AKI using claims data will be critical for enhancing the validity of future data-driven TDM research.

Keywords

acute kidney injury, hospital-based database, positive predictive value, serum creatinine

00199
Development and Validation of a Machine Learning-Derived Risk Stratification Model for Vancomycin-Associated Acute Kidney Injury

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Vancomycin-associated acute kidney injury (AKI) represents a major clinical challenge that increases morbidity, mortality, and medical costs. Conventional risk assessment approaches are often generic and insufficient for precise risk stratification among heterogeneous patient populations with diverse comorbidities. There is an urgent need for disease-specific predictive models to support personalized vancomycin therapy and nephrotoxicity prevention.

Materials and methods

This was a retrospective study aiming to establish and interpret a machine learning-based framework for stratified prediction of vancomycin-associated AKI. We reviewed the medical records of 724 patients who received vancomycin treatment from January 1, 2015, to September 30, 2020, and collected data including baseline demographics, vancomycin dosage and treatment duration, comorbidities, concomitant medications, and laboratory indicators. Based on the XGBoost algorithm, a series of risk prediction models were constructed for patients with different underlying diseases, including cancer, diabetes mellitus, and hepatic insufficiency. The performance of each sub-model was verified in the corresponding disease-specific datasets. In addition to model construction, interpretative analysis was conducted to quantify the contribution of clinical variables to the prediction results.

Results

Most sub-models achieved favorable predictive performance in the target populations. The results revealed distinct disease-specific risk profiles: traditional indicators such as serum creatinine and creatinine clearance rate remained important predictors, while some previously underappreciated factors were identified as key contributors in different subgroups. Specifically, serum cystatin C and cumulative vancomycin exposure duration were dominant in cancer patients; body weight and age were critical in diabetic patients; and neutrophil-to-hemoglobin ratio was pivotal in patients with hepatic insufficiency.

Discussion / Conclusion

This comorbidity-stratified machine learning framework enables accurate and interpretable prediction of vancomycin-associated AKI. Our findings highlight the critical role of personalized risk assessment in heterogeneous populations and provide a robust data-driven foundation for precision vancomycin stewardship and targeted prevention of nephrotoxicity.

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Keywords

vancomycin; acute kidney injury; machine learning; risk prediction; stratified model; personalized medicine

00201
Translating Model-Informed AUC-Guided Vancomycin Dosing into Clinical Practice: Stepwise Effects of Guideline Revision and Ward-Based Pharmacist Implementation

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Vancomycin dosing has shifted from trough-based to AUC-guided monitoring to optimize efficacy and reduce the risk of acute kidney injury (AKI). Despite strong PK/PD rationale and international endorsement, implementation in routine clinical practice remains challenging. Pharmacist-led antimicrobial stewardship programs improve dosing precision and outcomes, yet the independent contributions of structural guideline revision and ward-based pharmacist involvement to early AUC target attainment have not been clearly quantified.

Materials and methods

We conducted a single-center retrospective observational study of hospitalized patients who received intravenous vancomycin between April 2019 and March 2025. Two sequential system-level interventions were introduced: (1) a national guideline revision promoting AUC-guided dosing (April 2022), and (2) structured ward-based pharmacist involvement in initial dosing (January 2023). Interrupted time-series analysis assessed temporal changes in day 1 AUC target attainment (400–600 mg·h/L). Mixed-effects logistic regression was adjusted for key factors.

Results

Following guideline revisions, day 1 AUC target attainment increased markedly (OR 43.0, 95% CI 8.7–211.8). No additional stepwise increase was observed after operational implementation; however, target attainment remained consistently high. Ward-based pharmacist involvement was independently associated with improved attainment (OR 2.5, 95% CI 1.5–4.1), corresponding to an absolute increase from 39.5% to 54.6%. The incidence of early AKI remained unchanged despite improved exposure control. The reduction in piperacillin/tazobactam co-administration and the increase in early TDM order modifications observed during the ward-based pharmacist implementation period suggest that pharmacist-led early intervention contributed to mitigation of AKI risk. Exploratory spline analyses indicated lower target attainment among younger and lower-weight patients.

Discussion / Conclusion

Structural transition to AUC-guided vancomycin dosing produced an immediate improvement in early exposure control, while ward-based pharmacist involvement provided sustained and independent enhancement without compromising safety. These findings demonstrate that guideline reform and pharmacist-led implementation play complementary roles in advancing model-informed precision dosing and antimicrobial stewardship in real-world practice.

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Keywords

vancomycin, AUC-guided dosing, pharmacist-led implementation, model-informed precision dosing

00219
Prospective study for analysis of factors affecting the trough concentration and metabolic rate of voriconazole

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Voriconazole (VRCZ) exhibits significant inter-individual variability in steady-state plasma trough concentration (Ct), leading to the recommendation of therapeutic drug monitoring (TDM) both domestically and internationally. Furthermore, several previous reports indicate extremely high Ct levels in patients experiencing systemic inflammation. This prospective study aimed to evaluate factors affecting VRCZ metabolism and Ct by simultaneously measuring the plasma concentration (Cm) of VRCZ-*N*-oxide, a primary metabolite of VRCZ, and Ct of VRCZ, thereby contributing to dose design.

Materials and methods

This study included 34 patients administered VRCZ at Sakai City General Medical Center between July 2020 and September 2023, for whom both VRCZ and VRCZ-*N*-oxide plasma concentrations were determined by HPLC-UV method. We investigated previously reported factors influencing Ct, including age, sex, body weight, C-reactive

protein (CRP), the ALBI score, and *CYP2C19* gene polymorphism. Statistical analysis of the data was performed using Spearman's rank correlation analysis and multiple regression analysis.

Results

Ct, Cm, dose per kilogram (dose/kg), CRP, and sex were found to be significantly correlated with VRCZ metabolic rate (Cm/Ct). Cm/Ct, dose/kg, CRP, and sex were found to be significantly correlated with Ct, whereas ALBI and *CYP2C19* gene polymorphisms were not found to be significantly correlated with Ct or Cm/Ct.

Discussion / Conclusion

In this study, CRP was most significantly associated with the increase in Ct observed with decreasing Cm/Ct. Elevated CRP levels suggest a systemic inflammatory state, which implies reduced CYP2C19 expression due to the inhibitory effect of CRP on key CYP transcription factors in the liver. Therefore, it can be inferred that increased CRP levels lead to decreased hepatic metabolism of VRCZ, resulting in elevated trough concentrations.

Keywords

TDM of voriconazole and its metabolite, Metabolic rate, CYP2C19, CRP

00242
LC-MS-Based Serum Metabolomic Analysis Predicts the Risk of Tigecycline-Induced Coagulopathy in Critically Ill Patients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Tigecycline is widely used to treat multidrug-resistant infections. However, the high incidence of coagulopathy poses a significant clinical challenge. This observational study aimed to characterize the metabolomic profiles of critically ill patients receiving tigecycline and to identify potential metabolic traits to predict tigecycline-induced coagulopathy (TIC).

Materials and methods

A total of 53 patients were enrolled and classified into TIC and non-TIC groups. Serum samples were collected at trough (Cmin), mid-dose (C1/2), and peak (Cmax) tigecycline concentrations. LC-MS–based untargeted metabolomics was applied to characterize metabolic profiles across these timepoints and to identify metabolites potentially predictive of TIC.

Results

By sequentially applying univariate analysis and multivariate LASSO-penalized Cox proportional hazards regression analysis, we identified 10, 10, and 9 metabolites at the Cmin, C1/2, and Cmax timepoints, respectively, as predictive markers of TIC.

Importantly, patients with lower levels of lysophosphatidylcholines (LysoPCs) and lysophosphatidylethanolamines (LysoPEs) are more susceptible to coagulopathy following tigecycline therapy. In particular, receiver operating characteristic curve analysis of LysoPC(18:0), LysoPC(18:3), LysoPE(18:0), and LysoPE(18:4) measured at Cmin demonstrated an area under the curve close to 0.8, providing strong evidence for their potential as robust biomarkers for predicting TIC.

Discussion / Conclusion

Our study indicated that metabolomics could be a valuable tool for predicting the risk of TIC and suggested that LysoPCs and LysoPEs might serve as hypothesis-generating candidates for future studies exploring potential therapeutic interventions.

Keywords

critically ill patients; metabolomics; tigecycline; coagulopathy; prediction

00253
Low-Dose Amikacin therapy with Improved Therapeutic Target Attainment: A Pharmacokinetic Analysis from Clinical Perspective

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Amikacin remains a key agent to manage infections. However, achieving optimal peak and trough concentrations under standard dosing regimens (15–35 mg/kg q24–48 h) is challenging in real-world situation. In our practice, lower doses are usually favored to balance efficacy and safety. Here we performed a pharmacokinetic analysis from clinical perspective aimed to optimize the use of amikacin.

Materials and methods

A retrospective cohort study was conducted at a tertiary hospital from January to December, 2025. A total of 101 adult patients with 413 amikacin concentrations were included. Target pathogens comprised carbapenem-resistant Serratia marcescens, Klebsiella pneumoniae, Pseudomonus aeruginosa, non-tuberculous mycobacteria, and etc. Population pharmacokinetic modeling was conducted using a nonlinear mixed-effects approach with the stochastic approximation expectation–maximization (SAEM) algorithm implemented in MonolixSuite 2024R1. Covariate analysis was subsequently performed to identify factors influencing pharmacokinetic parameters.

Results

Median (q1-q3) starting dose of amikacin in this study was 7.9 (7.0-13.8) mg/kg, which was 23-53% of standard recommendation. Renal replacement therapy (RRT) was required in 38.7% of patients. Median (q1-q3) peak and trough level were 30.9 (23.5-39.1) and 4.5 (1.4-10.1) mcg/mL, respectively. The efficacy target (i.e., peak/MIC>=8) was achieved in 94% of patients with MIC<=2 mg/L. Safety target attainment (i.e., trough level <= 2.5 mcg/mL) was 35.0%, which was higher than previous studies (e.g., AMIDIAL-ICU, 5.4%). The incidence of acute kidney injury was 16.7%. Preliminary pharmacokinetic modeling showed that clearance (CL) was influenced by RRT and renal function (eGFR-EPI2021), while volume of distribution (Vd) was influenced by body weight and target pathogens. Population value of CL and Vd were approximately 2.4 L/hr and 21.9 L, respectively, with relatively high inter-individual variability (i.e., 22-44%).

Discussion / Conclusion

Low-dose amikacin therapy achieved favorable target attainment regarding efficacy and safety, particularly for pathogens with low MIC. Although parameter estimates were comparable to previous reports, model refinement is warranted to enhance predictive performance.

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Keywords

Amikacin, population pharmacokinetics, modeling, low dose strategy, Monolix, stochastic approximation expectation–maximization

00262
Prediction of trough amikacin concentrations in therapeutic drug monitoring

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Pharmacological monitoring of amikacin is recommended to ensure both the efficacy and safety of the drug, by measuring peak and trough concentrations (Cmin) respectively. In particular, a Cmin below 2.5 mg/L is required before a new dose can be administered. Compliance with the correct sampling times (ideally within one hour prior to re-administration for Cmin) is essential to ensure correct interpretation of the measurements. In hospital practice, sampling times are often inaccurate, requiring the prediction of Cmin using the half-life adjusted for the patient's GFR to enable proper interpretation of the results. The aim of this study was to evaluate these predictions.

Materials and methods

Our retrospective single-center study included patients treated with amikacin for whom at least two plasma concentrations were measured without re-administration. The later concentrations were estimated from the earlier concentrations, either using an estimation of the terminal elimination half-life corrected by the patient's glomerular filtration rate (GFR), or by population pharmacokinetics (PK-POP) using Posologyr (1). The differences between predicted concentrations and measured concentrations were evaluated for each method. Finally, the clinical impact was assessed by placing ourselves in an interpretation setting.

Results

Forty patients were included representing 54 concentrations. The measured trough concentrations averaged 8.9 mg/L, whereas the predicted concentrations were 3.8 mg/L when estimated using GFR and 8.1 mg/L when estimated using modeling. The modelling approach had the lowest average bias (1.62 mg/L vs 2.75 mg/L with half-life corrected by GFR), demonstrating its superiority. Nearly one-third of clinical interpretations based on the estimated half-life were incorrect, whereas only 7 percent of those estimated by PK-POP were incorrect.

Discussion / Conclusion

This study highlights the limitations of predicting amikacin concentrations based on half-lives estimated using GFR alone. Modelling appears to be the most reliable approach; however, the evaluation of PK-POP models in hospital practice remains challenging.

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Keywords

Therapeutic drug monitoring, amikacin, kidney failure

00263
Unbound cloxacillin levels during hip and knee arthroplasty: Time to reconsider the current prophylaxis regimen?

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Adequate perioperative antibiotic prophylaxis is important to prevent prosthetic joint infections (PJI) after arthroplasty of the hip and knee. A higher risk of reoperation for PJI has been suggested with cloxacillin compared to wider-spectrum alternatives such as cefazolin. It is currently unclear to what extent any efficacy differences might stem from suboptimal cloxacillin dosing.

Materials and methods

Unbound cloxacillin concentrations (n=496) from 200 patients undergoing elective arthroplasty of the hip (n=95) or knee (n=105) were analysed using HPLC-MS/MS after plasma ultrafiltration. Intravenous cloxacillin doses of 2 g were administered as 20-30 min infusions pre-surgery and repeated after 2 and 6 hours, in accordance with Swedish guidelines. Sampling occurred at three time points per patient, including at the start and end of surgery. An unbound cloxacillin concentration of >2 mg/L

throughout surgery was deemed appropriate. Nonlinear mixed effects modelling was performed to develop a population pharmacokinetic model. Using this model, alternative prophylaxis regimens were explored with Monte Carlo simulations.

Results

Unbound cloxacillin <2 mg/L was noted at the end of surgery in 13% of patients sampled at this time point (n=25/187). Furthermore, a model-predicted 18-22% (n=36-43/200) of patients failed to sustain unbound cloxacillin levels ≥2 mg/L throughout the 2 h dosing interval with the currently recommended 20-30 min infusion times. In contrast, a continuous 1 g/h cloxacillin infusion after a 1 g loading dose would ensure target attainment in >99% of patients, according to the model-based simulations.

Discussion / Conclusion

Short, intermittent 2 g cloxacillin infusions administered 2 h apart may fail to provide adequate target site concentrations in many patients undergoing hip and knee arthroplasty. Transitioning to a prolonged infusion regimen could increase attainment of PK/PD targets without exceeding currently recommended dose amounts.

00280
Subcutaneous piperacillin/tazobactam: a valuable alternative for elderly patients or a risk of underdosing?

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Subcutaneous (SC) administration of antibiotics is a therapeutic option, particularly in elderly patients with difficult vascular access and in the context of outpatient antimicrobial therapy. However, pharmacokinetic data regarding subcutaneous administration of the piperacillin-tazobactam (PTZ) remain limited. This study describes our experience with therapeutic drug monitoring (TDM) of SC PTZ.

Materials and methods

We conducted a retrospective 4-years observational study (01/2022-02/2026) including adult patients treated with SC PTZ at Groupe-Hospitalier-Paris-Saint-Joseph. Demographic, clinical, and pharmacological data were collected. Steady state plasma concentrations were measured using ultra-high-performance-liquid chromatography-coupled with high-resolution-mass-spectrometry and were compared with pharmacokinetic/pharmacodynamic (PK/PD) targets defined as 100%T>MIC and 100%T>4xMIC, using EUCAST epidemiological cutoff values.

Results

Sixteen elderly patients were included (median 83 years [IQR:71-90 year]) with hypoalbuminemia (26.9±7.8g/L) and median creatinin at 88mM (IQR:60-120mM). Most patients (81.3%) were treated for soft tissue infections (ulcers). Polymicrobial infections were observed in most cases, mainly involving P.aeruginosa and S.aureus. The median daily dose was 10g/1.25g (IQR:5g/0.625g-12g/1.5g). Median plasma concentrations were 17mg/L (IQR:14-47mg/L) for piperacillin and 5mg/L (IQR:3-9mg/L) for tazobactam. At MIC values of 4 and 16mg/L, 14 and 8 patients reached the PK/PD target of 100%T>MIC, respectively and only 8 and 3 patients achieved the stricter target of 100%T>4xMIC. Higher plasma concentrations were observed in patients who received an initial intravenous loading doses compared with those started directly on SC administration, even after normalization to the individual daily dose. TDM influenced clinical management, leading to dosage adjustments in 44% of cases due to underexposure (intravenous switch, prolonged infusion duration, increased daily dose).

Discussion / Conclusion

The SC route achieves effective therapeutic PTZ concentrations for pathogens with moderate MIC values. However, PK/PD targets for P.aeruginosa are rarely attained without an initial intravenous loading dose or dose optimization, especially in patients without renal impairment. In this context, TDM appears essential to adjust dosing according to renal function and pathogen-specific MIC values.

Keywords

Piperacillin/Tazobactam, Subcutaneous administration, Geriatrics, Pharmacokinetics, Therapeutic drug monitoring (TDM)

00283
Risk factors of isoniazid-induced hepatotoxicity in Tunisian tuberculosis patients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Isoniazid (INH) is a first-line anti-tuberculosis drug often linked to hepatotoxicity. INH-induced hepatotoxicity (IIH) ranges from asymptomatic enzyme elevations to acute liver failure and reflects individual demographic, physiological, and metabolic differences. We aimed to identify IIH risk factors in Tunisian tuberculosis patients for early recognition of high-risk cases

Materials and methods

This retrospective study included patients on anti-tuberculosis therapy who underwent INH therapeutic drug monitoring at the Clinical Pharmacology Department of the University Hospital of Monastir (January 2017–June 2025). INH C3h was measured by HPLC (target 1–2 µg/mL). Significance was set at $p < 0.05$, and ROC analysis determined the predictive threshold for IIH risk.

Results

A total of 347 Tunisian tuberculosis patients (167 males, 180 females; mean age 41.7 ± 17.7 years) were included. IIH occurred in 83 patients (24%), mainly cytolytic (75%), with a mean onset of 25 ± 14.7 days. Affected patients were older (median 45 vs. 37 years, $p = 0.008$), had higher C3h levels (median 2.39 vs. 1.71 µg/mL, p =

0.004), and were more often slow acetylators (71.1% vs. 56.4%, p = 0.018). ROC analysis identified a C3h threshold of 2.84 µg/mL with moderate specificity (79.2%) and limited sensitivity (43.4%), yielding 70.6% accuracy. Multivariate analysis confirmed C3h (OR 1.45 per µg/mL, p = 0.002) and age (OR 1.018 per year, p = 0.037) as independent predictors, while acetylator status and weight were not significant. Hepatic injury affected nearly one-quarter of patients, mostly cytolytic, highlighting TDM's value. Older age and C3h > 2.84 µg/mL were independent risk factors. Although slow acetylators were more frequently affected, this was not independently predictive. The moderate specificity but low sensitivity of C3h suggests greater utility for ruling out rather than diagnosing hepatotoxicity.

Discussion / Conclusion

Elevated plasma isoniazid levels (C3h > 2.84 µg/mL) and older age are independent risk factors for HII in Tunisian tuberculosis patients.

00306
Development and Validation of a LC MS/MS Method for Quantification of Dalbavancin in Pediatric Patients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Dalbavancin is a long-acting lipoglycopeptide with potent activity against Gram-positive pathogens, including methicillin-resistant staphylococci, and a terminal half-life exceeding 14 days (1). It is employed for prolonged treatment of acute bacterial skin and skin structure infections (ABSSSI). Despite its potential clinical relevance, dalbavancin Therapeutic Drug Monitoring (TDM) in children remains limited. Here, we developed a LC-MS/MS method to quantify dalbavancin in human plasma.

Materials and methods

The assay was validated according to EMA bioanalytical guidelines. Intra- and inter-day precision and accuracy were evaluated through % CV and % bias. Stability was tested in different conditions. Quantification was performed trough Agilent 1290 Infinity II UHPLC coupled to a 6470 triple-quadrupole mass spectrometer. Validated method was tested on n=20 pediatric patients with median age=13 years (range 2–17). Trough samples were collected before (Cmin) and 30–60 minutes after the end of infusion (Cmax). A median dose of 800 (200–1500) mg was administered at a median of 7(6–17) days after the first injection.

Results

Our method satisfied the EMA guidelines for accuracy, precision, selectivity, specificity, and carry-over. Intra- and inter-day accuracy and precision values remained within ≤15%. Dalbavancin was stable after 24 hours from sample preparation and after 48 hours of storage at room temperature in the autosampler. The calibration curve demonstrated linearity across the 1–1000 µg/mL range (R^2 = 0.996, y=2.26*x + 8.87). Plasma samples were collected after dalbavancin second dose administration. Median of Cmin levels was 31.05 (8.69–64.89) µg/mL, while median of Cmax concentration was 128.9 (70.95–672.42) µg/mL.

Discussion / Conclusion

This LC-MS/MS method enables reliable quantification of dalbavancin plasma levels. In our pediatric cohort, the Cmin values were all above the proposed therapeutic concentration target of > 8 mg/L (1). In conclusion, our method can be adopted to implement TDM of dalbavancin facilitating the achievement of pk/pd target overtime and reducing the risk of therapeutic failures.

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Keywords

Dalbavancin; Therapeutic Drug Monitoring (TDM); LC-MS/MS; Pediatric Pharmacokinetics; Gram-positive pathogens.

313
Rethinking Amoxicillin Dosing in the ICU: Beyond Weight-Based Schemes and Towards GFR-Stratified Dosing

#313

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Amoxicillin is widely used in ICUs to treat susceptible pathogens or as empirical therapy for endocarditis and meningitis. Doses are prescribed as total daily amounts or weight-based and are adjusted when estimated GFR (eGFR) falls below 30 mL/min/1.73m², resulting in variable dosing. ICU patients often have modified pharmacokinetics and renal function, which can affect antimicrobial exposure. This study examined the impact of renal function and body weight on amoxicillin exposure.

Materials and methods

In this multicenter retrospective ICU study, amoxicillin exposure was assessed using plasma concentrations and concentration-to-dose (C/D) ratios. Renal function was analyzed as indexed and deindexed CKD-EPI, modeled as continuous and categorical variables, including non-linear spline analyses. Obesity status was compared between groups. Theoretical daily doses to achieve target concentrations were estimated from C/D ratios.

Results

Ninety-two patients (30 obese), with a median eGFR of 90 [63–106] mL/min/1.73m², were included. Amoxicillin concentrations and C/D ratios increased progressively as renal function declined, with significant differences across eGFR categories ($p < 0.0001$). Renal function was the main independent predictor of concentration, whereas obesity did not affect exposure or absolute daily dose, despite lower weight-normalized dosing and lower indexed eGFR in obese patients. After deindexing eGFR, differences between obese and non-obese patients disappeared and the inverse relationship between renal function and C/D ratio persisted. Non-linear spline modeling significantly improved fit over linear models ($p < 0.001$), and C/D ratios were used to estimate theoretical daily doses to achieve a target concentration of 60 mg/L across deindexed eGFR categories.

Discussion / Conclusion

Amoxicillin exposure during continuous infusion is primarily determined by renal function, not body weight. Tailored dosing based on deindexed GFR may be considered, with higher doses required for normal (>90 mL/min) or augmented renal function. These results suggest that, for continuous infusion, prescribing daily doses may be preferable to weight-based dosing.

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Keywords

critical care; amoxicillin; continuous infusion; pharmacokinetics; renal function; dose adjustment

00334
Precision prophylaxis with therapeutic drug monitoring of valganciclovir reduces hematologic toxicity after lung transplantation

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Valganciclovir is the standard agent for cytomegalovirus (CMV) prophylaxis after lung transplantation, however, hematologic toxicity frequently necessitates dose reduction or discontinuation, potentially undermining efficacy. Although therapeutic drug monitoring (TDM) has been proposed to optimize ganciclovir exposure, its clinical utility during prophylaxis remains unclear. This study evaluated whether TDM-guided valganciclovir dosing improves safety and maintains prophylaxis continuity in lung transplant recipients.

Materials and methods

We conducted a prospective cohort study with a historical control at Kyoto University Hospital. Adult lung transplant recipients who received valganciclovir prophylaxis between April 2021 and March 2025 were included. From April 2023, valganciclovir dosing was individualized using TDM to achieve predefined ganciclovir trough concentrations of 300–800 ng/mL (TDM-guided group). Patients treated before this implementation received conventional dosing (control group). In patients with normal renal function, the standard initial dose was 900 mg once daily in both groups. Outcomes were assessed during the first 3 months after initiation. The primary endpoint was valganciclovir discontinuation due to adverse events. Secondary endpoints included toxicities and breakthrough CMV infection.

Results

Eighty-seven patients were included (control, n=42; TDM-guided, n=45). Target trough concentrations were attained more frequently in the TDM-guided group than in controls (62.2% vs. 40.5%). Final maintenance dosing differed substantially: 69% of control patients remained on 900 mg once daily, whereas 51% of TDM-guided patients received 450 mg once daily. TDM-guided dosing significantly reduced discontinuation due to adverse events (11.1% vs. 35.7%; hazard ratio 0.303, 95% CI 0.126–0.730). Severe leukopenia or neutropenia (grade ≥3) occurred in 2.2% of TDM-guided patients versus 19.1% of controls. No CMV infections occurred in the TDM-guided group, whereas one observed in controls.

Discussion / Conclusion

TDM-guided valganciclovir prophylaxis enabled precision dosing that significantly reduced hematologic toxicity and improved treatment continuity without compromising antiviral protection. These findings provide clinically actionable evidence supporting the incorporation of antiviral TDM into routine lung transplant care.

Keywords

therapeutic drug monitoring; valganciclovir; ganciclovir; lung transplantation; precision medicine; cytomegalovirus prophylaxis

00337
Plasma Concentrations of Tigecycline in Critically Ill Patients with Sepsis

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Background: The pathophysiological alterations in sepsis may significantly impact the pharmacokinetic profiles of antibiotics.

Objective: This study aimed to compare the differences in tigecycline plasma concentrations between critically ill patients with and without sepsis,, and to explore the contributing factors.

Materials and methods

A retrospective analysis was conducted on critically ill patients treated with tigecycline. Patients were divided into a sepsis group and a non-sepsis group according to the Sepsis-3.0 criteria. Baseline characteristics, clinical parameters, and steady-state trough concentrations of tigecycline were collected. Multivariate linear regression was used to analyze the total effect of sepsis status on drug concentration, and to further explore the roles of albumin, SOFA score, and continuous renal replacement therapy (CRRT).

Results

A total of 142 patients were enrolled, including 78 in the sepsis group and 64 in the non-sepsis group. Tigecycline concentrations were significantly lower in the sepsis group compared to the non-sepsis group (0.41±0.18 μg/mL vs. 0.68±0.22 μg/mL, P<0.001). After adjusting for confounders such as age, sex, and baseline hepatic and renal function, multivariate linear regression revealed that sepsis status was an independent influencing factor for tigecycline concentration (β=-0.253, 95%CI: -0.400 to -0.106, P=0.001). Furthermore, hypoalbuminemia, organ dysfunction, and CRRT were identified as major contributing factors.

Discussion / Conclusion

Tigecycline plasma concentrations are significantly lower in septic patients than in non-sepsis critically ill patients. Therefore, clinical monitoring of tigecycline concentrations should be strengthened in septic patients, and individualized dosing adjustments based on albumin levels and organ function should be considered.

Keywords

Sepsis; Severe infection; Tigecycline; Plasma concentration; Therapeutic drug monitoring

00344
Optimizing Meropenem Dosing and Comparing the Efficacy and Predictive Performance of Hybrid XGBoost–NLME Models in Critically Ill Patients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

This study aimed to develop and validate a population pharmacokinetic (PPK) model for meropenem in critically ill patients, with the goal of optimizing dosing strategies to achieve pharmacokinetic/pharmacodynamic (PK/PD) target attainment.

Materials and methods

Data were collected between January 2019 and October 2022. The dataset was randomly split into a training/test set (80%) and an external validation set (20%). PPK models were developed using nonlinear mixed-effects (NLME) methods to estimate clearance (CL) and volume of distribution (V). Additionally, XGBoost machine learning models were used to predict pharmacokinetic parameters. Monte Carlo simulations evaluated optimal dosing regimens (500, 1000, 2000 mg) and infusion durations (0.5, 1, 2 hours) under varying renal function scenarios.

Results

A total of 147 subjects contributed 554 concentration samples. The final PPK model showed a good fit, with clearance (CL) significantly influenced by creatinine concentration and red blood cell count. Typical clearance (tvCL) was estimated at 6.04 L/h, and volume of distribution (tvV) was estimated at 21.15 L. Monte Carlo simulations identified that a 500 mg dose every 12 hours was sufficient for MICs ≤4 mg/L at a 40% T>MIC target, with higher doses and longer infusion durations required for MICs of 8 mg/L. The hybrid XGBoost–NLME model outperformed the NLME model when a single concentration point was available, demonstrating better predictive accuracy. In the absence of concentration data, the hybrid XGBoost–NLME model showed superior performance with lower RMSE (13.99 vs. 16.13) and higher R^2 (0.544 vs. 0.393) compared to the NLME model.

Discussion / Conclusion

The PPK model developed in this study provides effective dosing strategies for meropenem in critically ill patients, accounting for renal function and other covariates. Notably, the hybrid XGBoost–NLME model offers a robust alternative when concentration data is unavailable, improving predictive accuracy in clinical settings.

00346
Investigation of Rifampicin Protein Binding Levels in Patients with Active Tuberculosis Associated with Hypoalbuminemia

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

In a previous study (Fage et al.), we investigated which biochemical parameters could impact the protein binding rate of rifampicin. We observed that albumin levels strongly influenced the binding rate, which decreased significantly in hypoalbuminemic patients (<30 g/L). These results were primarily based on spiked samples. The present study therefore aims to further explore the relationship between these two variables using clinical samples from tuberculosis patients.

Materials and methods

Twenty patients with multi-sensitive tuberculosis and hypoalbuminemia (<30 g/L) were included. The influence of albumin levels on the binding rate was assessed using Spearman's correlation. If a significant relationship was observed, we attempted to predict the free concentration (using the RMSE criterion) based on either the median binding rate or the binding rate normalized by albumin level.

Results

The median binding rate was 87.4%, with a wide range (51.5–92.2%). A significant positive correlation was observed between the binding rate and albumin levels (r_s =

0.598; p-value <0.001). However, the prediction of the free concentration remained unsatisfactory, and the normalization by albumin level did not improve performance (RMSE = 0.38, corresponding to an average bias of 33% in the predicted median free concentration).

Discussion / Conclusion

We observed substantial variability in the binding rate among hypoalbuminemic tuberculosis patients, which was only partially explained by the relationship between the binding rate and albumin levels. This variability may account for the inability to accurately predict the free concentration.
Our findings suggest that the total rifampicin concentration may not adequately reflect the free concentration in these patients. Further investigation is therefore needed to determine whether the free concentration should be directly measured in tuberculosis patients with hypoalbuminemia.

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Keywords

Antituberculosis drugs, rifampicin, protein binding, hypoalbuminemia

00351
Trough Concentration Threshold of Gentamicin for Predicting Late-onset Acute Kidney Injury in Patients with Infective Endocarditis

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Synergistic gentamicin remains essential in infective endocarditis (IE) treatment. Given its nephrotoxicity, guidelines recommend limiting therapy to 2 weeks and maintaining trough concentrations <1 μg/mL. Nevertheless, acute kidney injury (AKI) still leads to premature discontinuation of gentamicin. This retrospective study evaluated whether gentamicin dosage and exposure up to 7 days were associated with AKI occurring beyond this period and explored predictive thresholds.

Materials and methods

IE patients who received gentamicin for 8-20 days were included, excluding those who developed AKI within the first 7 days. Late-onset AKI was defined as AKI occurring beyond the first 7 days and up to 3 days after the last dose. Associations of gentamicin dosage and exposure up to 7 days, including mean daily dose, mean dosing frequency, cumulative dose, and mean trough concentration, with late-onset AKI were evaluated using logistic regression and receiver operating characteristic (ROC) analysis. For variables demonstrating significant association (p-value <0.05 in the regression) and acceptable discrimination (area under the ROC curve (AUROC) >0.7), optimal thresholds were determined and their associations with late-onset AKI were evaluated using logistic regression.

Results

Among 43 patients included, 8 (18.6%) developed late-onset AKI. Mean trough concentration was significantly associated with late-onset AKI (OR 1.09 per 0.1 μg/mL, p-value 0.0415) and showed acceptable discrimination (AUROC 0.748, 95% CI 0.579–0.917). Using Youden's index, the optimal mean trough concentration threshold for predicting late-onset AKI was determined at 0.625 μg/mL. Patients with mean trough concentration ≥0.625 μg/mL had higher risk of gentamicin-associated AKI (OR 13.42, p-value 0.007) after adjustments for baseline renal function, disease severity and concomitant vancomycin use.

Discussion / Conclusion

Mean trough concentration up to 7 days significantly associated with late-onset AKI. Lower trough concentration targets (<0.625 μg/mL) than currently recommended (<1 μg/mL) may help reduction of nephrotoxicity in IE patients receiving gentamicin.

00362
Quantifying the impact of sampling time discrepancies on area under the concentration-time curve forecasting for vancomycin in critically ill patients

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Although guidelines recommend vancomycin area under the concentration-time curve (AUC)-guided dosing via Bayesian forecasting, discrepancies between recorded and actual sampling times may compromise AUC estimation accuracy in therapeutic drug monitoring (TDM). We quantified the impact of these discrepancies on Bayesian vancomycin AUC estimation using 1-point (trough-only) and 2-point (peak/trough) strategies in critically ill patients.

Materials and methods

This secondary analysis used multicenter prospective study data with rich vancomycin sampling at five Japanese hospitals (October 2021 to March 2024).

Reference AUCs were calculated using trapezoidal methods from day 1 sampling (AUC_{day1}) and from days 3–5 (AUC_{ss}). Bayesian forecasting estimated AUC_{day1} from day 1 sampling and AUC_{ss} from both day 1 and days 3–5 sampling using 1- or 2-point strategies. Systematic time discrepancies were introduced for trough (up to 4 h earlier) and peak (-1 to +4 h) samples. Predictive performance was defined as estimated/reference AUC ratios within an acceptable range of 0.9–1.1.

Results

Twenty-five patients were enrolled; 21 and 14 contributed to the AUC_{day1} and AUC_{ss} analyses. For AUC_{day1}, 2-point sampling was more robust; the interquartile range (IQR) of estimated/reference AUC ratios across patients remained entirely within acceptable range for trough timing discrepancies up to 105 minutes, versus 30 minutes for 1-point sampling. Conversely, 2-point sampling was highly sensitive to peak timing with the IQR (-20 and +10 minutes). For AUC_{ss}, similar trends were observed, with 2-point sampling robust to trough timing discrepancies and sensitive to peak timing, as seen for AUC_{day1}. Overall, AUC_{ss} derived from days 3–5 sampling outperformed estimates based on day 1 sampling.

Discussion / Conclusion

Trough timing discrepancies impact AUC estimation less than peak discrepancies, especially with 2-point sampling. However, as 2-point AUC estimation is highly sensitive to peak timing, precise peak sampling is indispensable for reliable vancomycin TDM in critically ill patients.

Keywords

area under the concentration-time curve, Bayesian forecasting, time discrepancy, therapeutic drug monitoring, vancomycin

00363
Development of a Limited Sampling Strategy for Therapeutic Drug Monitoring of Ganciclovir in Neonates with Congenital CMV Infection

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Valganciclovir, are standard antiviral treatments for neonates diagnosed with congenital cytomegalovirus (CMV) infection. Standard dosing regiments are often resulting in suboptimal or excessive drug exposure, mainly due to rapid developmental changes and pharmacokinetic variability within the pediatric population. Volumetric absorptive microsampling (VAMS) presents a practical solution by requiring minimal volumes of capillary blood, thus facilitating the implementation of a limited sampling strategy (LSS). This study aims to develop and validate a VAMS-based LLS model to accurately estimate ganciclovir exposure in neonates with congenital CMV infection.

Materials and methods

This observational pharmacokinetic study enrolled neonates receiving (val)ganciclovir therapy for CMV. Capillary blood samples were collected via VAMS devices at specific post-dose time points (C2, C4, C8). Ganciclovir concentrations

were determined using a fully validated LC-MS/MS method, while reference AUC_{0-12} values were calculated using the trapezoidal rule. Linear regression was applied using two- and three-sample LSS models. Model performance was evaluated using the coefficient of determination and LOOCV RMSE.In instance where C8 concentration was unavailable, concentrations were estimated by log-linear extrapolation from elimination-phase samples.

Results

The most accurate predictive performance model was achieved by a three-point LSS model incorporating C2, C4 and C8: AUC_{0-12} = 0.373 + 1.885·C2 + 2.927·C4 + 5.674·C8. This model demonstrated high precision, with R^2 = 0.996 and LOOCV RMSE of approximately 1.16 mg·h/L (n = 23). By comparison, a two-sample model using C2 and C8 was notably less accurate (R^2 = 0.886; LOOCV RMSE ≈ 5.29 mg·h/L).

Discussion / Conclusion

The inclusion of mid-interval concentration points significantly improved the model's accuracy and robustness by better capturing the absorption and distribution phases. A combination of a three-point LSS with VAMS technique allows a better, highly accurate and clinically relevant estimation of ganciclovir exposure while drastically minimalizing blood sampling burden. This approach supports TDM-guided dose individualization for neonates suffering from congenital CMV.

Keywords

ganciclovir; congenital CMV; neonates; therapeutic drug monitoring; limited sampling strategy; VAMS

00372
A Multi-Drug Electrochemical Point-of-Care Platform for Rapid TDM of ICU Antibiotics and Antifungals

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic Drug Monitoring (TDM) for antimicrobials is often limited by reliance on complex, conventional analytical platforms associated with prolonged turnaround time. Furthermore, the accredited labs with these equipments are often concentated in metropolitan cities with limited accessibility in the remote areas. There exist analytical techniques for quantifying analytes by electrochemistry. We aimed to develop novel electrochemical assays that can be integrated into TDM and point of care (POC) device for rapid measurement of antibiotics and antifungals.

Materials and methods

Electrochemical analyses for 11 drugs were conducted using a calibrated three-electrode system with cyclic voltammetry and differential pulse voltammetry in buffered electrolyte. Drug-specific electrodes were fabricated by modifying base electrodes with hydrothermally/solvothermally synthesized novel metal–organic frameworks and nanocomposites to enhance electroactive performance. The sensors were comprehensively validated per bioanalytical guidelines and benchmarked against conventional analytical techniques. In addition, Interference studies were performed to assess specificity in the presence of co-administered drugs and endogenous biological substances.

Results

Assays were developed for 11 drugs: meropenem, posaconazole, voriconazole, asparaginase, linezolid, anidulafungin, vancomycin, ciprofloxacin, colistin, piperacillin/tazobactam and ceftazidime. All assays demonstrated linear response across the required concentration range (1–10 nM) required for TDM as per Clinical and Laboratory Standard Institute guidelines. Drug-specific electrode materials included MOF199-PANI (meropenem), MIL-Fe (posaconazole and voriconazole), BCN/Co nanorods (asparaginase), Co-Fe frameworks (linezolid), GO-wrapped ZIF-8 (anidulafungin), BCN-decorated nanorods (vancomycin), bimetallic hydroxide nanomesh (ciprofloxacin), Fe-MOF-decorated selenium nanoparticles (colistin), and cupric chloride wreathe hexapod nanoframes (ceftazidime), platinum nanoparticles /MOF (Piperacillin/Tazobactam). The developed electrodes were well validated and capable of quantifying the drug levels required for TDM. Validation with the patient samples showed a good concordance with HPLC results.

Discussion / Conclusion

The newly developed, potentially patentable electrodes achieved nanomolar detection limits with high analytical sensitivity across essential antibiotics and antifungals. In addition, our data support the feasibility of integrating the electrodes into a point-of-care (POC) device for TDM.

Reference(s)

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Xu, Zhou, et al. "A nanozyme-linked immunosorbent assay based on metal–organic frameworks (MOFs) for sensitive detection of aflatoxin B1." Food Chemistry 338 (2021): 128039.

Keywords

Therapeutic drug monitoring; point of care device; electrochemical sensor; antibiotics; antifungals; differential pulse voltammetry; metal organic frameworks

00375
Impact of measuring unbound versus total concentrations on the appropriateness of the flucloxacillin absorption in oral absorption tests

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Flucloxacillin is a highly plasma protein-bound, narrow-spectrum, beta-lactam commonly used for treating severe gram-positive infections, often requiring prolonged therapy. After initial treatment with intravenous flucloxacillin, continuation of treatment with oral flucloxacillin is an option. Because oral flucloxacillin bio-availability shows strong interpatient variability, assessing absorption adequacy prior to switching administration route is advised. In routine practice, total plasma concentrations are measured in flucloxacillin absorption tests. However, to date, no guidance or studies have determined whether total or unbound concentrations should be measured. This study assesses the impact on interpretation of flucloxacillin absorption when measuring unbound and total flucloxacillin concentrations.

Materials and methods

Total and unbound flucloxacillin concentrations were quantified in 36 plasma-sample sets, requested for an absorption test, using liquid chromatography–mass spectrometry. Plasma was collected before a test dose, and after 45 and 90 minutes. A 1 mg/L unbound threshold (2xMIC of 0.5 mg/L) versus 10 mg/L total threshold (assuming 10% free fraction) was evaluated. Unbound levels were obtained by ultrafiltration (Centrifree; 500 µL plasma incubated 10 min at 37°C, then centrifuged 30 min at 37°C at 1900 g).

Results

Thirty-six samples from 34 patients (52.9% male) were included (internal medicine (25), intensive care (1) and surgery ward (8)). Median total concentrations at 0, 45 and 90 min were 43.6; 55.5 and 53.6 mg/L. Corresponding unbound concentrations were 2.87; 5.52 and 4.51 mg/L. Albumin levels ranged from 17.0 to 43.8 g/L. The proposed thresholds led to discrepant interpretations in 4/36 cases: in three cases, total concentration indicated inadequate absorption, while in one the unbound concentration indicated inadequate absorption. However, the basis of both thresholds remains insufficiently defined.

Discussion / Conclusion

Despite occasional discrepancies, interpretation of oral flucloxacillin absorption was mostly comparable using total or unbound concentrations. Given the operational simplicity of total measurements, lack of validated unbound targets, and limitations of applied thresholds, total concentrations appear sufficient for routine absorption testing at present.

Reference(s)

Dijkmans, Anneke C. MD*,†; Hartigh, Jan den PharmD, PhD‡; van Dissel, Jaap T. MD, PhD§; Burggraaf, Jacobus MD, PhD†. A Simplified Oral Flucloxacillin Absorption Test for Patients Requiring Long-Term Treatment. Therapeutic Drug Monitoring 34(3):p 356-358, June 2012. | DOI: 10.1097/FTD.0b013e318257e8ac

Keywords

Flucloxacillin, unbound concentration, absorption test, beta-lactam, ultrafiltration

00411
Can vancomycin therapeutic drug monitoring detect acute kidney injury before serum creatinine?

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Vancomycin is a first-line antibiotic for multiple serious infections and surgical infection prophylaxis. Vancomycin is also s well-known nephrotoxin and can cause drug-induced acute kidney injury (AKI). AKI that causes functional decline is often clinically determined by serum creatinine (SCr), but SCr has been suggested to lag behind functional decline. Because vancomycin is primarily filtered by the kidney, serial vancomycin clearance assessments may identify AKI before SCr changes.

Materials and methods

Vancomycin therapeutic drug monitoring data from a large international cohort sampled between 2014-2025 were anonymised through an electronic clearinghouse (n = 71,561). Vancomycin clearances were calculated from validated models within a commercially available Bayesian dosing software. AKI was defined according to KDIGO (>/=26.5umol/L increase in 48 hours or 1.5x increase in 7 days). Among patient courses with at least 5 vancomycin clearance calculations in the 7 days prior to AKI, we characterized the time difference between AKI and >/= 30% decrease in vancomycin clearance occurring within +/-7 days of AKI.

Results

Of the 71,561 vancomycin courses analysed, 21,135 (29.5%) indicated AKI, of which 7695 (36.4%) exhibited a >/=30% decrease in vancomycin clearance from baseline, and 7332 (34.7%) were +/-7 days of AKI. Of these, 208 had >/=5 observations in the week prior to AKI. Vancomycin clearance drop >/=30% preceded AKI by a median of 26 hours (IQR: –5.9 to 89.9h). This trend was more pronounced in those with ≥6 drug observations (median [IQR]: 24.2 [0–94.9] hours earlier). Among courses without an AKI event, >/=30% decrease in clearance was detected in 10.3% of cases ($p<0.0001$).

Discussion / Conclusion

Our findings suggest that vancomycin clearance decrease may detect AKI earlier than traditional clinical approaches. Large retrospective studies with multiple vancomycin clearance and serum creatinine assessments are needed to minimize risk of bias. A prospective study is warranted to confirm these findings.

Keywords

pharmacokinetics/pharmacodynamics (PK/PD) of antibacterial drugs, therapeutic drug monitoring (TDM)

00415
Machine Learning-Assisted Prediction of Vancomycin Clearance to Improve AUC Target Attainment in the Initial Dosing Design

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Early attainment of the target vancomycin AUC is critical to optimize efficacy and minimize nephrotoxicity. Although population pharmacokinetic (PopPK) models are widely used for AUC-guided dosing, their predictive accuracy may be limited in patients with dynamic renal function or systemic inflammation. With recent advances in clinical pharmacology, machine learning (ML) has emerged as a promising tool to improve PK predictions. Therefore, this study was conducted to develop and evaluate an ML-assisted approach to enhance early AUC prediction during initial dosing.

Materials and methods

A single-center, retrospective, observational study was conducted at Nagoya City University Hospital between April 2019 and March 2024. Non–steady-state AUC was estimated using SAKURA-TDM. Twenty-seven candidate variables (demographics, laboratory data, and PopPK parameters) were assessed. After LASSO-based feature selection, ML models (Random Forest, LightGBM, CatBoost, Support Vector Regression) were developed to predict vancomycin CL. Model performance was evaluated using relative accuracy (±20%), mean absolute error (MAE), root mean square error (RMSE), and R^2. SHAP analysis was used for interpretability.

Results

In total, 291 patients were included in the analysis (231 for training and 60 for testing). Consequently, twelve variables were selected as important features using LASSO regression analysis. Random Forest exhibited the best predictive performance for the observed CL, with a relative accuracy of 61.7%, MAE of 0.559, RMSE of 0.74, and R^2 of 0.635. Kernel SHAP analysis identified PopPK-derived vancomycin CL, body weight, age, and predicted day 2 AUC as the most important features for predicting vancomycin CL. The Random Forest model demonstrated superior performance in predicting CL compared with the PopPK models, leading to improved prediction of non-steady-state AUC.

Discussion / Conclusion

ML-assisted updating of PopPK-derived clearance improved early vancomycin AUC prediction. This hybrid approach may enhance AUC target attainment during initial dosing and support precision antimicrobial therapy.

Reference(s)

Horita, Y. et al. Development and evaluation of a novel software program, SAKURA-TDM, for area under concentration-time curve-guided vancomycin dosing: A short communication. Ther. Drug Monit. 45, 245–250 (2023).

Keywords

vancomycin, population pharmacokinetics, machine learning, initial dosing design

00418
Limitations of Renal Function–Based Valganciclovir Dosing: Equation Choice Does Not Resolve Ganciclovir Underexposure

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Ganciclovir (GCV) exposure after standard valganciclovir (VGCV) prophylaxis exhibits substantial interindividual pharmacokinetic variability in kidney transplant recipients. As GCV clearance is primarily renal, VGCV dosing is adjusted to renal function. Although the Summary of Product Characteristics (SmPC) recommends creatinine clearance (CrCl), estimated by Cockcroft–Gault (CG), clinicians commonly rely on laboratory-reported estimated glomerular filtration rate (eGFR). Whether such adjustments achieve the target 24-hour exposure ($AUC_{0\text{-}24h}$ = 40–60 mg.h/L) remains uncertain. We aimed to determine whether the renal function equations used for dose adjustment influence GCV exposure and target attainment.

Materials and methods

A published population pharmacokinetic model of GCV (PMID 37140726) was used to simulate steady-state exposure in 2,000 virtual adult kidney transplant recipients receiving VGCV prophylaxis. Renal function was estimated using CG, CKD-EPI, and MDRD, and maintenance doses were assigned *per* SmPC categories. For each equation, we assessed reclassification, $AUC_{0\text{-}24h}$ distributions, and target attainment.

Results

Using CG, CrCl was ≥60 mL/min in 31.0% of patients, 40–59 in 28.0%, 25–39 in 29.7% mL/min, and 10–24 in 9.3%. MDRD and CKD-EPI reclassified 44.4% and 40.0% of patients, mainly toward lower renal function categories. However, exposure distributions were similar across equations, indicating limited impact of equation choice on GCV exposure. With CG-based dosing, underexposure increased with declining renal function: 12.8% (≥60 mL/min), 18.7% (40–59), 42.1% (25–39), and 59.2% (10–24). Overall, fewer than 40% of patients achieved the target $AUC_{0\text{-}24h}$, regardless of equation.

Discussion / Conclusion

Renal function–based VGCV dosing leads to poor target attainment and frequent underexposure, particularly in patients with impaired renal function. Despite substantial reclassification, equation choice does not meaningfully modify GCV exposure. These findings indicate that current dosing algorithms are inadequate and support the need for pharmacokinetic-guided strategies such as therapeutic drug monitoring and model-informed precision dosing.

Reference(s)

Lalagkas PN, Iliou J, Rigo R, Miarons M, Fernández-Alarcon B, Bestard O, Cruzado JM, Melilli E, Torras J, Grinyó JM, Lloberas N, Colom H. Comparison of Three Renal Function Formulas for Ganciclovir/Valganciclovir Dose Individualization in CMV-Infected Solid Organ Transplantation Patients Using a Population Approach. Clin Pharmacokinet. 2023 Jun;62(6):861-880. doi: 10.1007/s40262-023-01237-3. Epub 2023 May 4. PMID: 37140726; PMCID: PMC10256675.

Keywords

Valganciclovir, Cytomegalovirus Prophylaxis, Population Pharmacokinetics, Kidney Transplantation

00458
Performance of renal function estimation methods regarding beta-lactam overdose in intensive care: an observational multicenter study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

In critical care, appropriate prescription of beta-lactam antibiotics aims to rapidly achieve effective concentration while avoiding toxicity from overdose. This study evaluates the performance of methods for estimating renal function (RF) regarding beta-lactam overdose and examines associated factors in critically ill patients.

Materials and methods

This retrospective observational study included adult critical care patients who underwent therapeutic drug monitoring of beta-lactam antibiotic and cystatin C measurement within 72 hours. Overdose was defined as a plasma beta-lactam concentration exceeding values specified by French guidelines. Factors associated with overdose were first identified using univariate analysis and then subsequently assessed using multivariate logistic regression, including CKD-EPI-creatinine, sex, age, SOFA score, BMI, baseline creatinine, length of stay, uremia, proteinemia, and posology not adapted to RF. The different formulas used to estimate RF were compared according to their performance regarding overdose.

Results

Sixty-eight patients were included, with 77 beta-lactam concentrations measured, of which 33.8% were above the recommended levels. Univariate analysis showed associations between overdose and age, higher baseline creatinine, earlier onset of measurement, higher creatinine, urea, and cystatin C levels, lower eGFR at cystatin C dosage. Multivariate logistic regression confirmed the association with lower RF. Inappropriate beta-lactam dosage was not significantly associated with overdose. Cockcroft-Gault formula was the best predictor of overdose (AUC = 0.758, 95% CI [0.644; 0.872]), compared with CKD-EPI-creatinine, CKD-EPI-cystatin, CKD-EPI-creatinine-cystatin, EKFC-creatinine, EKFC-cystatin, and EKFC-creatinine-cystatin.

Discussion / Conclusion

Beta-lactam overdose is associated with impaired RF, but inappropriate dosing is not a significant factor, possibly indicating inaccurate adaptation of actual dosing. Cockcroft-Gault formula was most effective in predicting overdose, highlighting the importance of tubular secretion in addition to glomerular filtration of beta-lactams. Therefore, dosages should be adjusted based on total renal clearance rather than glomerular filtration alone. Resuscitators must distinguish between the assessment of kidney disease and the assessment of drug elimination function

00461
Predictive Performance of Two Population Pharmacokinetic Models for Therapeutic Drug Monitoring of Voriconazole

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

This study evaluated and compared the predictive performance of two population pharmacokinetic models (popPKm) of voriconazole, an antifungal used in severe infections.

Materials and methods

Retrospective pharmacokinetic study in adults with aspergillosis treated with voriconazole.

First, trough concentrations (Cmin) were predicted using the popPKm without concentration data, applying an empirical calculator (EC) based on population parameters. Subsequently, Bayesian estimation (BE) was performed using both popPKm and optimisation methods. Estimates were obtained with popPKm: Pascual et al. (2012), developed in adults (n=55, median age 58 years, weight 68kg), and Neely et al. (2015), developed in paediatric (n=85, median age 5.6 years, weight 22.7kg) and adult populations (n=56, median age 31.8 years, weight 75.8kg). Two optimisation methods were applied: Levenberg–Marquardt least squares [M2] and adaptive Metropolis sampling [MAS]. Pharmacokinetic analyses were conducted with Rx Studio software.

To assess predictive performance, prediction error (PE%), mean prediction error (MPE%) and median prediction error (MDPE%) were calculated. Accuracy and precision were further evaluated using median absolute prediction error (MAPE%) and the percentage of individual PE within ±20% (F20) and ±30% (F30).

Limitations: concentrations <0.5μg/mL were undetectable and imputed as 0.4μg/mL, and MAS was not applicable to Neely due to large numerical deviations.

Results

A total of 123 trough concentrations (0.5–11.9 μg/mL) were analysed in 20 adults (70% male), median age 63 years and weight 69.9kg. Intravenous and oral doses ranged from 50 to 540mg. Sixty concentrations were predicted using EC and 309 using BE. Performance metrics (MDPE, MAPE, F20 and F30, respectively) were calculated for each model-optimisation combination:

Pascual EC+MAS: -31.4%,41.8%,25%,30%.

Pascual EC+M2: -32.5%,43.8%,25%,35%.

Neely EC+M2: -72.7%,72.7%,0%,5%.

Neely BE+M2: -31.7%,53.6%,30.1%,35.9%.

Pascual BE+MAS: -13.1%,44.8%,28.2,36.9%.

Pascual BA+M2: -10.9%,35.7%,25.2%,41.8%.

Discussion / Conclusion

For both EC and BE approaches, the Pascual model combined with M2 showed the best predictive performance. Combinations using the Neely model performed worse, likely due to the inclusion of a paediatric population.

Reference(s)

Pascual, A., Csajka, C., Buclin, T., Bolay, S., Bille, J., Calandra, T., & Marchetti, O. (2012). Challenging recommended oral and intravenous voriconazole doses for improved efficacy and safety: Population pharmacokinetics–based analysis of adult patients with invasive fungal infections. Clinical Infectious Diseases, 55(3), 381–390. https://doi.org/10.1093/cid/cis437

Neely, M., Margol, A., Fu, X., van Guilder, M., Bayard, D., Schumitzky, A., Orbach, R., Liu, S., Louie, S., & Hope, W. (2015). Achieving target voriconazole

concentrations more accurately in children and adolescents. Antimicrobial Agents and Chemotherapy, 59(6), 3090–3097. https://doi.org/10.1128/AAC.00269-15

Keywords

TDM, Voriconazole, popPKm, Evaluation

00464
Construction of a Risk Prediction Model for Subtherapeutic Isoniazid Plasma Concentrations in Patients with Spinal Tuberculosis and Analysis of Influencing Factors

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Spinal tuberculosis is a common extrapulmonary tuberculosis with high disability risk. Isoniazid is a first-line antituberculosis drug, and its blood concentration directly affects efficacy and safety. However, factors influencing isoniazid therapeutic concentration in spinal tuberculosis patients are still unclear. This study aimed to analyze relevant factors and establish a risk prediction model to guide individualized medication and improve clinical treatment.

Materials and methods

Using real-world data from the hospital information system (HIS), we retrospectively enrolled 224 hospitalized spinal tuberculosis patients who received isoniazid treatment and underwent therapeutic drug monitoring at Qinghai Provincial People's Hospital from March 2020 to March 2024. Patients were categorized into target-achieved and non-achieved groups based on whether their blood concentration reached the therapeutic window (3–6 $\mu g \cdot mL^{-1}$) within 2 hours post-administration. Clinical data, including gender, age, body surface area, concomitant medications, and biochemical indicators, were collected. Univariate analysis and multivariate logistic regression were used to identify independent factors influencing suboptimal

isoniazid blood concentration. A receiver operating characteristic (ROC) curve prediction model was constructed based on these factors. Model discrimination was assessed by area under the ROC curve (AUC), model calibration by calibration curves, and clinical utility by decision curve analysis (DCA).

Results

The incidence of subtherapeutic blood concentration was 55.36% (124/224). Multivariate analysis showed that body surface area (OR=0.113), combined rifampicin (OR=0.407), alanine aminotransferase (OR=1.015), aspartate aminotransferase (OR=1.021) and total bilirubin (OR=1.072) were independent factors. The model AUC was 0.833 (95%CI: 0.779–0.886), with good discrimination, calibration and clinical net benefit.

Discussion / Conclusion

The established prediction model has good efficacy and can provide a reference for early identification of high-risk patients and individualized medication of isoniazid.

Keywords

spinal tuberculosis; isoniazid; plasma drug concentration; therapeutic drug monitoring; risk prediction model

00480
Developmental changes in ganciclovir clearance in a preterm infant: implications for catch up renal maturation

Poster only

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[1]Department of Pharmacy Practice and Sciences, School of Pharmacy and Pharmaceutical Sciences, University of Toyama - Toyama-Shi (Japan), [2]Division of Neonatology, Maternal and Perinatal Center, Toyama University Hospital, Toyama, Japan - Toyama-Shi (Japan)

Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Congenital cytomegalovirus (CMV) infection is a major cause of neonatal morbidity. However, optimizing ganciclovir (GCV) dosing in preterm infants is complicated by immature renal function and developmental pharmacokinetics. Population pharmacokinetic (PPK) parameters for GCV and valganciclovir (VGCV) have been reported, but data remain limited for extremely low birth weight infants. This study aimed to describe longitudinal changes in GCV clearance in a preterm infant and to assess whether the observed developmental increase could be interpreted in the context of catch-up renal maturation.

Materials and methods

A female preterm infant (27 weeks' gestation, 556 g) with congenital CMV infection received intravenous GCV followed by oral VGCV over a 15-week period. Repeated therapeutic drug monitoring was analyzed using a published population PK model1) to estimate individual pharmacokinetic parameters, and developmental changes in GCV clearance were evaluated using a Hill-type maturation model.

Results

GCV clearance increased from 0.048 to 0.273 L/hr/kg between postnatal days 30 and 93. Early-phase Bayesian estimates of GCV clearance closely matched ScrCL values, supporting the validity of the model. In the later treatment period, GCV clearance exceeded 100 mL/min/1.73 m², surpassing the expected glomerular filtration rate range for infants. The maturation model demonstrated a steep developmental trajectory (Hill coefficient 2.79) with an estimated half-maturation age of 96 days. These findings suggest that accelerated renal development in this preterm infant may reflect catch-up maturation.

Discussion / Conclusion

Longitudinal TDM combined with Bayesian PPK analysis revealed a rapid developmental increase in GCV clearance in a preterm infant, including clearance values exceeding the expected GFR range. These observations may reflect catch-up renal maturation and underscore the importance of considering developmental renal physiology when individualizing GCV/VGCV dosing in extremely preterm neonates. The full Bayesian analysis of this case has been published.2)

Reference(s)

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Keywords

ganciclovir, preterm infant, renal maturation, Bayesian analysis, catch-up development

00481
Metabolomic identification of predictive and early biomarkers of polymyxin B-induced acute kidney injury in ICU patients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Acute kidney injury (AKI) induced by polymyxin B represents a significant limiting factor in its clinical application. Although guidelines recommend therapeutic drug monitoring (TDM) to enhance efficacy and reduce the incidence of adverse reactions, the earliest onset of AKI may occur within 2-3 days after medication administration, and the predictive accuracy of TDM is limited. Thus, there is an urgent need to identify earlier and more reliable biomarkers. This study aims to employ an untargeted metabolomics approach to discover predictive biomarkers for AKI caused by polymyxin B.

Materials and methods

121 serum samples were collected from 87 patients receiving polymyxin B administration for untargeted metabolomics analysis. The metabolite profiles in serum were comprehensively captured using ultra-high-performance liquid chromatography-quadrupole-time-of-flight mass spectrometry (HPLC-Q/TOF-MS) technology. Differential metabolites were screened, and metabolic pathway enrichment analysis was conducted.

Results

Metabolic discrimination was observed between AKI patients and no AKI patients. Serum cis-4-Hydroxyproline, prolyphenylalanine, serylproline, prolyl-glutamate and 2-(3-hydroxy-1H-indol-2-yl) acetic acid were significantly different between AKI patients and no AKI patients prior to polymyxin B administration. The protein metabolism process may be involved in polymyxin B-induced AKI through various mechanisms, including direct damage to renal tubular cells, oxidative stress and inflammatio.

Discussion / Conclusion

We propose Serum cis-4-Hydroxyproline, prolyphenylalanine, serylproline, prolyl-glutamate and 2-(3-hydroxy-1H-indol-2-yl) acetic acid as predictive biomarkers of predisposition to polymyxin B -induced AKI, and Further validation studies with large sample sizes are needed.

Keywords

polymyxin B; acute kidney injury; biomarker; metabolomics.

00483
Implementation of a Multidisciplinary Therapeutic Drug Monitoring Pathway for Trimethoprim-Sulfamethoxazole in Non-HIV Pneumocystis Pneumonia: A Prospective Real-World Study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Trimethoprim-sulfamethoxazole (TMP-SMZ) is first-line therapy for *Pneumocystis jirovecii* pneumonia (PJP). Although guidelines recommend weight- and renal function-based dosing, this frequently causes unexpected adverse drug reactions (ADRs), particularly in heterogeneous non-HIV patients. Prospective evidence characterizing dual-target drug exposure and structured therapeutic drug monitoring (TDM) implementation remains limited. We evaluated a pharmacist-led multidisciplinary TDM care pathway to operationalize precision dosing in routine practice.

Materials and methods

This prospective single-arm study included 21 non-HIV PJP patients. Within a structured pharmacist-physician-nurse TDM pathway, initial TMP-SMZ dosing followed guideline recommendations based on body weight and creatinine clearance. Peak plasma concentrations of trimethoprim (TMP) and sulfamethoxazole (SMZ) were measured once at clinical steady state. Predefined therapeutic targets were TMP 5–10 μg/mL and SMZ 100–200 μg/mL. Dose adjustment was collaboratively executed based on TDM and ADRs. Primary outcomes were prevalence of

overexposure and ADR occurrence; secondary outcomes included ADR resolution and clinical response.

Results

Patients were highly heterogeneous (age 36–88 years) with prevalent renal impairment (mean creatinine clearance 54.33±25.42 mL/min). ADRs (predominantly gastrointestinal, hematological and renal) occurred in 81.0% (17/21), prompting empirical dose reduction even prior to first TDM in 42.9% (9/21). Initial TDM revealed that 38.1% experienced overexposure, with peak concentrations up to 25.6 μg/mL (TMP) and 316.0 μg/mL (SMZ). Only 42.9% achieved dual target exposure under standard dosing. Following TDM-guided optimization, median maintenance TMP dose decreased to ~8 mg/kg/day (a 30–40% reduction). All ADRs resolved after individualized adjustment, and clinical improvement was achieved in all patients.

Discussion / Conclusion

Standard dosing frequently causes toxic overexposure in non-HIV PJP. A multidisciplinary TDM pathway safely supports individualized dose modification while maintaining clinical response. These findings highlight the clinical impact of proactive TDM, providing a reproducible framework to translate precision medicine into infectious disease practice.

Keywords

Therapeutic Drug Monitoring; Dose optimization; Trimethoprim-sulfamethoxazole; *Pneumocystis jirovecii* pneumonia; Precision medicine in infectious diseases; Clinical pathway

00486
Precision dosing of meropenem in severe pneumonia: integrating host factors and the hidden risk of high peak concentrations

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Routine therapeutic drug monitoring (TDM) for meropenem conventionally targets trough concentrations to ensure sufficient time above the minimum inhibitory concentration (fT>MIC). Yet, clinical failures persist in critically ill patients despite strict target attainment. We sought to move beyond standard TDM by applying a multidimensional predictive framework to identify novel determinants of clinical success and refine individualized dosing strategies for severe pneumonia in the respiratory intensive care unit (RICU).

Materials and methods

This prospective observational study included 111 adult RICU patients. Two-dimensional HPLC was used to quantify 396 steady-state meropenem concentrations. To uncover multidimensional clinical determinants, we implemented a supervised classification algorithm based on multivariate logistic regression. Concurrently, a population pharmacokinetic (PPK) model was constructed to perform Monte Carlo simulations, mapping the probability of target attainment across diverse renal functions, pathogen MICs, and specific infusion modalities.

Results

The overall clinical success rate was 46.5%. The classification model identified total protein (OR=1.147) and platelet count (OR=1.007) as host protective factors. Elevated APACHE II scores (OR=0.904) and, notably, high steady-state peak concentrations (Cpeak; OR=0.953) emerged as independent risk factors for treatment failure. Combining these variables yielded a high-performance prognostic tool with an AUC of 0.914. PPK modeling (clearance=20.51 L/h, volume of distribution=8.45 L) and subsequent simulations revealed that default 3-hour prolonged infusions offered marginal analytical benefits over 0.5- or 2-hour infusions. Superiority of the 3-hour regimen was mathematically restricted to extreme scenarios, such as targeting 100% fT>MIC against pathogens with an MIC of 8 mg/L.

Discussion / Conclusion

Establishing high Cpeak as a distinct risk factor shifts the TDM paradigm from merely preventing under-dosing to actively mitigating over-exposure. Integrating patient host metrics with pharmacological parameters generates a highly robust clinical decision model. Our analytical simulations also challenge the routine application of 3-hour infusions, offering evidence to streamline nursing administration protocols safely.

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Keywords

Therapeutic drug monitoring; Meropenem; Population pharmacokinetics; Intensive care unit; Precision medicine.

00488
Electrochemical, aptamer-based sensors enable real time monitoring of drugs and small molecule uremic toxins in a rat model of acute kidney injury

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Vancomycin is a crucial antibiotic that is often our best defense against severe infections that are resistant to weaker treatments. However, it is also toxic to a number of organs, including the kidneys. The vancomycin-induced increased risk of developing acute kidney injury (AKI) is particularly problematic given that this drug is solely cleared by renal filtration. Therefore, clinicians monitor vancomycin levels and kidney function via daily blood sample collection and benchtop analysis of uremic toxins like creatinine and urea. The cumbersome and time-consuming nature of these techniques provides a profile of vancomycin pharmacokinetics that lacks time resolution and delays AKI diagnosis by hours to days.

Materials and methods

In contrast, electrochemical, aptamer-based sensors (EABs) can collect real-time, seconds-resolved measurements of vancomycin as well as biomarkers of kidney function, such as the uremic toxins, in plasma that could be invaluable for diagnosing AKI more quickly and informing guidelines on altered vancomycin pharmacokinetics. Here, we have employed EAB sensors in a rat model of AKI produced by occlusion of the renal veins.

Results

Upon induction of AKI, we observed early (within 1 hour) increases in plasma levels of uremic toxins and a lack of vancomycin elimination.

Discussion / Conclusion

Together with recent adaptation of EABs to human subjects, multiplexed drug and biomarker monitoring is likely to enhance management of AKI, as well as other disease states, by enabling the implementation of early life-saving interventions.

Keywords

biosensors, pharmacokinetics, kidney injury, vancomycin, uremic toxins

00489
Determination of voriconazole concentration in human serum by two-dimensional liquid chromatography and its clinical application

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Voriconazole is a second-generation triazole antifungal agent with broad-spectrum antifungal activity. It is a first-line treatment for invasive aspergillosis and infections caused by Candida krusei. In adults, the pharmacokinetic profile of this drug is characterized by nonlinearity and exhibits substantial intra- and inter-individual variability. The aim of this work was to establish a sensitive and rapid analytical method for the blood concentration determination of voriconazole and to evaluate the importance of therapeutic monitoring of voriconazole in clinical practice.

Materials and methods

In this study, a new two-dimensional liquid chromatograph was used to establish a method for the determination of blood concentration of voriconazole. One-dimensional column Aston SC2-1A (3.5 × 25 mm, 5 μm), two-dimensional column Aston SCB-2A (4.6 × 125 mm, 5 μm), flow rate: 1.0 mL·min-1, column temperature: at 45 ℃. The UV detection wavelength was 254 nm and the sample size was 200μL. After verifying the specificity, standard curve and lower limit of quantification, precision and recovery, and stability of the method, it was applied to the blood concentration monitoring of voriconazole in clinical patients.

Results

The standard curve equation of voriconazole in plasma was Y= 51407.6X + 764.539 (R2= 0.9999), which showed a good linear relationship in the range of 0.47 ~ 7.76 μg·mL-1. The accuracy of low, medium, and high concentrations was within ±15% of the labeled value, and the relative standard deviation (RSD) of precision was less than 15%. Serum samples were collected from 20 patients receiving voriconazole, and the test results showed that 60% of the patients had serum concentrations outside the therapeutic window.

Discussion / Conclusion

The method was successfully validated. It is suitable for high-throughput analysis and monitoring of clinical blood drug concentrations. There is significant individual variability among patients using voriconazole, and therapeutic drug monitoring (TDM) is essential for patients to establish individualized optimal pharmacotherapy.

Keywords

voriconazole, two-dimensional liquid chromatography, therapeutic drug monitoring

00506
Therapeutic drug monitoring in patients on intermittent hemodialysis treated with high-dose ceftriaxone: time to re-evaluate current dosing guidelines?

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Ceftriaxone is administered at high doses (2g twice daily) for severe infections [1]. In patients receiving intermittent hemodialysis (iHD), dose adjustments are not recommended[2,3,] despite evidence that the elimination half-life of ceftriaxone increases twofold in iHD patients[4]. To evaluate current dosing practice, we measured ceftriaxone concentrations in iHD patients receiving high-dose ceftriaxone.

Materials and methods

Beginning January 2024, we measured total and unbound trough concentrations in iHD patients treated with high-dose ceftriaxone at our academic hospital. Dosages were adjusted based on clinical judgement of the treating physician and hospital pharmacist, considering a target exposure of 100% fT>4xMIC and a toxicity threshold

of total concentrations >100 mg/L [5,6]. Follow-up concentrations were measured after dose reductions.

Results

Five iHD patients were included: three anuric and two with minimal residual renal function. Median total and unbound ceftriaxone trough concentrations were 175 mg/L (range 149–611), and 55 mg/L (range 36–374), respectively, with protein binding ranging from 24% to 61%. In all patients, the dose was reduced to 2g once daily, resulting in median total and unbound concentrations of 103 mg/L (range 53–319) and 22 mg/L (range 4–138), respectively. In one patient, a further reduction to 1.5 g once daily resulted in total and unbound concentrations of 136 and 26 mg/L, respectively. Neurological adverse effects occurred in the patient with the highest concentrations and resolved after dose reduction.

Discussion / Conclusion

Ceftriaxone concentrations in iHD patients treated with high-dose ceftriaxone were substantially higher than those reported in individuals with normal renal function, whose mean concentration is 59 mg/L[7]. All concentrations exceeded the toxicity threshold. In addition, we measured relatively high unbound concentrations, which can cross the blood–CSF barrier and cause neurotoxicity [8].Our findings demonstrate the potential role of TDM in this setting and urge reconsideration of current high dosing recommendations in patients undergoing iHD.

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Keywords

Ceftriaxone, hemodialysis, therapeutic drug monitoring

00509
Implementation of vancomycin Model-Informed Precision Dosing: A process evaluation

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

In 2023, a vancomycin Model-Informed Precision Dosing (MIPD) intervention was developed and implemented at a Swedish tertiary hospital (1). We evaluated implementation fidelity, feasibility (time consumption), and target attainment based on $AUC_{0\text{-}24h}$ (400-600 mg*h/L) (2).

Materials and methods

The intervention was implemented at the Blood and Tumour division, Uppsala University Hospital, Sweden. Data were obtained from electronic medical records, case report forms, and the MIPD software (InsightRx settings and estimated AUC24). Time measurements were performed by clinical pharmacists and MIPD consultants.

Results

In total, 42 vancomycin courses and 215 monitoring samples from 37 patients were evaluated. Of all samples, 79% (169/215) had a corresponding MIPD report, with

dose reduction advice in 30% (50/169). Median (range) time from reported concentration to dose advice was 2.4 (0.08-54.2) hours; <3h in 60% (101/169) and >16h in 11% (18/169) of the cases. Two-thirds (44/64) of missing or late reports (>16h) occurred during weekends.

Overall, 85% (144/169) of dose decisions aligned with MIPD advice, and decision support from clinical pharmacists was documented in 72% (121/169) of cases. Time was primarily spent on predictions and communication. MIPD consultants spent on average, 3.4 (±3.8) minutes on data entry and 13.9 (±5.7) minutes on predictions and documentation. Clinical pharmacists spent 5.7 (±2.8) minutes on data entry and 12.4 (±9.1) minutes on participation in rounds and documentation. Target attainment (AUC24 400-600 mg*/L) was 54% (23/42) before first dose advice, with 29% (12/42) above target. It improved to 88% (113/129) following MIPD-guided dose advise (sampling occasions ≥2).

Discussion / Conclusion

The workflow for vancomycin MIPD was implemented as planned, was feasible, and improved AUC target attainment. Improvements should focus on better weekend procedures and earlier sampling to enable timely dosing advice.

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Keywords

Vancomycin, Model-informed precision dosing, Implementation

00513
Exposure Prediction and Dose Optimization of Polymyxin B Based on Bayesian and Machine Learning

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

With the rise of multidrug-resistant Gram-negative bacteria, Polymyxin B (PMB) has become a last-line therapy, and its AUC/MIC ratio is a key PK/PD target. However, accurate AUC estimation is limited by sparse sampling and the lack of standardized TDM strategies. Although PopPK models with Bayesian estimation are commonly used, machine learning methods such as XGBoost show strong predictive potential. This study developed a PopPK model from routine TDM data, trained an XGBoost model using simulated data, and compared XGBoost with MAP-BE for predicting PMB $AUC_{0\text{-}12h}$ across four scenarios to optimize individualized dosing strategies.

Materials and methods

Retrospective data were used to develop a PopPK model for Polymyxin B, followed by Monte Carlo simulations to generate modeling and test datasets. $AUC_{0\text{-}12h}$ was calculated using the trapezoidal rule with PKNCA and defined as the reference.The predictive performances of MAP-BE and XGBoost were compared under four dense and sparse sampling scenarios. Accuracy and precision were assessed using RMSE, MAE, R^2, and prediction error proportions, with visualization performed using ggplot2.

Results

A stable two-compartment PopPK model for Polymyxin B was developed and used for Monte Carlo simulations. Under dense-data modeling, both MAP-BE and XGBoost showed high accuracy for $AUC_{0\text{-}12h}$ prediction, with optimal performance at 6h sampling. Sparse PopPK models with single trough points performed poorly for MAP-BE, whereas two-point models markedly improved accuracy. XGBoost maintained robust performance even with limited sampling. An online tool (https://pmb.xy3yx.com/) was developed to support AUC prediction and dose optimization.

Discussion / Conclusion

This study compared MAP-BE and XGBoost for predicting $AUC_{0\text{-}12h}$ of Polymyxin B. Bayesian estimation excelled with dense data, while ML performed best with sparse single-point data. Overall, ML complements PopPK and Bayesian methods for precision dosing.

Reference(s)

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Keywords

limited sampling strategy, maximum a posteriori Bayesian estimators, polymyxin B, population pharmacokinetics model, XGBoost

00516
Population pharmacokinetic modeling and individualized dosing of polymyxin B during continuous renal replacement therapy: an integrated study of residual renal function and extracorporeal clearance

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Existing population pharmacokinetic (PopPK) models for polymyxin B in CRRT patients remain limited, and all of them have neglected the impact of membrane materials on drug adsorption. Recently, a few studies have attempted to develop integrated PopPK models by combining PK parameters based on non-CRRT patients with CRRT-specific parameters. However, current integrated models only consider non-renal clearance (CL_{NR}) and CRRT clearance (CL_{CRRT}), excluding residual renal function (RRF). This study aimed to develop an integrated PopPK model for polymyxin B incorporating RRF clearance (CL_R), CL_{NR}, and CL_{CRRT}, with CL_{CRRT} comprising transmembrane (CL_{TM}) and adsorptive (CL_{ads}) components.

Materials and methods

CL_{CRRT} allocation was set to 0% CL_{ads} for the PS membrane and 100% CL_{ads} for the AN69 membrane. Model validation used two literature datasets (n=53 and n=30) and

a prospective cohort (n=10). Using a comprehensive pharmacodynamic and safety evaluation (targets: PTA ≥ 90% and probability of $AUC_{0\text{-}24\ h}$ > 100 mg·h/L ≤ 14.5%), four dosing regimens were evaluated under varying filter types, RRF, and CRRT intensity.

Results

The model accurate prediction of polymyxin B exposure in non-CRRT and CRRT patients (prediction error <30%). Simulation showed that filter type was the primary determinant of exposure, exceeding the effects of RRF or CRRT intensity. For the PS membrane (AV600S filter), for MIC = 0.5 mg/L pathogens, dose should be stratified based on CrCL with standard or lower doses. For the AN69 membrane (OXIRIS filter), a high-dose regimen (200 mg LD + 150 mg MD q12h) should be considered for infections with an MIC of 0.5 mg/L. An interactive Shiny application (https://xy3yx-cn.shinyapps.io/polymyxin-B-crrt-dosing/) is provided to facilitate clinical dosing optimization.

Discussion / Conclusion

An integrated PopPK model incorporating RRF and membrane-specific adsorption enables optimized polymyxin B dosing in CRRT, identifying filter type as the dominant determinant. The R Shiny application enables precision dosing in complex clinical scenarios

Reference(s)

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Keywords

Polymyxin B, Continuous renal replacement therapy, Membrane adsorption, Residual renal function, Population pharmacokinetic model, PTA analysis, Shiny application

00519
Individualized dosing regimen of ceftazidime-avibactam stratified by CRRT intensity and residual renal function: A population pharmacokinetic study integrating CRRT clearance parameters

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Ceftazidime-avibactam (CAZ-AVI) is effective against infections caused by multidrug-resistant Gram-negative bacteria. However, critically ill patients often require continuous renal replacement therapy (CRRT), which presents challenges in optimizing its dosing. Currently, there is a lack of population pharmacokinetic (PopPK) models for CAZ-AVI in CRRT patients, and the sample size in existing pharmacokinetics studies is limited (mostly case reports, with the largest sample size being only n=21), restricting the development of evidence-based dosing adjustment strategies. This study aims to explore a stratified dosing strategy based on CRRT intensity and residual renal function (RRF) through an integrated modeling approach.

Materials and methods

A literature review identified PopPK models for CAZ-AVI (n=3), validating them with independent CRRT data. New models (n=2) were developed using patient data from literature and our center, resulting in five models for integrated analysis. Model

validation used two literature datasets (n=6 and n=4) and a prospective cohort (n=8). Monte Carlo simulations evaluated probability of target attainment (PTA) for different dosing regimens, CRRT intensities, and RRF (estimated using creatinine clearance [CrCL]), with dose recommendations based on PTA ≥ 90% at MIC = 8 mg/L.

Results

Quantitative validation showed that the model developed using our center's data was selected for the final simulation.The simulation results indicated that CRRT intensity and RRF are the main determinants of CAZ-AVI clearance. As CRRT intensity or CrCL increases, the PTA decreases. Extending the infusion time or shortening the dosing interval significantly improved PTA. A stratified dosing strategy was established, with most patients receiving 2.5 g q8h as the baseline regimen and individualized adjustments via infusion time.

Discussion / Conclusion

Through an integrated modeling strategy, this study clarified the impact of CRRT intensity and RRF on the clearance of CAZ-AVI and pharmacodynamic targets, thereby establishing an individualized dosing regimen that provides evidence-based guidance for dosing optimization.

Reference(s)

1.Shirley M. 2018. Ceftazidime-Avibactam: A Review in the Treatment of Serious Gram-Negative Bacterial Infections. Drugs.78(6):675-692.

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Keywords

Ceftazidime-avibactam; multidrug-resistant Gram-negative bacteria; Continuous renal replacement therapy; Population pharmacokinetics model; Monte Carlo simulation; Dosing recommendations

00529
A single-factor analysis study on the trough concentration of linezolid in children

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

To explore the influencing factors of linezolid trough concentration in children treated with oral or intravenous administration, so as to provide guidance for the clinical development of individualized dosing regimens and realize precise treatment.

Materials and methods

Clinical data of 42 pediatric patients who received linezolid treatment in the Children's Hospital, Zhejiang University School of Medicine were collected through the hospital's electronic medical record system. A retrospective analysis was performed on the linezolid trough concentration values of patients with different characteristics (gender, age, BMI, liver function, renal function,CRP, the distribution of basic patient characteristics in different trough concentration groups , and the distribution of linezolid trough concentrations under different medication conditions.

Results

1. Baseline characteristics: The median age of the included patients was 6.5 years (IQR, 1.2-7.8 years), and 54.76% were male. Among them, 52.84% received the

conventional linezolid dose of 10 mg·kg^{-1} every 8 hours (q8h), and 19.04% received 600 mg once daily (qd). 2. Distribution of trough concentrations: The linezolid trough concentration ranged from 0.1 to 41.58 μg·mL^{-1} , with a median of 1.24 μg·mL^{-1}. Among all patients, 61.9% had trough concentrations below 2 μg·mL^{-1},and only 14.3% reached the target trough concentration. Univariate analysis: There were statistically significant differences in linezolid trough concentrations among children with different ages, body weights, albumin levels, glomerular filtration rates (GFR), white blood cell (WBC) counts, and γ-glutamyl transferase (GGT) levels (all $P<0.05$)，but no statistically significant differences were observed in terms of gender, body mass index (BMI), C-reactive protein (CRP), and alanine aminotransferase (ALT).

Discussion / Conclusion

The proportion of children who achieve the target linezolid trough concentration under the conventional dosing regimen is low, and the trough concentration is significantly affected by multiple single factors such as age, body weight, renal function, and hypoalbuminemia.

00535
Population pharmacokinetics and dosing simulations of piperacillin/tazobactam administered by intravenous and subcutaneous routes in older patients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The subcutaneous (SC) route may be a useful alternative to the intravenous route (IV) for the administration of beta-lactams [1]. We aim to report a population pharmacokinetic (PK) and dosing simulation analysis of piperacillin/tazobactam (PIP/TAZ) administered by SC or IV route in older patients.

Materials and methods

This study enrolled patients aged ≥ 65 years who were administered PIP/TAZ 4 g / 0.5 g q8h by IV or SC route. Concentrations of both drugs were measured pre-dose (Cmin) and at 2 to 3 times post-dose at steady state.

Population PK modelling was carried out with the Monolix software. The Pmetrics program was used to perform dosing simulations and compute probabilities of target attainment (PTA). For PIP, two efficacy and overexposure targets were considered.

Results

Forty-five patients (55% of women, mean age of 84 ± 8 years, mean creatinine clearance - CLCR of 53.8 ± 26.9 mL/min) were included, with 23 and 22 patients receiving PIP/TAZ by IV and SC routes, respectively.

Compared with IV, SC administration was associated with higher Cmin (PIP, 35 ± 24 vs 19 ± 27 mg/L vs, p=0.03; TAZ, 9.9 ± 11.6 mg/L vs 3.6 ± 2.8 mg/L p=0.02). The two final PK models adequately described the data. Typical value of SC bioavailability was 99% for both PIP and TAZ. CLCR influenced clearance of both drugs.

PTA results varied with renal function, pathogen and target. A regimen of 4 g / 0.5 g q12h SC was associated Cmin and PTA values similar to that of 4 g / 0.5 g q8h IV and should be effective and safe in patients with moderately impaired renal function.

Discussion / Conclusion

These first PK data in older patients suggest a superiority of the SC over the IV route in terms of drug exposure and PTA for PIP/TAZ.

Reference(s)

1. Forestier et al. Infect Dis Now. 2026 Feb;56(2):105232. doi: 10.1016/j.idnow.2025.105232.

Keywords

piperacillin, tazobactam, pharmacokinetics, subcutaneous route, older patients

00557
Interest of Therapeutic Drug Monitoring (TDM) of vancomycin administered by continuous infusion

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Vancomycin remains the cornerstone therapy for serious infections, particularly in intensive care. The prescription of an optimal dosing regimen ensuring efficacy and safety remains a challenge because of its intra-and interpatient pharmacokinetic variability. Thus, therapeutic drug monitoring (TDM) is mandatory to optimize pharmacokinetic exposure to maximize efficacy while minimize toxicity. Our aim is to evaluate the impact of dose adjustment on achieving therapeutic vancomycin serum concentrations during continuous infusions (CI).

Materials and methods

We conducted a longitudinal study that included patients receiving vancomycin CI with at least two documented serum concentration measurements. TDM was performed at steady state, in the Department of Clinical Pharmacology-Monastir University Hospital-Tunisia (2008-2025). An initial vancomycin concentration(TDM1) was measured, followed by individualized dose adjustments aimed to achieve the predefined therapeutic target (20–30µg/mL). The subsequent measurement(TDM2) evaluated target attainment after dose optimization.

Results

A total of 155 patients receiving vancomycin CI were included. The median age was 49 years-IQ[29-63] with gender ratio of 2.9. The median body weight was 75 kg-IQ[65-80]. The median initial vancomycin dose was 2000 mg-IQ[2000-3000]. Median creatinine clearance was 100.45mL/min-IQ[35-203]. On TDM1, 40 patients (25.8%) were within therapeutic range, whereas 115 (74.2%) were outside the therapeutic range: 83 (53.5%) subtherapeutic and 32 (20.6%) supratherapeutic.

After dose adjustment (TDM2), 87 patients (56.1%) achieved therapeutic concentrations, while 68 (43.9%) remained out of the therapeutic range: 41 (26.4%) subtherapeutic and 27 (17.4%) supratherapeutic). The increase in therapeutic target attainment after dose adjustment was statistically significant ($p < 0.001$).

Discussion / Conclusion

Initial vancomycin CI therapeutic target attainment was low, with one in four patients achieving therapeutic concentration. Although individualized dose adjustment based on TDM significantly improved target attainment in 30.3%, almost half of the patients remained outside the therapeutic range, highlighting the limitations of conventional dose adjustment strategies and the need for precise model-informed dosing approaches.

Keywords

Therapeutic Drug Monitoring (TDM), vancomycin, pharmacokinetic variability

00589
Comparison of two- and a three-compartment pharmacokinetic models for model-informed precision dosing of dalbavancin

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Model-informed precision dosing (MIPD) may be useful to determine the maintenance dosage of dalbavancin when used (off-label) for prolonged therapy. The objective of the study was to compare the performance of a two- and a three-compartment model for MIPD of dalbavancin.

Materials and methods

This was a retrospective analysis over 2 years of dalbavancin concentrations collected in routine therapeutic drug monitoring (TDM) in patients under prolonged therapy. A two- (2C) and a three-compartment (3C) model from the manufacturer were imported into the Tucuxi software [1, 2]. First, the entire data set of each patient was fitted using both models. Then, data were analyzed for each TDM occasion with estimation of past concentrations (fit) and prediction of future concentrations (forecasting) of the next occasion. Predictive performance was assessed by mean error (ME), mean absolute prediction error (MAPE), absolute prediction error ≤ 30% (PE30) and R^2 of the regression of predictions vs observations.

Results

171 plasma concentrations from 41 patients (29 men and 12 women, 69 ± 17 years, 93% of bone and joint infections) were available for analysis. The two models fitted the entire dataset very well with comparable performance: ME = 3.8 ± 18.3 and -0.3 ±19.7 mg/L, MAPE = 20.8% and 21%, R^2 = 0.95 and 0.94 for the 2C and 3C models, respectively.

On the first TDM occasion, the 3C model was better in fitting past concentrations (MAPE = 12.95% vs. 21.99%, p = 0.005; PE30 = 93% vs 67%) and forecasting future concentrations (ME = –0.2 ± 3.1 vs. –2.8 ± 3.9 mg/L, p = 0.004; PE30 = 80% vs 63%). The two models showed comparable results upon the third TDM occasion.

Discussion / Conclusion

These findings support the use of a 3C model for early MIPD and dose adjustment of dalbavancin.

Reference(s)

1. Buckwalter et al. M. J Clin Pharmacol. nov 2005;45(11):1279-87.

2. Carrothers et al. Clin Pharmacol Drug Dev. jan 2020;9(1):21-31.

Keywords

dalbavancin, pharmacokinetics, therapeutic drug monitoring, model-informed precision dosing, bone and joint infections

00596
Real-world exposure-response evaluation of GS-441524 in hospitalized COVID-19 patients despite renal function-dependent exposure increases

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

GS-441524, the predominant circulating metabolite of remdesivir, exhibits increased exposure in patients with renal impairment[1]. Phase I and phase III studies supported regulatory label expansion permitting remdesivir use without dose adjustment across all stages of renal dysfunction, including dialysis[2,3]. However, data on exposure-response relationships in real-world hospitalized COVID-19 patients are limited.

Materials and methods

This retrospective study included 160 hospitalized patients receiving standard remdesivir dosing (200 mg on day 1; 100 mg on days 2–5). GS-441524 plasma concentrations obtained from residual samples collected during routine clinical care were analyzed. Population pharmacokinetic modeling was performed to characterize GS-441524 disposition and quantify the impact of renal function on exposure. Individual exposure (AUC_{5days}) was subsequently derived from the model.

Associations between AUC_{5days} or eGFR and grade ≥2 hepatic enzyme elevations were evaluated. Time-to-event outcomes (discharge and mortality) were analyzed using cause-specific Cox models, including both AUC_{5days} and eGFR as covariates.

Results

The median (range) eGFR was 72 (23–135) mL/min/1.73 m². eGFR was identified as a significant covariate on apparent clearance (power exponent 0.57), resulting in renal function-dependent increases in GS-441524 exposure, with a median (range) AUC_{5days} of 18.7 (8.1–81.3) mg·h/L. Despite these exposure increases, AUC_{5days} and eGFR were not associated with grade ≥2 hepatic enzyme elevations. In cause-specific Cox analyses, neither AUC_{5days} nor eGFR was independently associated with discharge or mortality.

Discussion / Conclusion

Despite renal function-dependent increases in GS-441524 exposure, no clinically meaningful exposure-response relationship was observed in real-world hospitalized COVID-19 patients. These findings support current labeling and indicate that routine dose adjustment or therapeutic drug monitoring of GS-441524 may not be necessary in hospitalized COVID-19 patients.

Reference(s)

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2. Zhang H, Humeniuk R, Regan S, et al. Clinical pharmacokinetics and safety of remdesivir in phase I participants with varying degrees of renal impairment. Clin Pharmacokinet. 2025;64(1):67–78.

3. Gilead Sciences. FDA approves Veklury (remdesivir) for COVID-19 treatment in patients with severe renal impairment, including those on dialysis. Press release. 2023 Jul 14.

Keywords

COVID-19, remdesivir, GS-441524

00598
Exceptional long-term stability of acyclovir and its principal metabolite 9-carboxymethoxymethylguanine (CMMG) in archived human serum and urine biobank samples

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Introduction – Aciclovir has long been used for the treatment of herpes infections. It generally has few and mild side effects; however, acute kidney injury and neurotoxicity do occur. We have previously shown that patients with neurotoxicity have increased concentrations of the aciclovir metabolite 9-carboxymethoxymethylguanine (CMMG) in serum and cerebrospinal fluid (CSF) [1,2].

No studies have investigated the long-term stability of aciclovir and CMMG in serum and urine. If stable, older biobanked aciclovir samples could be reanalysed for elevated CMMG concentrations, thereby supporting the diagnosis of neurotoxicity.

Materials and methods

Materials and Methods – We reanalysed 83 serum and 38 urine samples from four subjects who participated in a pharmacokinetic (PK) study of intravenous (IV) and

oral aciclovir conducted between 2001 and 2004. Healthy subjects received 400 mg oral aciclovir, whereas patients with chronic kidney disease (CKD) received 200 mg orally. The intravenous doses were 100 mg and 50 mg, respectively. The samples had been stored for 12 to 17.5 years at −20°C and were subsequently reanalysed 2022 using an LC–MS/MS method developed and performed in Lund, Region Skåne, Sweden.

Results

Results – Aciclovir and CMMG concentrations in serum and urine were highly stable. The percentage differences for aciclovir and CMMG in serum were median (interquartile range, IQR) 3.40% (−6.65 to 11.47) and 4.24% (−7.81 to 17.38), respectively; in urine, the corresponding values were 2.36% (−21.97 to 13.69) and −14.50% (−24.17 to 3.56), respectively.

The differences in µmol/L for aciclovir and CMMG in serum were median 0.08 (IQR −0.12 to 0.43) and 0.02 (−0.15 to 0.05), respectively; in urine, the corresponding values were 0.12 (−2.52 to 1.01) and 0.83 (−3.94 to 0.29), respectively.

Discussion / Conclusion

Conclusion – Old biobanked serum and urine samples from aciclovir-treated patients can be reanalysed and used for the reevaluation of, for example, suspected but previously unconfirmed aciclovir intoxication.

Reference(s)

1. Helldén A, Odar-Cederlöf I, Diener P, Barkholt L, Medin C, Svensson JO, et al. High serum concentrations of the acyclovir main metabolite 9-carboxymethoxymethylguanine in renal failure patients with acyclovir-related neuropsychiatric side effects: an observational study. Nephrol Dial Transplant. 2003 Jun 1;18(6):1135–41. doi:10.1093/ndt/gfg119

2. Helldén A, Lycke J, Vander T, Svensson JO, Odar-Cederlöf I, Ståhle L. The aciclovir metabolite CMMG is detectable in the CSF of subjects with neuropsychiatric symptoms during aciclovir and valaciclovir treatment. J Antimicrob Chemother. 2006;57:945–9. doi:10.1093/jac/dkl067

Keywords

Keywords: Aciclovir, CMMG, stability, neurotoxicity, serum, urine

00614
Imipenem/cilastatin/relebactam for treatment of Sepsis -- Results of therapeutic drug monitoring in blood, urine and abdominal drainage fluid

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Imipenem/cilastatin/relebactam, a novel carbapenem β-lactamase inhibitor combination, has been approved for the treatment of infections caused by multi-drug-resistant Gram-negative bacteria. At present, few data are available on the pharmacokinetics of this substance in critically ill patients.

Materials and methods

Here, we report on a 59-year-old male patient who developed sepsis early after combined liver–kidney transplantation. The perioperative bacterial culture of the University of Wisconsin solution of organs revealed carbapenem-resistant *Acinetobacter baumannii* (CRAB). Empiric administration of imipenem/cilastatin/relebactam was initiated at a renal-adjusted dose of 0.625g i.v. q6h. In addition to serum concentration, drug monitoring was performed in the urine and abdominal drainage fluid via a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay.

Results

Serum, urine and abdominal drainage fluid at steady state yielded imipenem concentrations from 4.48 to 17.52 µg/mL abdominal drainage fluid and from 55.84 to

168.97 μg/mL in urine. The concentration ratio of $C_{abdominal}/C_{serum}$ ranged from 0.15 to 1.47, while the ratio of C_{urine}/C_{serum} range from 6.42 to 20.11. Relibactam concentrations was 28.12 to 32.33 μg/mL in abdominal drainage fluid and 132.52 to 186.29 μg/mL in urine. The concentration ratio of $C_{abdominal}/C_{serum}$ ranged from 0.87 to 1.16, while the ratio of C_{urine}/C_{serum} range from 5.26 to 5.60.Infection was successfully treated with eradication of *A. baumannii*.

Discussion / Conclusion

Our results indicate that recommended dose of imipenem/cilastatin/relebactam under renal dysfunction is sufficient to treat complicated infection in sepsis with effective penetration of both imipenenm and relibactam. Individualized dosing guided by PK/PD indices may further optimize efficacy and safety.

Keywords

imipenem/cilastatin/relebactam, sepsis, combined liver-kidney transplantation, renal failure

00622
Recent milestones in the use of wearable technology for therapeutic drug monitoring.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic drug monitoring (TDM) aims to optimize patient outcomes however current standards provide only a fraction of the desired information due to use of laborious, slow and invasive ex vivo analyses. Here, we describe our recent advances in use of electrochemical aptamer-based sensors (EABs) for achieving continuous monitoring of drugs and metabolites. Key limitation of current TDM addressed are development of a wearable device suitable for patients, enabling simultaneous monitoring of multiple targets, and extending monitoring duration to 1 week.

Materials and methods

We employed previously reported EABs against the therapeutic antibiotics, vancomycin and tobramycin as well as a novel EAB against the kidney function biomarker, creatinine. First, in a collaborative effort, vancomycin EABs were placed on microneedles and incorporated into a wearable patch placed on the dermis of human subjects and then vancomycin was delivered intravenously. Second, we used the vancomycin EAB along with a novel creatinine EAB for simultaneous molecular monitoring in the dermis of rats. Third, we employed our tobramycin EAB which is constructed from artificial nucleotides (a.k.a. “XNA”) and placed in rat dermis 1 week.

Results

Consistent with studies in rats, the patch sensor worked seamlessly in human dermis to capture full vancomycin pharmacokinetic profiles of individual subjects, including expected heterogeneity across subjects. Using dual sensors in rat dermis demonstrated that each of the previously validated EABs performed as expected to capture, again complete profiles for each target without an detectable interaction between sensors. Lastly, placement of our XNA sensor in the dermis of the rat allowed continuous measurements (comprising >40,000 scans) with fully correctable drift and consistent response to drug challenge across 7 days.

Discussion / Conclusion

EAB sensors exhibit tremendous opportunity for establishing truly patient-specific pharmacokinetics through minimally-invasive measurements over multi-day periods in a multiplexed fashion.

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Keywords

vancomycin, tobramycin, aptamer, sensor

00643
Isoniazid Acetylation Patterns in Paediatric Tuberculosis patients : A Tunisian case series

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Accounting for 11% of global cases, pediatric tuberculosis remains a major public health concern. Isoniazid (INH), a cornerstone of treatment, exhibits metabolic polymorphism with slow and rapid acetylator phenotypes, supporting the role of therapeutic drug monitoring (TDM) to tailor dosing and optimize efficacy. We aimed to assess acetylation profiles and the clinical value of INH TDM in children

Materials and methods

A 9-year retrospective study (2017–2025) in the Clinical Pharmacology Department of Monastir included pediatric Isoniazid C3 measurements (3 hours post-dose) by HPLC, with dose adjustments to maintain concentrations within the 1–2 µg/mL therapeutic range.

Results

Fifty-nine patients (33 M/26 F, sex ratio 1.27) were included in our study and underwent 82 C3 measurements. The mean age was 10.88 years (0.5-17 years), and the mean weight was 41.12 kg (4.5-98 kg). The main indication for INH was tuberculous lymphadenitis (n=41). The mean dose of INH was 191.23 mg/day [5-500 mg/day]. The prescribed therapeutic form was separate in 37.8% of cases and

combined in 66.3% of cases. The mean acetylation index was 0.86 ± 0.41. 35.3% of the concentrations were therapeutic, 53.7% supratherapeutic, and 11% subtherapeutic. 54% of patients were SA and 46% RA. In 71% of cases, dose adjustment with a switch to the separate form was required. The median weight-based doses were 2.7 ± 1.5 mg/kg (SA) and 5.3 ± 2.1 mg/kg (RA). After adjustment, more than 50% of the C3 measurements were within the therapeutic range.

Discussion / Conclusion

Dose adjustment guided by therapeutic drug monitoring and phenotype was essential. Switching to separate formulations in 71% of cases enabled individualized dosing (2.7 mg/kg in slow vs. 5.3 mg/kg in fast acetylators) and brought over half of concentrations back within the therapeutic range. Early identification of acetylation profile and prompt dose adaptation are therefore key to optimizing isoniazid therapy in children.

00661
LC-MS/MS Method for measuring the plasma concentration of letermovir and its application in pediatric allogeneic hematopoietic stem cell transplant recipients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Cytomegalovirus (CMV) infection is a common complication among recipients of allogeneic hematopoietic stem cell transplantation (allo-HSCT). As an inhibitor of the CMV DNA terminase complex, letermovir has demonstrated efficacy in preventing clinically significant CMV infection after allo-HSCT. To address the limitations of existing methods for analyzing the plasma concentration of letermovir, a simple, rapid, and robust liquid chromatography-tandem mass spectrometry (LC-MS/MS) method was developed to quantify the plasma concentration of letermovir in this study, employing d3-letermovir as the internal standard.

Materials and methods

Following the addition of the internal standard and protein precipitation procedure, the sample was analyzed using a C_{18} column with gradient elution completed in three minutes, free from interference.

Results

The calibration curve exhibited good linearity over a 1000-fold concentration range (0.02 to 20 μg/mL) with determination coefficients (r^2) exceeding 0.99. Precision and accuracy (both intra- and inter-day) met acceptance criteria (±15%) across all quality control levels. The method showed no significant matrix effects in normal, hemolyzed, lipemic, or hyperbilirubinemic samples, and demonstrated good stability under tested conditions without significant degradation. After validation, the method was successfully employed to measure the plasma concentrations of letermovir in sixteen Chinese pediatric allo-HSCT recipients for the first time.

Discussion / Conclusion

A straightforward, rapid, and robust LC-MS/MS method was developed for measuring the plasma concentration of letermovir in this study, which was thoroughly validated and successfully implemented in pediatric Allo-HSCT recipients. Due to its simplicity, brief analysis time, and high accuracy and precision, this study may serve as a methodological reference for future pharmacokinetic studies or therapeutic drug monitoring of letermovir.

Keywords

Letermovir, Allogeneic hematopoietic stem cell transplantation, LC-MS/MS, Pediatric patient

00674
Population pharmacokinetic modeling of isavuconazole in Chinese patients with invasive fungal disease

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

This study aimed to develop a population pharmacokinetic (PopPK) model for isavuconazole using real-world clinical data and to evaluate the impact of potential covariates on drug exposure and treatment efficacy. The findings are intended to support individualized dosing strategies for Chinese patients with invasive fungal disease.This study aimed to develop a population pharmacokinetic (PopPK) model for isavuconazole using real-world clinical data and to evaluate the impact of potential covariates on drug exposure and treatment efficacy. The findings are intended to support individualized dosing strategies for Chinese patients with invasive fungal disease.

Materials and methods

In this study, a total of 88 trough concentration measurements were retrospectively obtained from 44 patients enrolled for the treatment of invasive fungal disease. Plasma samples were quantified using ultra-high-performance liquid chromatography-tandem mass spectrometry. A population pharmacokinetic (PopPK) model was subsequently developed using a nonlinear mixed-effects modeling approach implemented in NONMEM (version 7.4).

Results

A one-compartment model with first-order elimination provided the best fit to the data. Allometric scaling based on body weight and the inclusion of albumin as a covariate were found to significantly influence drug clearance, while sex was identified as a significant covariate affecting the volume of distribution. The final model estimated a typical clearance of 1.43 L/h and a volume of distribution of 330 L. The interindividual variabilities (IIV) for CL and V were 51.1% and 29.8%, respectively. The population pharmacokinetic model was evaluated using bootstrap analysis, goodness-of-fit plots, and visual predictive checks, all of which confirmed the model's satisfactory performance.

Discussion / Conclusion

The established population pharmacokinetic model for isavuconazole provides a valuable theoretical foundation to inform the development of optimized dosing strategies and to facilitate the advancement of individualized treatment.

Keywords

Isavuconazole; Invasive Fungal Disease; Population pharmacokinetics; Chinaese patients.

00687
Analysis of Adverse Drug Reaction Signals for the Antimicrobial Agent Voriconazole Based on the FAERS Database

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Objective: By analyzing real-world data related to voriconazole in the FAERS database, this study systematically explores the occurrence of adverse reactions of voriconazole and further enhances the ability to identify adverse reactions related to voriconazole in clinical practice. At the same time, it preliminarily validates a new scoring method for the comprehensive evaluation of four methods: ROR, PRR, BCPNN, and MGPS, discovers new signals of adverse reactions. Method: The original data used in this study was downloaded from the FDA's official website, the FAERS database. The adverse reaction signals were processed using the Reporting Odds Ratio (ROR) method, Proportional Reporting Ratio (PRR) method, Bayesian Confidence Propagation Neural Network (BCPNN) method, and Multi-item Gamma Poisson Shrinker (MGPS) method. Result: Comprehensive evaluation revealed that voriconazole adverse reactions primarily affect the central nervous system, skin, and digestive system. A new comprehensive analysis method was proposed, identifying novel adverse reaction markers. Conclusion: This study identified new voriconazole adverse reaction signal.

Materials and methods

The original data used in this study was downloaded from the FDA's official website, the FAERS database. The adverse reaction signals were processed using the Reporting Odds Ratio (ROR) method, Proportional Reporting Ratio (PRR) method,

Bayesian Confidence Propagation Neural Network (BCPNN) method, and Multi-item Gamma Poisson Shrinker (MGPS) method. Statistical analysis was conducted using SAS 9.4, and data visualization was performed using Excel 2019 and PyCharm 2024.1.

Results

A total of 12,284 voriconazole-related adverse reaction reports were identified in the FAERS database. Comprehensive evaluation revealed that voriconazole adverse reactions primarily affect the central nervous system, skin, and digestive system. A new comprehensive analysis method was proposed, identifying novel adverse reaction markers.

Discussion / Conclusion

This study identified new voriconazole adverse reaction signals, contributing to improved understanding of drug safety and supporting safe and rational clinical use of voriconazole

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Keywords

Voriconazole ;FAERS Database ;Rational use of drugs; Adverse drug reaction

00690
Clinical implementation of ceftazidime therapeutic drug monitoring in critically ill patients: initial experience from the ZAVICONT trial

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Critically ill patients exhibit substantial pharmacokinetic variability that may result in suboptimal β-lactam exposure and increased risk of treatment failure. Therapeutic drug monitoring (TDM) has emerged as promising strategy to optimize antibiotic dosing in intensive care settings. However, validated analytical methods for ceftazidime quantification are not widely available in routine clinical practice. In response to clinical need identified by ICU clinicians conducting the ZAVICONT trial (NCT06811727), high-performance liquid chromatography (HPLC) method for ceftazidime quantification in human serum was developed and implemented to enable TDM in critically ill patients.

Materials and methods

An in-house HPLC method with diode-array detection and chloramphenicol as internal standard was developed and validated at the University Hospital Centre

Zagreb, Croatia. Serum samples underwent protein precipitation with acetonitrile:methanol mixture (1:1, v/v), followed by centrifugation and dilution with phosphate buffer. Method performance was evaluated for linearity, precision, accuracy, recovery and lower limit of quantification. The assay was implemented for TDM in patients enrolled in ongoing ZAVICONT trial, comparing continuous infusion (CI) versus intermittent dosing (ID) of CZA.

Results

The developed method demonstrated excellent analytical performance. The assay was applied for TDM in first four patients enrolled in the trial. A total of 10 plasma samples were analyzed. Three patients received CZA by CI and one patient by ID. Measured ceftazidime plasma concentrations ranged from 21.48 to 129.20 µg/mL, demonstrating substantial inter-patient variability and enabling preliminary assessment of pharmacokinetic/pharmacodynamic (PK/PD) target attainment relative to pathogen minimum inhibitory concentration. CI was associated with higher ceftazidime concentrations (49–129.20 µg/mL) compared with trough concentrations observed during ID (21.48–36.89 µg/mL).

Discussion / Conclusion

The developed HPLC assay provides a reliable analytical tool for ceftazidime TDM in critically ill patients. Its implementation within ZAVICONT trial enables PK/PD analysis of measured concentrations and provides a foundation for future integration of β-lactam TDM into routine clinical practice to support individualized PK-guided dosing strategies.

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Keywords

ceftazidime, TDM, HPLC, intensive care, ZAVICONT trial

00693
Predicting Vancomycin Clearance in Critically Ill Patients: A Comparison of Measured and Equation-Based Renal Function Estimators During Continuous Infusion

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Renal function estimators are commonly used to guide vancomycin dosing in critically ill patients, yet their ability to reflect true vancomycin clearance remains uncertain, particularly in augmented renal clearance (ARC). This study evaluated the association and predictive performance of regularly used renal function equations for estimating vancomycin clearance during continuous infusion.

Materials and methods

This retrospective cohort study included adult ICU patients receiving continuous intravenous vancomycin and a timed 6-hour urine collection. Vancomycin clearance (CLvan) was calculated at presumed steady state as infusion rate divided by steady-state concentration. Renal function estimators included measured creatinine clearance (mCrCl), Cockcroft–Gault, CKD-EPI 2009, and Jelliffe equations; CKD-EPI and Jelliffe values were de-indexed for body surface area, and the conventional upper cap of 90 mL/min was removed for CKD-EPI. Associations with CLvan were assessed using correlation analyses and linear mixed-effects models with leave-one-patient-out cross-validation. ARC was defined as creatinine clearance ≥130 mL/min.

Results

A total of 66 patients contributing 103 paired measurement sets were analyzed; 32% met criteria for ARC. Median CLvan was 51 mL/min (IQR 33–77; range 13–148). CLvan correlated most strongly with mCrCl (Pearson r 0.81, 95% CI 0.74–0.86), followed by Cockcroft–Gault (r 0.79, 95% CI 0.70–0.85), CKD-EPI (r 0.78, 95% CI 0.68–0.83), and Jelliffe (r 0.77, 95% CI 0.66–0.84). In mixed-effects models, predictive performance was moderate (R^2 0.52–0.57). Cockcroft–Gault demonstrated the best overall performance with the lowest AIC and cross-validated RMSE, closely followed by mCrCl.

Discussion / Conclusion

In critically ill patients mCrCl demonstrates strong correlation with vancomycin clearance but only moderate predictive performance. No estimator of renal clearance, Cockcroft–Gault, CKD-EPI or Jelliffe, clearly outperformed. These findings support the continued role of therapeutic drug monitoring, particularly in patients with ARC. When drug concentrations are unavailable at treatment initiation, measured creatinine clearance may provide a reference for estimating vancomycin clearance to guide initial dosing.

Keywords

Vancomycin, ICU, Creatinine clearance, Augmented renal clearance, Therapeutic drug monitoring

00696
Tissue penetration of piperacillin-tazobactam in critically ill children with severe infections

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Antibiotic PK/PD target attainment is typically evaluated using plasma exposure, yet severe illness in children may alter both pharmacokinetics (PK) and tissue penetration. Data describing piperacillin–tazobactam (PIP-TAZ) exposure in interstitial fluid (ISF) in critically ill children with severe bacterial infections are not available, hindering evidence-based dose selection for infections with large tissue involvement.

Materials and methods

Paired plasma (total and unbound) and muscle tissue ISF concentrations were collected over multiple days in 10 critically ill children (1 month-14-year-old) receiving PIP–TAZ. ISF was sampled using microdialysis with internal-standard calibration penicillin. Monte Carlo simulations were performed to evaluate probability of target attainment (PTA) in the first 48 h of treatment for 1) 80 mg/kg every 4/6/8 hour (Q4/6/8h) with 0.5h infusion duration; 2) Loading dose of 80 mg/kg and 300 mg/kg/24h continuous infusion; 3) 100 mg/kg Q6/8h with 3h infusion duration. A target time during which the unbound drug concentration is above the Minimal Inhibitory Concentration of 100% (fT>MIC =100%) was selected. A PTA≥ 90% was defined as optimal. A EUCAST breakpoint MIC of 16 mg/L for Pseudomonas aeruginosa infections was chosen.

Results

Plasma PK for PIP–TAZ was described by a one-compartment model. Unbound fractions were 91.2%±3.01% for PIP and 98.3%±1.41% for TAZ. Simulations demonstrated systematically higher PTA in ISF than in plasma across all regimens. An 80 mg/kg loading dose (0.5 h infusion) followed by 300 mg/kg/day continuous infusion achieved near-optimal PTA in both matrices (ISF 97.4–99.6%; plasma 97.6–99.9%). Among intermittent regimens, 80 mg/kg q4h (0.5 h) provided the highest PTA in ISF (86.3–97.1%), whereas q6h/q8h regimens (short or 3 h prolonged) were frequently suboptimal, especially in children >1 year (PTA range in ISF: 38.9%).

Discussion / Conclusion

Plasma PK may misrepresent infection-site exposure. For high-MIC infections, continuous infusion provides optimal target attainment in both plasma and muscle ISF across age groups.

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Keywords

piperacillin-tazobactam, critically ill children, tissue penetration, model-informed precision dosing

00708
Beyond the Scale: Rifampicin Starvation in Indian TB Program – TDM to Prevent Acquired Resistance and Rethink FDC Dosing

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

India’s National TB Elimination Programme relies almost exclusively on weight-based fixed-dose combinations (FDCs) without routine therapeutic drug monitoring (TDM). Subtherapeutic rifampicin exposure is a well-recognised driver of acquired drug resistance, yet real-world Indian data demonstrating this gap remain scarce. This prospective TDM study quantifies target attainment of first-line anti-TB drugs in a tertiary referral cohort and highlights its implications for the national programme.

Materials and methods

Patients on standard first-line regimens (mostly FDCs) underwent full 9-point pharmacokinetic profiling (0.5–6 h post-dose) using validated LC-MS/MS. Therapeutic targets were rifampicin Cmax 8–24 mg/L, isoniazid 3–7 mg/L, and pyrazinamide 20–50 mg/L. Dose-optimisation recommendations and repeat TDM were provided when indicated. Demographic, indication, and clinical data were analysed to identify patterns of suboptimal exposure.

Results

Twenty-six rifampicin, 23 isoniazid, and 10 pyrazinamide profiles from 30 patients (median age 44 years; weight range 10.4–94 kg; 63% extrapulmonary or disseminated TB) were evaluable. Subtherapeutic levels were observed in 9/26 (34.6%) rifampicin, 4/23 (17.4%) isoniazid, and 1/10 (10%) pyrazinamide profiles. Rifampicin “starvation” was particularly frequent in extrapulmonary and deep-seated TB (lymphadenopathy, Pott’s spine, abdominal, disseminated). Supratherapeutic pyrazinamide exposure occurred at standard ~25 mg/kg doses, with one patient developing drug-induced liver injury (DILI) during the early phase of therapy. Rifampicin dose escalation (750–1200 mg/day) successfully achieved therapeutic Cmax on repeat TDM in every re-tested patient, and all patients attaining the rifampicin target concentration achieved clinical cure at treatment completion.

Discussion / Conclusion

Standard FDC dosing in the Indian TB Programme results in rifampicin starvation in approximately one of three patients while simultaneously risking supratherapeutic pyrazinamide exposure and DILI. Targeted TDM is feasible, immediately actionable, and directly prevents under-dosing. These findings provide compelling local evidence to integrate TDM into high-risk pathways in tertiary care and urgently prompt a national rethink of FDC-based dosing strategies to safeguard the TB programme from further resistance emergence.

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Keywords

Therapeutic drug monitoring, Rifampicin starvation, Extrapulmonary TB, Fixed-dose combinations, Acquired resistance, India

00722
The untapped potential of therapeutic drug monitoring: preventing resistance development during antibiotic treatment, a systematic review

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The SAMPLE-IT project aims to assess the value of Therapeutic Drug Monitoring (TDM) in preventing development of antimicrobial resistance (AMR).

The mutant prevention concentration (MPC) has been proposed as an alternative to the minimum inhibitory concentration (MIC) as a susceptibility index. The MPC represents the MIC of the most resistant mutant of a heterogeneous bacterial population. Theoretically, TDM-based dosing achieving antimicrobial concentrations that exceed the MPC will prevent selection of resistant bacteria. However, as data on this subject have not been pooled before, the scientific basis for TDM for this specific purpose remains unclear.

Objectives:
1. Assess whether development of antimicrobial resistance occurs during exposure to therapeutic dosages or serum concentrations of antibiotics.
2. Summarize the evidence regarding the potential value of TDM in counteracting AMR.

Materials and methods

Articles without language or publication date restriction were searched in PubMed, Embase, Web of Science, and grey literature. Search terms included TDM, PK/PD parameters, resistance and antibiotic types. Studies reporting AMR development or lack thereof during treatment with, or exposure to, therapeutic dosages of antibiotics were included. We used Covidence software with dual assessment in all steps. In case of disagreement a third researcher was consulted.

Results

We identified 4280 articles, 423 of which were included for full-text screening and 140 for data extraction. Summarized evidence from both in vitro and clinical studies indicates that resistant bacteria are indeed selected during exposure to (standard) therapeutic doses of many different antibiotics across a wide range of bacterial species.

Discussion / Conclusion

Pooled evidence from different study types supports TDM as a potential strategy to prevent resistance development when achieving concentrations above the MPC. Toxicity associated with higher (i.e. supratherapeutic) dosing seems limited for most antibiotics and may allow for this strategy. However, prospective clinical studies are needed to assess whether application in clinical practice is feasible and effective.

Keywords

Antibiotics, TDM, PK/PD, AMR, MPC, Stewardship

00725
Development, validation and clinical application of novel method for concomitant determination of vancomycin and teicoplanin in Mitra™ microsampling devices collected from pediatric petients treated at PICU.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Glycopeptide antibiotics (vancomycin, teicoplanin) are used for serious infections caused by Gram-positive pathogens which are time-dependently active with pharmacodynamics that correlate with exposure. PK/PD targets for vancomycin are AUC_{0-24}/MIC≥400-600 being optimal. Target trough concentrations of 10-20 mg/L are most commonly used in clinical practice. For teicoplanin, trough concentrations of 15-20mg/L (20-30mg/L for serious infections) are used, and therapeutic drug monitoring is required in severely ill children due to a wide variability of pharmacokinetics in this population. Conventional sampling methods are obstructed by the small blood volumes available in the pediatric intensive care unit. Volumetric absorptive microsampling (VAMS) with the Mitra™ device allows low-volume sampling for TDM.

Materials and methods

A quantitative LC–MS/MS method was developed for simultaneous determination of vancomycin and teicoplanin extracted from 10µL Mitra™ VAMS devices. Method validation followed international bioanalytical guidelines. Calibration curves were linear over 0.5–100mg/L for vancomycin and 0.2–100mg/L for teicoplanin ($r^2 \geq 0.995$). Precision, accuracy, recovery, and matrix effects were evaluated. Clinical applicability was assessed using a PICU therapeutic drug monitoring registry including 50 patients receiving vancomycin and 50 receiving teicoplanin. For each patient, two pharmacokinetic samples were collected: peak concentration (Cmax) and trough concentration (Cmin).

Results

The validated method demonstrated intra- and inter-day precision <10%CV and accuracy within 95–108%. Extraction recovery ranged from 73–78%, with negligible matrix effects after internal standard normalization. The LLOQ was 0.5mg/L for vancomycin and 0.2mg/L for teicoplanin. Vancomycin trough concentrations ranged from 8–22mg/L, corresponding to estimated $AUC_{0\text{-}24}$/MIC values of approximately 350–650 assuming MIC=1mg/L. Teicoplanin trough concentrations ranged from 12–32mg/L, enabling evaluation of pharmacodynamic targets≥15–20mg/L. Concentrations measured in Mitra™ microsamples showed strong agreement with paired plasma samples (vancomycin r≈0.97; teicoplanin r≈0.96).

Discussion / Conclusion

The validated LC–MS/MS method enables reliable simultaneous quantification of vancomycin and teicoplanin from Mitra™ microsamples across a clinically relevant range. Microsampling-based TDM may facilitate individualized glycopeptide dosing in PICU patients while minimizing blood loss.

Keywords

therapeutic drug monitoring; vancomycin; teicoplanin; VAMS; Mitra microsampling; pediatric intensive care.

00727
Human PK-PD of intravenous bacteriophage in treatment of Mycobacterium abscessus

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Mycobacterium abscessus (MAB) causes severe pulmonary disease in people with cystic fibrosis (CF). MAB has a high rate of intrinsic and acquired resistance, and treatment failure is common, despite regimens containing 3-4 antibiotics for over a year. Bacteriophages, viruses that infect bacteria, represent a promising new option for MAB treatment. However, little is known about the PK-PD of bacteriophages to guide dosing regimens. Despite in vitro efficacy, many patients do not improve with phage therapy, which may be due to inadequate dosing.

Materials and methods

We studied PK-PD in a 17-year-old female with CF receiving intravenous Muddy_HRMN0052 bacteriophage, 3x10^9 PFU once daily Monday-Friday, for refractory MAB pulmonary disease. We collected sputum 1-2 times following dose administration sporadically over two months. We quantified phage levels by qPCR and bacterial levels by CFU counting. Using these data, we used a Pmetrics model modified from Chae (1) to simulate dosing with 3x10^9 PFU given: 1) q24h on weekdays only; 2) q24h every day; and 3) q12h every day. We assumed an initial bacterial load of 1x10^6 CFU/mL.

Results

The model fitted the patient data acceptably, with phage quantity steadily rising during the week to a peak of ~1×10^6 copies/mL; approximately one-third of administered phage reached sputum. Phage concentrations then fell to ~3×10^3 copies/mL before Monday's dose. The estimated half-life of phage in sputum was ~6 hours, consistent with animal data for similar viruses (2,3). Bacterial counts fluctuated inversely, ranging from 1×10^4 CFU/mL on Monday to 5×10^2 CFU/mL on Friday. Simulated dosing every 12 hours resulted in substantially higher phage concentrations and greater bacterial growth inhibition, nearing eradication.

Discussion / Conclusion

Phage and bacterial concentrations fluctuate over time, with bacterial growth rebound occurring if the phage dose is held for greater than 24 hours. Our model indicates that more frequent dosing of Muddy_HRMN0052 may improve efficacy.

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Keywords

Bacteriophage, pharmacokinetics, pharmacodynamics

00763
A prospective PK-PD study to investigate therapeutic drug monitoring and exposure-driven toxicity of linezolid during programmatic treatment of multidrug-resistant tuberculosis in India

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The long-term use of linezolid therapy for MDR TB frequently leads to significant toxicity. To inform dose-optimization strategies, we aimed to examine therapeutic drug monitoring and PK-PD modelling of linezolid in the Indian MDR-TB population.

Materials and methods

This prospective, single Centre, observational study was conducted at a tertiary care facility in New Delhi, India. Patients aged 18 years or older, microbiologically confirmed with MDR-TB, and who received linezolid 600 mg daily were enrolled in the study. For Cmin concentrations, 48-hour samples were collected. For PK studies, samples were collected at 0 h (pre-dose), 2 h, 4 h, 6 h, 8 h, 12 h, and 24 h post-dose at 4 weeks to adequately characterise individual concentration–time profiles and estimate exposure metrics. Participants were followed prospectively for up to 18 months. The PK parameters, along with disease covariates, were assessed for PK/PD modelling using NONMEM.

Results

In this prospective observational cohort conducted within the National TB Elimination Programme in India, patients receiving standard linezolid-containing regimens for multidrug-resistant tuberculosis were systematically followed to characterise treatment-related toxicity and pharmacokinetic exposure. Longitudinal monitoring demonstrated a gradual decline in haemoglobin levels and the progressive development of neurological symptoms. These adverse events often necessitated clinical interventions, including dose reduction or discontinuation of linezolid in several patients. Importantly, toxicity was observed despite uniform dosing across the cohort, suggesting considerable inter-individual variability in drug exposure.

Discussion / Conclusion

This study provides prospective programmatic evidence from a high-burden Indian setting demonstrating that linezolid toxicity is common during prolonged MDR-TB therapy under routine clinical practice. The temporal pattern of adverse events observed in this cohort indicates that toxicity develops gradually with cumulative exposure, particularly for haematological and neurological complications. These findings reinforce previous evidence suggesting that linezolid-associated toxicity is primarily exposure-dependent rather than dose-dependent alone.

Keywords

TDM, MDR-TB, PK/PD MODELLING, LINEZOLID, TOXICITY

Clinical Toxicology/Drugs of Misuse

00006
The Hidden Opioid: Severe Loperamide Dependence Facilitated by P-Glycoprotein Inhibition

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Loperamide, a widely used over-the-counter antidiarrheal, acts as a peripheral mu-opioid receptor agonist. Under standard therapeutic conditions, central nervous system (CNS) effects are minimal due to limited blood-brain barrier penetration mediated by P-glycoprotein. Supratherapeutic use or co-administration with P-glycoprotein inhibitors can produce opioid-like effects including euphoria, sedation, and dependence. While loperamide abuse has been increasingly reported in the United States, similar trends in France remain rare. This case report highlights a severe instance of loperamide dependence and illustrates the role of drug-drug interactions in facilitating misuse.

Materials and methods

Case Report

We describe a 29-year-old man who developed severe loperamide dependence after self-medicating with codeine for anxiety. Following codeine discontinuation, he substituted loperamide to prevent withdrawal and stabilize mood. At presentation, he consumed 60–72 tablets of 2 mg loperamide every third day (120–144 mg), along with daily alprazolam (15 × 0.25 mg) and paroxetine. He exhibited classic opioid withdrawal symptoms including sweating, piloerection, insomnia, headaches, and mydriasis. Paroxetine, a selective serotonin reuptake inhibitor with P-glycoprotein inhibitory effects, likely enhanced CNS penetration of loperamide, potentiating its abuse potential.

Results

A structured tapering protocol under specialized addiction care gradually reduced loperamide intake. Paroxetine was switched to vortioxetine to remove P-glycoprotein interactions. Segmental hair analysis revealed markedly elevated loperamide concentrations, peaking at 4300 pg/mg, far exceeding therapeutic levels. The patient met 8 of 11 DSM-5 criteria for severe opioid use disorder and showed gradual improvement with declining loperamide concentrations.

Discussion / Conclusion

This case underscores loperamide as an emerging substance of abuse, particularly in vulnerable psychiatric populations. Clinicians should remain alert to potential drug-drug interactions affecting P-glycoprotein and monitor over-the-counter medication misuse. Multidisciplinary management, combining pharmacological tapering with psychiatric support, is essential for safe and effective treatment.

Reference(s)

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Keywords

Loperamide misuse, paroxetine, p-glycoprotein interaction, anxiety, self-medication, addiction

00013
A Retrospective Toxicology Study of Polysubstance Use Patterns Associated with Xylazine

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

In recent years, xylazine, has emerged as a cutting agent combined with illicit drugs to extend their effects. The present study aimed to discover drug use patterns associated with xylazine- positive and negative urine toxicology drug screens and to assess whether xylazine can be used as a marker for exposure to designer drugs/ new psychoactive substances.

Materials and methods

A retrospective analysis of urine toxicology results from two different analytical platforms using 7167 unique, recent urine samples from the Denver area in Colorado: a targeted, structurally confirmatory, high-performance liquid chromatography- tandem mass spectrometry assay that quantifies 136 drugs and metabolites including xylazine; non-targeted ThermoFisher Orbitrap Tribrid mass spectrometry system in combination with database searches for the identification of unknown drugs.

Results

The drug patterns found in xylazine-positive and negative urine samples were statistically significantly different ($p<0.001$) indicating different consumption patterns.

Moreover, the overall concentrations of drugs (normalized to creatinine) were also statistically significantly different with higher concentrations in the urine samples that tested negative for xylazine. In contrast, samples that were positive for xylazine contained significantly higher concentrations of various designer drugs/ new psychoactive substances from the untargeted platform ($p<0.0001$).

Discussion / Conclusion

The results indicated that Xylazine has become increasingly common in Colorado's drug circulation and that xylazine is a marker that should trigger reflex testing with non-targeted high-resolution mass spectrometry assays in combination with database searches to test for the exposure to designer drugs/ new psychoactive substances.

Keywords

LC-MS/MS, Xylazine, Polysubstance Abuse, Biomarker, Urine Drug Testing, Novel Psychoactive Substances

00035
Akkermansia muciniphila–regulated microbial bile acid 7-ketodeoxycholic acid exerts hepatoprotective effects in olanzapine-induced MAFLD

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Metabolic dysfunction–associated fatty liver disease (MAFLD) is an increasing public health burden owing to its high prevalence, progressive nature, and strong association with cardiovascular morbidity and mortality. Olanzapine (OLZ), a commonly prescribed atypical antipsychotic drug, frequently induces metabolic abnormalities that predispose patients to MAFLD. Akkermansia muciniphila (AKK) is a beneficial gut bacterium with established metabolic protective properties. However, its key bioactive metabolites and relevant hepatoprotective mechanisms remain incompletely explored.

Materials and methods

Male Sprague–Dawley rats were treated with OLZ with or without AKK supplementation, following antibiotic pretreatment when indicated. Hepatic biochemical parameters, histopathological alterations, and expression of metabolic and inflammatory markers were assessed. Gut microbiota composition was analyzed using 16S rRNA sequencing, and cecal metabolomic profiling was performed by LC-MS/MS. Differential metabolites were identified via untargeted metabolomics, and 7-ketodeoxycholic acid (7-ketoDCA) was identified and selected for validation in an independent intervention model. Network pharmacology, molecular docking, western blotting, and surface plasmon resonance were employed to predict and validate molecular targets and signaling pathways.

Results

OLZ administration induced hepatic steatosis, inflammation, and dyslipidemia, accompanied by significant gut microbiota dysbiosis and depletion of AKK. AKK supplementation markedly ameliorated these abnormalities, improving liver histology and restoring microbial homeostasis. Metabolomic analysis identified 7-ketoDCA as a key bile acid metabolite closely associated with AKK abundance. In vivo validation demonstrated that high-dose 7-ketoDCA administration significantly attenuated OLZ-induced MAFLD and modulated pathways related to insulin resistance, lipid metabolism, and atherosclerosis. Integrative analyses highlighted STAT3 as a core target mediating bile acid-dependent hepatoprotection.

Discussion / Conclusion

AKK mitigates olanzapine-induced MAFLD by modulating gut-liver bile acid signaling, with the microbial bile acid 7-ketodeoxycholic acid acting as a key downstream functional mediator. These findings delineate a microbiota-bile acid-liver regulatory axis and provide a mechanistic rationale for precision microbiome-based strategies to prevent antipsychotic-associated metabolic liver injury.

Keywords

Olanzapine, Metabolic-associated fatty liver disease (MAFLD), Akkermansia muciniphila, Secondary bile acids, Gut-liver axis

00050
In vitro monoamine oxidase inhibition potential of eight dimethoxyamphetamine-derived cyclopropylamines

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

2,5-Dimethoxy-4-methylphenylcyclopropylamine (DMCPA), known for its psychedelic properties, is closely related to the antidepressant drug and monoamine oxidase (MAO) inhibitor tranylcypromine [1]. The aim of the current study was to investigate the MAO inhibition potential of DMCPA and seven novel dimethoxyamphetamine-derived cyclopropylamines (CPAs).

Materials and methods

A previously validated inhibition assay based on incubations of recombinant human MAO isoforms A or B with the non-selective MAO substrate kynuramine followed by hydrophilic interaction liquid chromatography-high-resolution tandem mass spectrometry analysis was applied [2]. If statistically significant inhibition was detected during prescreening (10 µM inhibitor concentration), IC50 values were determined by plotting the relative metabolite concentration formed over the logarithm of the inhibitor concentration (10 different inhibitor concentrations, each). Tranylcypromine was used as positive control and for comparison.

Results

The prescreening revealed statistically significant inhibition of all CPAs and tranylcypromine towards MAO-A and MAO-B. MAO-A activity decrease ranged from 50% (DMCPA) to 98% (2,4,6-trimethoxyphenylcyclopropylamine), and from 37% (DMCPA and 2,5-dimethoxy-4-bromophenylcyclopropylamine) to 97% (2,4,6-trimethoxyphenylcyclopropylamine) for MAO-B. Tranylcypromine decreased MAO activities by 87% (MAO-A) and 98% (MAO-B). Lowest IC50 values towards MAO-A (0.16µM) and MAO-B (0.26µM) were determined for 2,4,6-trimethoxyphenylcyclopropylamine, but IC50 values of 2,6-dimethoxy-4-fluorophenylcyclopropylamine were only slightly higher (MAO-A: 0.46µM, MAO-B: 1.2µM). IC50 values of tranylcypromine were 0.78µM (MAO-A) and 0.15µM (MAO-B).

Discussion / Conclusion

Amphetamine-type stimulants represent a major segment of the global drugs of abuse market. Novel derivatives are continuously introduced without preclinical (safety) studies making pharmacological effects and risk of drug interactions hard to predict. IC50 values towards MAO-A and MAO-B of 2,4,6-trimethoxyphenylcyclopropylamine and 2,6-dimethoxy-4-fluorophenylcyclopropylamine were directly comparable to tranylcypromine. As both MAO isozymes were found to be significantly inhibited by all CPAs, clinically relevant MAO inhibition might be expected, especially after repeated abuse, as irreversible inhibition in accordance with tranylcypromine is most likely. Nevertheless, clinical studies or case series would be needed for final assessment.

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Keywords

enzyme inhibition; in vitro assay; HILIC-HRMS/MS; human MAO

00111
Shifts in the Fentanyl Supply: Emergence of Carfentanil, Medetomidine and Novel Benzodiazepines

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The unregulated opioid supply is rapidly evolving, with fentanyl and its analogues frequently co-occurring with diverse adulterants and stimulants. The emergence of veterinary sedatives and novel psychoactive benzodiazepines complicates clinical management and challenges conventional urine drug testing. This study characterized temporal trends in fentanyl detection and associated co-exposures in an opioid-dependent population in Alberta, Canada.

Materials and methods

Urine samples collected between July 2024 and January 2026 were analyzed for fentanyl, fentanyl analogues, other opioids, cocaine, benzodiazepines, amphetamines, and veterinary sedatives. Mass spectrometry analysis was performed using an internally developed dynamic multiple reaction monitoring method on Agilent 6470 triple quadrupole instruments.

Results

A total of 12,432 samples were tested. Fentanyl positivity increased from 26.7% in July 2024 to 34.0% in January 2026. Among fentanyl-positive samples, amphetamine, methamphetamine, cocaine, and hydromorphone detection rates

remained stable. Heroin detection rose beginning January 2025 and declined after April 2025.

Marked shifts were observed in veterinary sedatives with fentanyl, with a substantial rise in medetomidine accompanied by a significant decrease in xylazine. Carfentanil prevalence rose sharply beginning January 2025, peaking at 89.8% in August 2025. Para-fluorofentanyl remained predominant, stabilizing near 88% of fentanyl-positive samples in late 2025, while ortho-methylfentanyl declined. Bromazolam decreased in mid-2025, whereas desalkylgidazepam became the most prevalent benzodiazepine with an average prevalence of 81.6%. Ethylbromazolam increased significantly from 6% to 57.3%.

Discussion / Conclusion

The unregulated fentanyl supply demonstrated rapid and continuous change over the study period. Increasing fentanyl positivity was accompanied by substantial shifts in co-exposures, including replacement of xylazine by medetomidine, dynamic fluctuations in fentanyl analogues, and major transitions in novel psychoactive benzodiazepines.

Reliance on traditional immunoassay screening alone and infrequently updated targeted mass spectrometry panels may fail to detect evolving exposures. Rapidly adaptable mass spectrometry panels can provide near-real-time surveillance of the drug supply and can inform harm-reduction strategies, clinical management, and public health responses.

00197
Glycyrrhiza Radix-derived Nanovesicles Attenuate Acetaminophen-Induced Liver Injury by Promoting Liver Regeneration via Macrophage Reprogramming

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Acetaminophen (APAP) overdose is a leading cause of acute liver failure with limited clinical interventions. Licorice (Glycyrrhiza uralensis) is a medicinal plant with a remarkable hepatoprotective effect. Plant-derived extracellular vesicles hold therapeutic promise, yet whether Glycyrrhiza Radix-derived nanovesicles (GNVs) protect against APAP-induced liver injury (AILI) remains unknown.

Materials and methods

Here, we have successfully isolated and purified GNVs for the first time, and performed systematic characterization of their physicochemical properties. Integrative bioinformatics analysis predicted their potential mechanisms in regulating inflammation and liver regeneration, which were subsequently validated in vivo and in vitro.

Results

In vivo, GNVs significantly ameliorated AILI, as evidenced by reduced serum ALT/AST levels and alleviated hepatic necrosis. Meanwhile, GNVs induced the

protein expression of β-catenin, Cyclin D1, and CDK4, and increased the number of Ki67+ hepatocytes, indicating enhanced liver regeneration. Mechanistically, GNVs reprogrammed hepatic macrophages toward an anti-inflammatory M2 phenotype, facilitated the transition of monocyte-derived macrophages(MoMφ) to tissue-resident Kupffer cells(KC), and upregulated the expression and secretion of hepatocyte growth factor (HGF). These changes established a reparative microenvironment conducive to liver repair. Macrophage depletion abolished the protective effects of GNVs, whereas recombinant HGF(rHGF) partially restored them,identifying macrophages and HGF as critical mediators of the hepatoprotective effects of GNVs. In vitro, GNVs directly modulated macrophage polarization, accompanied by decreased pro-inflammatory and increased anti-inflammatory cytokine expression. Co-culture experiments further confirmed that GNV-treated macrophages promoted hepatocyte proliferation.

Discussion / Conclusion

These findings reveal GNVs as a promising natural nanotherapeutic that targets macrophages to drive liver regeneration after AILI.

Keywords

Glycyrrhiza uralensis Fisch; Exosome-like nanovesicles; Macrophage; Liver regeneration; APAP-induced liver injury

00233
Cannabinoids-Cisplatin combinations induce apoptosis and mitotic arrest in cervical cancer cells

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Cervical cancer remains a primary cause of mortality among women, particularly in low-resource settings where accessible treatments are vital. This study investigated the cytotoxic and synergistic effects of tetrahydrocannabinol (THC) and cannabidiol (CBD) when used in combination with the standard chemotherapeutic agent, cisplatin, in cervical cancer cell lines.

Materials and methods

HeLa and SiHa cervical cancer cell lines were employed, while non-tumorigenic MCF-12A mammary epithelial cells were included as the control. Cells were treated with varying concentrations of THC, CBD, cisplatin, and their combinations. Cytotoxicity was measured via sulforhodamine B (SRB) assay, while drug interactions were analysed using checkerboard assays and Bliss Independence modelling. Additional assessments included light microscopy for morphology, flow cytometry for cell cycle distribution and apoptosis, and confocal microscopy for autophagic activity.

Results

The combination of THC, CBD, and cisplatin significantly reduced cell viability by 48% in HeLa and 46% in SiHa cells. Morphological analysis of treated HeLa cells revealed high rates of rounding (79.7%), cell shrinkage, and apoptotic body

formation. Flow cytometry confirmed increased sub-G1 populations and metaphase arrest. In HeLa and SiHa cells, viable fractions dropped from 94% to roughly 40% and 32%, respectively, following combination exposure. Notably, autophagic puncta formation was observed in cancerous cells, while non-cancerous MCF-12A cells maintained normal morphology and were largely spared from these cytotoxic effects.

Discussion / Conclusion

The study demonstrates that THC and CBD significantly enhance the cytotoxic efficacy of cisplatin by promoting mitotic arrest and apoptosis specifically in cervical cancer cells. The selective nature of this combination, sparing healthy cells while inducing autophagy and apoptosis in malignant ones, suggests that cannabinoids hold strong potential as adjunct therapies in cervical cancer treatment.

00245
Complementary workflow in Medical Biology Laboratories for Suspected Drug Facilitated Assault: Inovie Laboratory Experience

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

A national experimentation to combat drug-facilitated assault (DFA) began in January 2026, aiming to ensure simplified access to medical biology testing in order to improve the management of potential victims. Since 2024, the Inovie Laboratory has implemented a similar protocol for patients presenting to its laboratories, with objectives: (i) facilitating access to biological evidence through a pathway complementary to the existing forensic system; (ii) performing comprehensive urinary toxicological screening using mass spectrometry to provide reliable and rapid results; and (iii) improving patient care pathways and strengthening the vigilance system by directing individuals toward regional reference centers (CEIP-A).

Materials and methods

Potential victims are received at one of Inovie's 550 sites. A clinical and biological interview is conducted, documented through an information sheet and a clinical questionnaire, followed by urine and blood sampling. Toxicological screening is performed at the centralized Toxicology platform of Inovie, targeting all substances identified in SFTA recommendations. Results are communicated to patients by the medical biologist and to pharmacologists at the local CEIP-A for case reporting and patient follow-up when requested.

Results

530 patients were tested during the study period. Women represented two-thirds of cases (average age = 30.3 years). Most samples (76%) were collected within 48 hours of the suspected exposure. At least one substance was detected in 59% of patients, most commonly cocaine, antihistamines, and cannabinoids. Samples are stored for potential future legal proceedings, and over half of patients requested CEIP-A follow-up.

Discussion / Conclusion

This complementary pathway enabled early and standardized care thanks to Inovie's extensive territorial coverage. The toxicological profile observed mirrors national trends reported in 2022. The partnership with CEIP-A ensures that patients are directed toward appropriate medical, psychological, or legal support. Importantly, the system also provides a reliable and rapid diagnostic option for individuals who do not wish to initiate legal action, while maintaining compliance with SFTA recommendations.

00256
Bioactiviation and in vitro/in vivo metabolism of two novel MDA amino acid prodrugs in comparison to the amphetamine prodrug lisdexamfetamine

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The therapeutic use of amino acid conjugates as prodrug motif is known e.g., for lisdexamfetamine in treatment of attention deficit hyperactivity disorder. 3,4-methylenedioxymethamphetamine (MDMA) and 3,4-methylenedioxyamphetamine (MDA) are still under discussion for therapeutic use to treat psychiatric disorders. Recently, their lysine prodrugs were tested in vivo and MDA-lysine showed similar effects than direct application of MDA [1]. To date, no detailed information is available about the metabolism and bioactivation mechanisms of MDA amino acid prodrugs. Thus, the aim of this study was to investigate the prodrug cleavage of MDA-lysine and MDA-tryptophan in comparison to lisdexamfetamine and to elucidate their in vitro and in vivo metabolism.

Materials and methods

Prodrug cleavage (MDA-lysine, MDA-tryptophan, lisdexamfetamine) was studied by exposure (37°C, 240 min, 25 µM) to pooled fresh human plasma (pFHP) or pFH whole blood (pFHWB). The incubations at 25 µM in pooled human liver S9 fraction (pHLS9) were performed for 360 min at 37°C. Zebrafish embryos (ZE) were exposed to the compounds (100 µM) via surrounding medium for 24 h at 28°C, following a maximum tolerated concentration test. All samples were analyzed via liquid chromatography high-resolution mass spectroscopy.

Results

Bioactivation for all three compounds through prodrug cleavage did not occur after exposure to pFHP but after pFHWB exposure. Furthermore, MDA and amphetamine release was also observed during the in vitro and in vivo metabolism experiments. However, MDA-tryptophan was also directly metabolized via hydroxylation of the tryptophan residue in pHLS9. Free MDA was further metabolized to 4-hydroxy-3-methoxy-amphetamine (HMA) in pHLS9 and ZE.

Discussion / Conclusion

Bioactivation of lysine prodrugs depends on enzymes present in pFHWB [2]. Metabolism studies showed that besides bioactivation, unique metabolites of at least MDA-tryptophan besides MDA metabolites could be identified. This would allow to analytically discriminate between prodrug intake or direct MDA consumption. All in all, MDA-lysine and MDA-tryptophan demonstrated prodrug properties similar to lisdexamfetamine.

Reference(s)

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Keywords

Amino acid prodrugs, LC-HRMS/MS; zebrafish; pHLS9; MDA

00277
High-Risk Acute Pesticide Poisoning in the Emergency Setting: A Hospital-Based Case Series

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Highly hazardous pesticides remain a major cause of severe self-poisoning in many settings. We describe high-risk pesticide intoxications presenting to the emergency department of a Moroccan hospital and their in-hospital course.

Materials and methods

We performed an observational analysis of a clinician-maintained registry of acute poisonings collected over 7 months (February–August 2024). Cases classified as “pesticides and fertilizers” were included. Extracted variables included demographic characteristics, exposure characteristics (agent, route, circumstance, location), level of care (emergency department vs intensive care unit [ICU]), toxicology testing, and outcome at discharge. Descriptive statistics are reported.

Results

Twenty of 54 poisonings (37.0%) involved pesticides/fertilizers. All cases involved oral ingestion with suicidal intent and occurred predominantly at home. Women

accounted for 85.0% of cases (17/20). Age was available for 15 patients (median, 28 years; IQR 21.5–31.5). Rodenticides were implicated in 70% of cases (14/20, including two mixed ingestions), followed by aluminium phosphide (“Phostoxin”) in 20% (4/20, including one mixed ingestion). Alphachloralose accounted for 10% (2/20) and organophosphates for 5% (1/20). Half of patients required ICU admission (10/20); ICU use was universal in alphachloralose cases (2/2) and occurred in 50% of rodenticide-only cases (6/12). Toxicology screening was documented in 1/20 patients. Favorable outcomes were observed in 5/20 cases. Final outcomes were unavailable for 14/20 patients because they left against medical advice or were transferred to psychiatric care. One death occurred following alphachloralose ingestion.

Discussion / Conclusion

In this series from a Moroccan hospital, high-risk pesticides, especially rodenticides and aluminium phosphide, were a leading cause of intentional poisoning and frequently required ICU care. Limited toxicological confirmation highlights the need for improved diagnostic pathways and biomarker monitoring to guide treatment. Missing outcome data limited risk assessment and emphasizes the importance of follow-up and stronger regulation of hazardous pesticides.

Keywords

Clinical Toxicology, Pesticide, Poisoning, Self-poisoning

00286
Fatal intoxication involving methiodone (IC-26): first documented case with analytical confirmation

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Methiodone (IC-26) is a synthetic opioid structurally related to methadone. Recently identified in European drug seizures, it has not previously been reported in fatal intoxication. We describe the first forensic case in which methiodone was confirmed in femoral blood and considered a major contributory factor in death.

Materials and methods

A 27-year-old male was found deceased at home. Autopsy revealed a non-specific asphyxial syndrome, including pulmonary congestion and edema, without any traumatic or structural pathology. At the scene, a sachet containing round tablets labelled “IC-26” was recovered. Comprehensive toxicological screening of femoral blood was performed using LC-HRMS. An unidentified peak was detected and characterized by exact mass measurement, isotopic distribution and high-resolution MS/MS fragmentation. LC-HRMS analysis of the seized tablets demonstrated a compound with identical retention time and superimposable fragmentation spectra. A certified reference standard of methiodone was subsequently obtained, enabling definitive confirmation through chromatographic and spectral concordance between blood extract, seized material and authentic standard. Methiodone was then quantified using a LC-MS/MS dedicated method.

Results

Methiodone was confirmed in femoral blood and measured at a concentration of 250 ng/mL. Additional substances detected included loxapine, quetiapine and bromazepam at therapeutic or sub-therapeutic concentrations. 2-Fluorodeschloroketamine was also identified but at a concentration markedly below those reported in fatal intoxications. Analysis of the seized tablets confirmed methiodone as the sole active compound. In the absence of any alternative cause of death and given the pharmacological profile of methiodone as a μ-opioid receptor agonist, methiodone-induced respiratory depression was considered as the most plausible mechanism of death.

Discussion / Conclusion

This case represents the first documented fatality involving methiodone (IC-26). It illustrates the rapid emergence of newly marketed synthetic opioids iand underscores the necessity for adaptable analytical frameworks enabling prompt identification of previously unreported substances. Continuous surveillance and early analytical integration are essential in the evolving synthetic opioid landscape.

00310
Driver’s License Suspension and Urine Toxicology Testing: Should Mandatory Verification of Urine Sample Integrity Be Required?

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

In France, following the suspension of a driver’s license due to an offense involving drug use, the individual must undergo a medical evaluation before the Prefectural Medical Commission. A urine toxicology test is frequently requested to assess chronic drug consumption. Although urine testing offers excellent analytical performance, several methods of tampering can lead to falsely negative results. To address this issue, the Inovie laboratory has implemented systematic urine integrity checks to verify sample conformity (according to SAMHSA/DOT criteria) and ensure the accuracy of toxicology results.

Materials and methods

We present the characteristics of urine sample qualification performed in the laboratory for drug screening between January 1, 2023, and December 31, 2025. SAMHSA/DOT criteria include verification of urine temperature immediately after voiding, measurement of pH, specific gravity, nitrites (colorimetry), and creatinine concentration (immunoenzymatic method – Abbott). Drug screening is performed using immunoassay (Abbott) or an in-house LC-MS/MS method.

Results

More than 5,000 screenings were conducted. A preliminary analysis of 2,500 samples showed 7% positive results (mainly cannabis). Among the negative samples, over 10% were non-compliant, presenting at least one abnormal parameter (suggesting attempted dilution in most cases). A biological advisory note is then added to the report, indicating that non-compliance prevents confirmation of sample validity and may lead to falsely negative results. The Medical Commission physician can rely on this information to request a repeat test.

Discussion / Conclusion

Implementing urine integrity qualification allowed the detection of more than 10% potential tampering. This procedure—unique among French laboratories—appears essential to strengthen analytical reliability and reduce the risk of fraud in the context of driver's license suspension. These requirements align with ongoing efforts to improve road safety and combat the use of psychoactive substances.

Reference(s)

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00335
Fatty Acid Accumulation and TCA Cycle Inhibition in Polymyxin B-Induced Acute Kidney Injury: An Integrated Metabolomics Study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Approximately one third of patients receiving polymyxin B (PB)—a key drug for multidrug-resistant Gram-negative infections—develop acute kidney injury (AKI), a complication closely linked to increased mortality. However, both the diagnostic measures and mechanistic understanding of PB-induced AKI are still limited.

Materials and methods

A total of 83 patients receiving PB-based regimens were enrolled in our study, including 60 non-AKI and 23 AKI patients, from whom 207 plasma samples were collected. Simultaneously, male Sprague-Dawley rats were administered subcutaneous injections of PB or saline for 10 consecutive days. Plasma and kidney samples were collected 24 hours after the final dose. Furthermore, we performed targeted quantification of polymyxin B1 (PB1), PB2, PB3, isoleucine-polymyxin B1 (ILE-PB1), and PB6 using ultra-performance liquid chromatography coupled with high-resolution Orbitrap mass spectrometry (UPLC-HRMS), mapped their spatial distribution in the kidney using Airflow-assisted desorption electrospray ionization (AFADESI)-based mass spectrometry imaging (MSI), and profiled metabolite alterations via untargeted metabolomics with an in-house database.

Results

We successfully identified two distinct biomarker panels: a panel of PB components for therapeutic drug monitoring, and a panel of circulating plasma metabolites to differentiate non-AKI from PB-AKI. Importantly, we identified that PB induced nephrotoxicity through a dual mechanism: excessive activation of renal fatty acid uptake and transport pathways, concomitant with marked inhibition of the TCA cycle.

Discussion / Conclusion

This study presents a pioneering metabolomics investigation that integrates clinical cohort data with animal models to elucidate the nephrotoxic mechanisms of PB, thereby improving early detection and providing actionable therapeutic strategies.

Keywords

Polymyxin B; Acute kidney injury; Biomarker; Metabolic pathways; Metabolomics

00336
Photo-reflection signal as a novel surrogate marker for site-specific lung deposition: A non-invasive and real-time monitoring approach for inhaled medicines

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Intoduction: Inhalation therapy is used for the management of respiratory conditions. Site-specific deposition influences efficacy in the lung and local adverse effects in the oropharynx. Although regional deposition shows wide interindividual variability, the clinical utility of blood concentration-based TDM for inhaled drugs remains controversial. Therefore, the focus of alternative TDM approach for inhaled medicines should be shifted from systemic exposure to regional respiratory deposition. Our previous study demonstrated that non-invasive, real-time monitoring of the particle emission signals using the photo reflection method (PRM) can estimate lung deposition via dry powder inhaler (DPI)[1,2)].

Objective: To evaluate the PRM signals as an alternative surrogate for site-specific respiratory deposition via DPI.

Materials and methods

Methods: In vitro drug deposition in the whole lung (fine particle fraction; FPF_{WL}), peripheral airways (FPF_{PA}), and the oropharyngeal region of budesonide via Symbicort® Turbuhaler® were measured using an Andersen Cascade Impactor. Four inhalation patterns across different peak flow rates (PFR: 30 or 60 L/min) and flow increase rates (FIR: 3.2–9.6 L/s^2) were simulated using a human inhalation flow simulator. The inhalation flow rate and particle emission profile were measured using a flow meter and a PRM, respectively. The relationships between particle emission signals and deposition performance were analyzed using four univariate models: linear, logarithmic, Hill, and Emax.

Results

Results: Increased PFR and FIR enhanced drug deposition in both the lungs and oropharyngeal region. FPF_{WL} and FPF_{PA} were strongly correlated with the total particle emission intensity over time with the Hill model (R^2 = 0.86 and 0.74 for FPF_{WL} and FPF_{PA}, respectively), which reflects nonlinear deagglomeration behavior. Oropharyngeal deposition correlated with the flow rate at the particle emission peak, fitting a linear model (R^2 = 0.82), consistent with inertial impaction mechanisms.

Discussion / Conclusion

Conclusions: PRM signals provide surrogate markers for site-specific deposition from a DPI, and can support a new concept for inhaled drug monitoring.

Reference(s)

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Keywords

Key Words: Dry powder inhaler; real-time monitoring; alternative marker; non-invasive; photo reflection method

00342
Identification of diagnostic biomarkers and risk factors for early detection and prevention of vildagliptin-induced idiosyncratic drug-induced liver injury

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Vildagliptin has been reported to cause idiosyncratic drug-induced liver injury, but its mechanism remains unclear. Elucidation of this mechanism could help to predict and prevent liver injury. We previously demonstrated that covalent binding of vildagliptin induces inflammasome activation and contributes to the development of liver injury. Damage-associated molecular patterns (DAMPs) are mediators of immune responses, including inflammasome activation, and are released from stressed cells. This study evaluated whether vildagliptin induces oxidative stress and DAMPs release in hepatocytes. Furthermore, we assessed the effect of immune tolerance on the onset of vildagliptin-induced liver injury.

Materials and methods

Functional liver cell (FLC)-4 cells were treated with four DPP-4 inhibitors, including vildagliptin, for 7 days for comparison. H_2O_2 production was quantified using the ROS-Glo^{TM} H_2O_2 assay. DAMPs, including heat shock proteins (HSPs) and S100 calcium-binding proteins A, in the culture supernatant were analyzed by Western blotting. To assess the impact of immune tolerance, vildagliptin was administered to

PD-1$^{-/-}$ mice treated with anti-CTLA-4 antibody. Serum AST /ALT were measured weekly. Liver tissues were collected at week 4 and evaluated by HE staining.

Results

In vildagliptin-treated FLC-4 cells, H_2O_2 production was increased, and HSP40 levels were elevated in the culture supernatant. In immune checkpoint-blocked mice, vildagliptin caused significant increases in serum AST/ ALT at weeks 3 and 4. Histological analysis of the liver revealed a pronounced increase in granulomatous inflammation.

Discussion / Conclusion

Vildagliptin may induce oxidative stress in hepatocytes via covalent bonding and activate the inflammasome through HSP40 release. Vildagliptin-induced liver injury has been reported not to occur in normal mice. However, we observed liver injury in immune checkpoint-blocked mice, suggesting that immune tolerance plays a crucial role in its pathogenesis. These findings suggest that HSP40 serves as an early biomarker for vildagliptin-induced liver injury and that concomitant immune checkpoint inhibition may increase the risk of hepatotoxicity.

Keywords

Damage-associated molecular patterns; Idiosyncratic drug-induced liver injury; Immune checkpoint inhibition; Inflammasome activation; Oxidative stress; Vildagliptin.

00400
Pediatric intoxication to the synthetic cannabinoid 5F-ADB via vaping devices: An alarming case series

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Adolescent use of e-cigarettes and 'puffs' increasingly involves substances like 'Buddha Blue,' 'Spleen,' or 'PTC.' The synthetic cannabinoid 5F-ADB (5F-MDMB-PINACA) is often found in these vaping devices and has been associated with severe adverse effects, including reported fatalities. This study aims to describe a pediatric poisoning cluster associated with the use of 5F-ADB via vaping devices.

Materials and methods

Since April 2025, 39 poisoning, with three recurrences, involving the consumption of 5F-ADB have been recorded at the Grenoble Alpes University Hospital. 5F-ADB or one of its metabolites was identified following a targeted NPS (Novel Psychoactive Substances) screening performed using liquid chromatography coupled with high-resolution mass spectrometry (LC-HRMS) and an inclusion list from HighResNPS database.

Results

The median age of the patients was 15 years (range: 12 to 17 years), with a 3:1 male-to-female ratio. In some cases, 5F-ADB was detected at trace levels in the plasma, however, the M7 metabolite (C19H26FN3O3) was the primary compound identified in both plasma and urine samples.

The predominant clinical presentations observed were neurological (n=24) and cardiological (n=10), characterized primarily by impaired consciousness, chest pain and tachycardia. All patients arrived via the emergency department and 13 were hospitalised at least one day as a result of their symptoms, including one in intensive care. According to patient statements, half of them had a chronic use of PTC.

Discussion / Conclusion

We have observed a resurgence in the number of 5F-ADB cases in the Grenoble region. The M7 metabolite has been identified as a key biomarker of interest for detecting the consumption of this specific cannabinoid. Given its widespread prevalence, an update of the databases used in toxicological screening is essential. According to data from the CFSRE, 5F-ADB is one of the predominant synthetic cannabinoids in the United States this year as well.

00536
A case report of poisoning caused by fentanyl transdermal patch in a Chinese patient with cancer pain

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Fentanyl transdermal patch (FTP) is commonly used in treatment of cancer pain. It is indicated for patients who cannot tolerate the adverse drug reactions (ADRs) of oral strong opioid receptor agonists or are unable to take oral analgesics. In clinical practice, there are significant individual variations in the dosages of FTP. We herein present a case of poisoning with large dose FTP treatment.

Materials and methods

Case presentation and therapeutic drug monitoring.

Results

A 62-year-old Chinese male patient with lung adenocarcinoma was originally treated with oxycodone but complained significant nausea and vomiting, requesting transferring to FTP treatment. He was found unresponsive by his family member 3.5

hours after initiation of fourteen 50-μg/h fentanyl transdermal patches. Physical examination showed that pupil diameter was approximately 2mm, respiration was at approximately 3-4 breaths/min. Cardiac monitoring showed that BP was 134/88mmHg, blood oxygen saturation was 91%. After administration of oxygen at 3L/min, blood oxygen saturation increased to 99%. The medical team removed all the fentanyl patches and administered naloxone hydrochloride injection 0.4mg intravenously. Patient regained consciousness approximately 10 minutes later, but could not recall the situation upon awakening. We then established a detailed toxicological analysis procedure to quantify fentanyl, in human plasma by high-performance liquid chromatography-tandem mass spectrometry. The measured fentanyl concentrations were 7.1 ng/ml (17h) and 2.4 ng/ml (36h), respectively. The patient received oxycodone treatment 22h after fentanyl poisoning based on fentanyl concentrations.

Discussion / Conclusion

The patient's poisoning can be attributed to the FTP. The concentration monitoring of FTP was able to offer references for future pain management.

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Keywords

Fentanyl transdermal patch, cancer pain, poisoning, therapeutic drug monitoring, individualized treatment

00537
Contribution of pharmacogenetics for the interpretation of toxic concentrations of zuclopenthixol.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Zuclopenthixol decanoate (3x200mg 1d/28) has regularly been prescribed in a young patient of Asian origin, for 5 years. Unexpectedly, 4 days after the last injection, he is found dead. The early toxicological analysis found a toxic theoretical concentration of zuclopenthixol. In this context, we wanted to rule out the hypothesis of a genetic variation, as a CYP2D6 and CYP3A4 poor metaboliser.

Materials and methods

Biological samples were taken during external examination and after autopsy. Toxicological screening and quantification were carried out by UHPLC-HRMS (Thermoscientific) and UHPLC-MS/MS (TQSmicro, Waters). Following DNA extraction (Promega, Qiasymphony), NGS library constitution and sequencing (Illumina, MySeq), phenotypes were predicted using SophiaDDM solution, Pharmcat and PyPgx.

Results

Toxicological screening highlighted the presence of zuclopenthixol in blood, urine, bile, gastric contents and vitreous humor. Highest blood concentrations are measured at 770 ng/ml and 137 ng/ml in samples from external examination and

autopsy . Genotypes for CYP2D6 and CYP3A4 were normal (*1/*1) after checking gene copy number and absence of hybrids with CYP2D7 pseudogene.

Discussion / Conclusion

The metabolic status of the young patient predicted by the genotype (normal metaboliser) does not explain overexposure to zuclopenthixol. After 200 mg of zuclopenthixol every 15 days, the expected through blood concentration is approximately 10 ng/ml [1]. The lethal concentration range is generally defined for concentrations above 900 ng/ml [2]. Maximum zuclopenthixol concentrations are obtained between the 3rd and 7th day after an IM injection [3,4,5] with a 1/2 lifespan of 19 days, explaining the observed concentrations in our case. Furthermore, after analyzing the medical file, a break in treatment has been found. The resumption of treatment without dose adjustment, or close follow-up as recommended [6] could explain the occurrence of death. In conclusion, a toxicogenetic approach is valuable to exclude or to encourage the metabolic hypothesis, thus completing classical toxicological analysis.

Reference(s)

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Keywords

toxicology, pharmacogenetics, zuclopenthixol, drug related death

00540
UPLC-MS/MS Determination of Phosphatidylethanol Using Volumetric Dried Blood Microsampling: validation and comparison with venous blood

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Volumetric microsampling technology offers many practical advantages for blood collection, particularly when conventional venous blood sampling is uncomfortable or inconvenient for patients. In this study, we investigated the use of two fingerprick devices - Capitainer®B Vanadate and Mitra® Clamshell - for the UPLC-MS/MS determination of phosphatidylethanol (PEth) in dried blood samples. We evaluated the analytical performance of microsampling compared to routine venous blood sampling, with the aim of developing and validating a clinical UPLC-MS/MS method compatible with microsampling techniques.

Materials and methods

Calibration curves of Peth 16:0/18:1 (Chiron AB) were prepared at 0.025-5.0 µM in isopropanol with internal standard PEth-d5.

Dried blood spot (DBS) samples were collected in Capitainer® B Vanadate card (10 µL, Capitainer AB), and dried blood in Mitra® sampler (DB-Mitra) (Mitra® Clamshell 20 µL, Neoteryx LLC, Trajan Scientific). One venous blood, two DBS and two DB-Mitra samples for each individual were obtained and used.

Each sample (venous blood, DBS and DB-Mitra respectively) was mixed with internal standard in isopropanol in a 96-well plate (NUNC™ or Sirocco™) and then subjected

to shaking, followed by centrifugation. Supernatants were injected into a LC-MS/MS system (Waters Xevo -TQS µ) to determine Peth 16:0/18:1.

Results

UPLC-MS/MS methods were developed and validated for the quantification of PEth 16:0/18:1 and proved fully compatible with both volumetric microsampling devices. Good sample stability and analytical performance were achieved. Strong agreement was observed with our existing routine venous blood method (SWEDAC accredited): DBS samples showed--$y \approx 0.9647x$ ($R^2 > 0.9909$, $n = 31$), and DB-Mitra samples--$y \approx 1.1592x$ ($R^2 = 0.9711$, $n = 30$).

Discussion / Conclusion

Our findings support the suitability of Capitainer® and Mitra® microsampling in clinical labs for convenient and reliable PEth testing. Methods were successfully applied in a collaborative study between the Stockholm Centre for Dependency Disorders, Sollentuna, and our department.

Keywords

Phosphatidylethanol (PEth), microsampling, volumetric dried blood spot (qDBS), volumetric absorptive microsampling (VAMS), clinical UPLC-ESI-MS/MS

00581
Gut-Microbiome, Inflammatory Bowel Disease and Neuro-Psycho-Pharmacology

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The inflammatory bowel diseases (IBD), which include Crohn's Disease (CD) and Ulcerative Colitis (UC), are multifactorial, chronic conditions of the gastrointestinal tract. IBD has been associated with dramatic changes in the gut microbiota and serum cytokines. There are changes in the gut metabolome at the molecular interface between host and microbiota. Cannabis sativa is widely used for medicinal purpose. Cannabidiol reduction of symptoms was observed in IBD patients.

Materials and methods

We performed LC-MS metabolomic and cytokine profiling (ELISA) of cross-sectional stool samples from CD [total (n=15), cannabis users (5)] and UC [Total (n=15) cannabis users (7) and 10 non-IBD control subjects. Metabolomic profiles correlated with fecal calprotectin levels. In sera we identified chemokines and cytokines in IBD, including tumor necrosis alpha, Interleukin 1 beta, interleukin 6, 8, 17.

Results

We identified 122 robust associations between severity of the disease and these biomarkers, indicating possible mechanistic relationships that are perturbed in IBD. Finally, we found that metabolome- and inflammasome-based classifiers of IBD status are accurate.

Discussion / Conclusion

Both CD and UC cannabis users presented lower inflammatory markers and lower inflammation when compare with non-users. Cannabis could improve UC and CD scores. A treatment criterion is still needed since there is no standardization regarding the variety of the plant that is used, route of administration and doses. Therefore, we suggest caution in the use of CS in the therapeutic approach of IBD.

Our findings thus provide an improved understanding of perturbations of the microbiome-metabolome interface in IBD, including identification of many potential diagnostic and therapeutic targets.

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Keywords

IBD, Crohn’s Disease, Ulcerative Colitis, Cannabis

00615
Development of sample preparation and LC-MSMS method for analysis of semi-synthetic cannabinoids and findings in clinical urine samples

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The semi-synthetic cannabinoid (SSC) hexahydrocannabinol (HHC), typically produced from cannabidiol (CBD), was first reported in Europe in 2022. Since then, the market has expanded rapidly with SSCs such as tetrahydrocannabivarin (THCV), tetrahydrocannabiphorol (THCP), and hexahydrocannabiphorol (HHCP). The appearance of these new SSCs and their structural similarity to THC complicates routine drug testing. Urine samples are first screened using immunochemical assay and positive findings are confirmed using LC-MS/MS. A fraction of samples are screened positive but are confirmed negative for HHC-COOH and THC-COOH, suggesting the presence of other cannabinoids. The coelution of an unknown interference with HHC-COOH further complicated the confirmation analysis. This study aimed to develop an improved sample preparation and LC-MS/MS method to address the interference and include emerging SSCs.

Materials and methods

LC-MS/MS detection was performed using a 0.1% formic acid and methanol gradient for urine analysis on a PFP column. Identification was achieved by comparing retention times and ion ratios with certified reference materials.

Results

Chromatographic separation was achieved for all analytes. D8-THC-COOH (m/z 343.5>245.3/299.4; ion ratio 0.33) eluted at 4.19 min, d9-THC-COOH (m/z 343.5>245.3/299.4; ion ratio 0.31) eluted at 4.58 min; R-HHC-COOH (m/z 345.3>191.2/301.3; ion ratio 0.82) eluted at 3.96 min; and S-HHC-COOH (m/z 345.3>191.2/301.3; ion ratio 0.44) eluted at 4.23 min. Internal standards eluted at 4.56 min (THC-COOH-d9) and 3.96 min (HHC-COOH-d9). The previously unidentified interference was successfully separated, eluting at 4.56 min.

Discussion / Conclusion

The developed method is quick, robust, and selective making it ideal for high-throughput clinical laboratories. By successfully separating the unknown interference from HHC-COOH and incorporating several new SSC metabolites, this method significantly improves the accuracy of cannabinoid detection in clinical urine samples.

Keywords

cannabis, hexahydrocannabinol, semi-synthetic cannabinoids

00650
Severe diltiazem poisoning managed with CytoSorb® hemoadsorption and supportive therapies: a case report

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Severe intoxication with nondihydropyridine calcium channel blockers, such as diltiazem, is associated with high morbidity and mortality. Evidence supporting extracorporeal treatment strategies remains limited. This case integrates serial toxicokinetic measurements with adjunctive hemoadsorption in sustained-release diltiazem poisoning.

Materials and methods

A 73-year-old man presented with coma, complete atrioventricular block, refractory hypotension, and severe lactic acidosis. Despite optimized supportive therapy including vasopressors, calcium supplementation, hyperinsulinemic–euglycemic therapy, and continuous renal replacement therapy, he remained hemodynamically unstable. CytoSorb® hemoadsorption was initiated six hours after intensive care unit admission. Shortly thereafter, sinus rhythm was restored, serum lactate rapidly declined, and vasopressor and insulin requirements were progressively reduced, allowing discontinuation of extracorporeal support. The patient recovered and was discharged home.

Results

Retrospective analysis demonstrated elevated diltiazem concentrations with delayed, capacity-limited elimination.

Discussion / Conclusion

This case supports considering hemoadsorption in unstable patients with severe diltiazem poisoning despite conventional measures and highlights the need for systematic pharmacokinetic evaluation in future studies.

Keywords

Calcium channel blocker poisoning; Diltiazem; Extracorporeal Circulation; CytoSorb®; Toxicokinetics

00688
Clinical Prediction Models for Immune-Related Adverse Events: What Do We Know and Why Are They Not Yet Ready for Clinical Practice?

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Immune-related adverse events (irAEs) are major contributors to morbidity and treatment interruption during immune checkpoint inhibitor therapy. Although numerous machine learning (ML) models have been developed to predict irAEs, their clinical integration remains limited. This review evaluated the methodological quality and implementation readiness of ML-based irAE prediction models.

Materials and methods

A systematic search of PubMed, Embase, Cochrane Library, and Web of Science was conducted from inception to November 30, 2024. Studies developing or validating ML-based models for irAE prediction were included. Two reviewers independently screened studies and extracted data using the CHARMS checklist. Risk of bias was assessed with the PROBAST+AI checklist, and reporting quality was evaluated using the TRIPOD+AI checklist. A narrative synthesis was performed. The protocol was registered in PROSPERO (CRD42025641054).

Results

Of 27 studies included, most were retrospective (85%) and single-center (67%), with limited sample diversity. Only six studies performed external validation, and none conducted prospective impact analyses in clinical workflows. All studies were rated as high risk of bias, predominantly in the analysis domain due to inadequate handling of missing data, overfitting risk, and insufficient calibration assessment. Calibration was unreported in 59% of studies, and 78% did not perform decision curve analysis. Mean TRIPOD+AI adherence was 55.3%, indicating substantial reporting deficiencies. Three major translational barriers were identified: (1) Methodological fragility, including high risk of bias and limited external validation; (2) Insufficient clinical performance characterization, particularly lack of calibration and clinical utility evaluation; (3) Absence of implementation planning, with few studies specifying deployment format, integration pathways, or real-world testing.

Discussion / Conclusion

Despite promising discrimination performance, ML-based irAE prediction models demonstrate limited implementation readiness. Deficiencies in methodological rigor, external validation, calibration reporting, and clinical utility assessment constrain reproducibility and real-world applicability. Future research should prioritize multicenter validation and prospective evaluation to support safe integration into oncology practice.

Keywords

Immune-related adverse events; Machine learning; Prediction model; Clinical Toxicology

00701
TNF-α as a Candidate Toxicity Biomarker for Obinutuzumab-induced Thrombocytopenia: A Pilot Multi-Omics Study with Experimental Validation

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Obinutuzumab, a humanized anti-CD20 monoclonal antibody, is widely used in various lymphoma and autoimmune diseases. However, obinutuzumab therapy-related thrombocytopenia occurs in up to 30–40% of patients and may compromise therapeutic continuity. Reliable biomarkers for early toxicity identification are still lacking. This pilot study aimed to explore molecular signatures associated with obinutuzumab-induced thrombocytopenia and to identify candidate toxicological biomarkers.

Materials and methods

In this prospective exploratory study, lymphoma patients receiving obinutuzumab were stratified into thrombocytopenia and non-thrombocytopenia groups based on post-treatment platelet decline (≥ grade 1, CTCAE). Propensity score matching was applied to reduce baseline imbalance. Plasma samples underwent LC-MS–based metabolomics and TMT-labeled quantitative proteomics to identify differentially expressed molecules ($P<0.05$). Pathway enrichment and protein–protein interaction network analyses were conducted to identify key signaling hubs. Candidate targets were subsequently validated by Western blot analysis. Exploratory receiver operating characteristic (ROC) analyses were performed to assess discriminatory performance.

Results

Twelve patients were included (n=6 per group). Multi-omics analysis identified 17 differential proteins and 47 metabolites. Network analysis highlighted extracellular matrix remodeling proteins (POSTN, COL1A1, SPARC) and inflammatory pathways centered on TNF-α signaling. Western blot validation confirmed significantly elevated TNF-α expression in patients who developed thrombocytopenia ($P<0.05$), consistent with proteomic findings. Exploratory ROC analysis demonstrated acceptable discriminatory capacity of TNF-α for identifying patients at risk.

Discussion / Conclusion

Through integrated multi-omics profiling with experimental validation, TNF-α–associated inflammatory signaling was implicated in obinutuzumab-related platelet decline. Circulating TNF-α represents a candidate toxicity biomarker requiring confirmation in larger cohorts. These findings provide preliminary evidence supporting biomarker-informed monitoring strategies to enhance the safety of anti-CD20 therapy.

Keywords

Obinutuzumab; Thrombocytopenia; Toxicity Biomarker; Multi-Omics Analysis

00726
Are We Missing Fentanyl? False-Negative Immunoassay Results and Associated Clinical Presentations

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Fentanyl immunoassays (IAs) are widely utilized for urine drug screening but are susceptible to false-positive (FP) and false-negative (FN) results. While high FP rates are reported, FN rates against mass spectrometry reference methods in clinical settings remain poorly understood. Evaluating FN results is critical to mitigate diagnostic confusion, unnecessary investigations, and adverse psychosocial consequences. This study analyzes the FN rate of the SEFRIA™ fentanyl IA and characterizes associated metabolite profiles and patient presentations.

Materials and methods

A retrospective review was conducted at a central laboratory serving multiple tertiary care facilities between December 1, 2023, and November 30, 2025. We evaluated cases undergoing SEFRIA™ urine fentanyl IA (LOD: 1.0 ng/mL) and/or toxicology screening on Sciex 4600 Quadrupole Time-of-Flight mass spectrometer (QTOF-MS) (LOD: 2.5 ng/mL for fentanyl, 5.0 ng/mL for norfentanyl). Primary outcomes were IA FP and FN rates relative to QTOF-MS. Secondary outcomes included identified metabolites, co-ingested substances, and ICD-10 diagnoses.

Results

Over 24 months, 12,206 IAs and 4,163 QTOF-MS tests were performed. Analysis of 3,999 paired, same-day results revealed a 3.27% FP rate (124/3,787) and an 11.32% FN rate (24/212). Among the 24 FN patients, QTOF-MS identified norfentanyl alone in 15 specimens, fentanyl alone in 3, and both analytes in 6. Top co-detected substances included cannabinoids (n=4), ketamine (n=4; potentially iatrogenic), and methamphetamine (n=2). Predominant clinical presentations were altered mental status (n=7), acute respiratory failure (n=6), and unspecified convulsions (n=3).

Discussion / Conclusion

The SEFRIA™ urine IA demonstrated a 3.27% FP rate—partially attributable to varying detection limits—and a substantial 11.32% FN rate. The predominance of FN specimens containing solely norfentanyl underscores the critical need for screening assays with cross-reactivity to both fentanyl and its major metabolite. Characterizing the associated clinical presentation provides valuable insights regarding patient populations whose fentanyl exposure may not be detected by standard IA screening.

Reference(s)

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Keywords

fentanyl, false-negative, immunoassay, mass spectrometry

00749
Comprehensive Drug Testing in Dried Blood Spots for Multi-Year Surveillance of Unregulated Drug Use in Rhode Island

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Dried blood spots (DBS) are an emerging patient sampling technique, allowing detection of compounds in blood years after collection with small sample volumes. As part of a randomized controlled trial in Rhode Island, blood spots were collected from participants who reported recent drug use from 2021 to 2023. These DBS, comprised of only 50-80 µL of blood before drying, were screened against a panel of 350+ prescription and over-the-counter drugs, unregulated substances, adulterants, and metabolites to characterize drug use patterns and assess the presence of potent adulterants in the drug supply.

Materials and methods

DBS were collected by trained personnel, dried overnight, and stored at -80°C until processing. Samples were then thawed, extracted, and injected into a high-resolution mass spectrometer (LC-QTOF-MS) for analysis. The untargeted analysis method was used to screen for over 350 drugs and metabolites, as well as emerging psychoactive substances and adulterants.

Results

Of the 420 total samples, fentanyl and related analogs were detected in 102 (24.3%). The veterinary sedative xylazine, a potent adulterant recently designated as a national public health concern, was found in 32 samples (30.4% of fentanyl positive samples, 7.6% of overall samples). Other analytes of interest included cocaine (74.5%), methamphetamine (14.3%), and heroin (1.2%).

Discussion / Conclusion

Our comprehensive drug screen method by LC-QTOF-MS in DBS enables definitive testing in traditionally vulnerable populations, who may not present to a healthcare center for routine testing. This provides insight into drug use patterns and drug supply variation otherwise inaccessible, valuable especially when triangulating with data from hospitals and drug checking information. This study provides support for future use of DBS in clinical studies involving samples collected over long periods of time, allowing significant cuts on resources needed for transportation and storage, or with patients for which typical blood draws are not feasible, such as neonates or individuals with no access to healthcare.

Keywords

dried blood spots, LC-QTOF, HRMS, comprehensive screening, polysubstance use

00759
Pharmacological Toxicity assessment by Global Pill Testing (PhaT-GPT): Application of activity-based opioid screening in drug checking

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The rapid emergence of new synthetic opioids (NSOs) on the recreational drug market poses a major public health threat. NSOs have been detected in a variety of recreational drugs and counterfeit medications, in which their presence is often not known, which greatly increases the risk of intoxication and overdose. Drug-checking services play an important role in this context, as these organizations can rapidly send out warnings about circulating pills or powders that are particularly dangerous. However, conventional mass spectrometry- or immunoassay-based screening may fail to detect newly emerging compounds. In addition, risk communication becomes increasingly complicated when dealing with mixed drug preparations.

Materials and methods

We set up a new drug testing initiative, coined “PhaT-GPT”, which applies activity-based screening for the detection of opioid activity in drug samples. Using a μ-opioid receptor (MOR) bioassay, extracts from drug preparations were checked (blind-coded) for opioid activity. Filter paper cards used in routine newborn screening programs were spiked with 5 µl of a methanolic extract that was generated according to the WEDINOS routine pill/powder testing protocol (i.e. dissolving ~10mg in ~1ml of methanol). Samples were sent via regular mail to Ghent University for testing. As the ried drug spots (DDS) contain only small amounts of drug, there are no regulatory complications during transport.

Results

An optimized extraction protocol encompassed extraction of full DDS (n=145) in 24-well plates for 1h using 500µl of 80% methanol/20% OptiMEM® (v/v). Following 5-fold dilution with OptiMEM, 20µl was applied to an in-house developed MOR bioassay. The assay reliably (sensitivity & specificity >90%) identified the presence of opioids and allowed the derivation of ‘fentanyl activity equivalents’, by comparing the signal to a fentanyl calibration curve.

Discussion / Conclusion

By focusing on functional activity rather than chemical structure, the proposed approach provides a universal screening method that can be applied for drug-checking purposes

Keywords

new synthetic opioids

drug checking

Mu opioid receptor assay

00760
Identification of ethylbromazolam in the unregulated drug supply in Toronto: an analytical journey

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The ongoing addition of Novel Psychoactive Substances to unregulated drug supplies continues to pose serious risks to public health worldwide. Their real-time identification is challenging, requiring combined expert knowledge, advanced analytical technologies and critical data evaluation. We present the laboratory investigation that led to the identification of ethylbromazolam for the first time in Toronto's street drug supply, where it first emerged on November 8, 2024.

Materials and methods

A drug sample acquired as alprazolam was submitted to the Toronto's Drug Checking Service (DCS) laboratories. Analytical investigations included: GC-MS using 6890N GC/5975 MSD equipment (Agilent Technologies); and LC-HR-MS/MS using Q-Exactive/UHPLC Vanquish equipment (Thermo Fisher Scientific). NMR analysis was referred to the Drug Analysis Service (DAS) laboratory. Ethylbromazolam standard (Cayman Chemicals) was used for validation.

Results

GC-MS analysis did not identify alprazolam, but indicated a potential bromazolam analogue, based on bromazolam-characteristic fragments, with a molecular ion of 366 Da nominal mass. LC-HR-MS/MS analysis (± 5 ppm exact mass accuracy)

showed a 367.0551 M+H+ molecular ion with brominated isotopic peak of 369.0529, and bromazolam-shared fragmentation pattern. The MW difference of 14.0160 between bromazolam and the suspected analogue suggested an extra methylene (-CH2) group but fragmentation data gave no indication of its structural position. Sample analysis by NMR at a referral laboratory reported ethylbromazolam, establishing the -CH2 group attachment to the methyl group on the triazole ring of bromazolam. The ethylbromazolam commercial reference material validated our GC-MS and LC-HR-MS/MS investigation of the unknown compound as ethylbromazolam based on retention time, fragmentation and isotopic pattern.

Discussion / Conclusion

Initial GC-MS bromazolam-related fragmentation observed in a Toronto street drug sample sold as alprazolam, followed by LC-HR-MS/MS investigation, NMR analysis and validation with reference standard led to the identification of ethylbromazolam. Since November 8, 2024, this new designer benzodiazepine continues to be identified, most commonly in samples submitted to Toronto's DCS as fentanyl.

Keywords

ethylbromazolam, designer benzodiazepines, novel psychoactive substance, drug checking

Immunosuppressive Drugs & Biomarkers

00067
Early Supratherapeutic Tacrolimus Exposure and Early Infection Risk After Lung Transplantation: Evidence of a Quantitative Exposure–Response Trend

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Early lower respiratory tract infection (LRTI) is a major cause of morbidity and mortality after lung transplantation. The first postoperative week represents a critical window during which infection risk may be influenced by perioperative organ support intensity and immunosuppressive exposure. Although tacrolimus overexposure is biologically plausible as a contributor to infection, its quantitative exposure–response relationship with early LRTI remains unclear. We aimed to develop and internally validate a model predicting early (≤7 days) LRTI, focusing on supratherapeutic tacrolimus exposure.

Materials and methods

We conducted a single-centre retrospective cohort study including 106 adult lung transplant recipients (2017–2025). Early LRTI was defined according to ATS/IDSA criteria within 7 days. Forty perioperative variables were screened using LASSO regression. Selected predictors were entered into multivariable Firth penalized logistic regression. Supratherapeutic tacrolimus exposure was modelled as tacrolimus_excess, defined as 0 for concentrations ≤15 ng/mL and (Tac − 15) for levels >15 ng/mL. Discrimination, calibration, decision-curve analysis, and 1,000-bootstrap internal validation were performed.

Results

Early LRTI occurred in 55/106 recipients (51.9%) and was associated with increased mortality (HR 3.86, P<0.001). The final model included preoperative oxygenation index, ECMO duration, mechanical ventilation duration, and tacrolimus_excess. Each 1 ng/mL increase above 15 ng/mL corresponded to a 12.2% higher odds of infection (OR 1.122; 95% CI 0.990–1.294; P=0.072), indicating a quantitative exposure–response trend. The model showed good discrimination (AUC 0.821), maintained after bootstrap validation (AUC 0.832), with acceptable calibration and clinical net benefit.

Discussion / Conclusion

Early post-transplant LRTI is common and strongly associated with mortality. A quantitative exposure–response signal was observed between supratherapeutic tacrolimus levels and infection risk, supporting the importance of early therapeutic drug monitoring and individualized dose adjustment after lung transplantation.

00114
Decoding the Optimal Window: A Real-World Data Odyssey of Tacrolimus Therapeutic Monitoring Across Transplant Populations

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Tacrolimus is essential to prevent allograft rejection but requires therapeutic drug monitoring (TDM) due to its narrow therapeutic index and pharmacokinetic variability. While guidelines recommend target ranges, real-world evidence across transplant types is limited. This study leverages real-world data to evaluate tacrolimus TDM patterns and assess current strategies, aiming to inform individualized therapy.

Materials and methods

We retrospectively analyzed tacrolimus TDM data from outpatients and inpatients at the First Affiliated Hospital of University of Science and Technology of China between January 1, 2024 and December 31, 2025. The study included liver, kidney, cardiac, and hematopoietic stem cell transplant recipients. Steady-state trough concentrations were measured, and statistical analyses compared concentration distributions and compliance rates across transplant types, care settings, and monitoring frequencies.

Results

A total of 21,234 TDM episodes were analyzed, comprising 17,280 outpatient visits and 3,954 inpatient admissions. The overall interquartile range (IQR) of tacrolimus concentrations was 4.35–7.46 ng/mL. Outpatient episodes ranged 4.72–7.23 ng/mL (compliance rate 69.23%), while inpatient episodes ranged 4.80–9.98 ng/mL (compliance 74.53%). Patients with multiple TDM sessions had significantly higher compliance than those with a single measurement ($P < 0.01$). By transplant type, IQRs and compliance rates varied significantly ($P < 0.05$): renal (4.57–7.32 ng/mL; 64.12%), liver (3.60–9.15 ng/mL; 64.26%), hematopoietic stem cell (3.57–9.11 ng/mL; 63.21%), cardiac (5.58–9.15 ng/mL; 84.71%), and lung transplantation (4.89–10.45 ng/mL; 65.76%).

Discussion / Conclusion

Considerable variability in tacrolimus concentrations and compliance across transplant populations suggests current therapeutic windows need population-specific refinement. The association between frequent TDM and improved compliance underscores the value of continuous monitoring. These real-world insights lay the groundwork for developing machine learning models integrating clinical and pharmacokinetic variables to predict optimal doses, ultimately advancing precision therapy.

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Keywords

Tacrolimus; Therapeutic drug monitoring; Transplant recipients; Therapeutic window; Real-world study; Individualized therapy

00117
A Unified Machine Learning Framework for Next-Visit Tacrolimus Concentration Prediction and Model-Informed Dose Individualization in Renal Transplant Recipients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Tacrolimus serves as a cornerstone immunosuppressant in kidney transplantation, playing a critical role in preventing allograft rejection and ensuring long-term graft survival. However, its clinical utility is constrained by a narrow therapeutic index and substantial inter-individual and intra-individual pharmacokinetic variability, which collectively present significant challenges for dose optimization and therapeutic management. This study aimed to develop and validate a unified machine learning framework capable of predicting next-visit tacrolimus trough concentrations and supporting model-informed dose adjustment in renal transplant recipients.

Materials and methods

We conducted a retrospective analysis of therapeutic drug monitoring data collected from 556 kidney transplant recipients, yielding a comprehensive dataset of 5,793 clinical records. A pharmacokinetically-inspired feature engineering approach was developed, specifically incorporating concentration-to-dose ratio dynamics to effectively capture individual patterns of drug clearance over time. To identify the optimal predictive model, we systematically compared eleven distinct prediction approaches, including advanced gradient boosting methods, ensemble techniques,

and conventional baseline models. Model performance was rigorously evaluated using patient-level 5-fold cross-validation to ensure generalizability and minimize overfitting.

Results

For next-visit concentration prediction, the tuned ensemble model demonstrated robust performance, achieving a coefficient of determination (R^2) of 0.66 and a mean absolute error (MAE) of 1.57 ng/mL. For dose prediction tasks, the ensemble model exhibited superior accuracy, attaining an R^2 of 0.89 and an MAE of 0.43 mg. SHAP analysis revealed that previous tacrolimus concentration, previous concentration-to-dose ratio, historical mean concentration-to-dose ratio, and patient age were the most influential predictors driving model predictions.

Discussion / Conclusion

The proposed unified framework demonstrates robust and reliable predictive performance for both concentration forecasting and dose adjustment support, effectively integrating pharmacokinetic principles with machine learning techniques. This approach offers a promising and clinically actionable tool for enhancing tacrolimus therapeutic drug monitoring and facilitating personalized medicine in renal transplant recipients.

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Immunosuppressants in Kidney Transplantation. Pharmaceuticals (Basel). 2026;19(1):165.

Keywords

Tacrolimus; Therapeutic drug monitoring; Renal transplantation; Machine learning; Dose individualization

00224
REtrospective analysis of the inFLuence of antibiotic treatments on the pharmacokinEtics of taCrolimus in kidney Transplant patients (REFLECT study)

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Kidney transplant recipients (KTR) require lifelong immunosuppression, typically based on tacrolimus (TAC), a first-line immunosuppressant with a narrow therapeutic index. TAC pharmacokinetics (PK) exhibit considerable intra- and inter-patient variability. Emerging evidence suggests the gut microbiome may modulate TAC dose requirements. Given the frequent use of antibiotics (ATB) in this population, investigating the impact of ATB on TAC PK represents a clinically relevant approach to probing the gut microbiome's role in TAC PK variability.

Materials and methods

REFLECT is a retrospective, longitudinal, monocentric trial designed to investigate how TAC PK evolve during antibiotherapy in KTRs. Clinical and PK data were collected on 4 occasions: (i) baseline (pre-ATB), (ii) infection diagnosis before ATB initiation, (iii) during ATB and (iv) 1-month after ATB discontinuation. Data were analysed using mixed-effects modelling.

Results

Data from 89 KTR (107 ATB regimens and 760 TAC Ctrough) were analysed. Three PK variables were modelled: TAC dose-adjusted concentrations (TAC Ctrough/(dose/kg)), TAC Ctrough and TAC dose/kg.

In addition to age, CYP3A5 genotype, haematocrit, creatinine, CRP, period post-transplantation and standard of care ATB prophylaxis, ATB intake was significantly associated with all three TAC PK parameters. During ATB treatment, TAC dose-adjusted concentrations increased by 15.3%. TAC Ctrough alone increased by 16.5% despite stable dosing. One month after ATB discontinuation, TAC dose/kg decreased by 12.2%, restoring Ctrough to baseline levels.

Moreover, an interaction between ATB effect on TAC PK parameter and ATB spectrum was observed, indicating that broad-spectrum ATB associated with higher C. difficile infection risk are linked to greater increase in dose-adjusted TAC Ctrough.

Discussion / Conclusion

TAC levels increase significantly during ATB regimens, yet TAC daily dose remains unchanged by the clinicians. The interaction with antibiotics associated with C. difficile infection risk supports the hypothesis that ATB-induced gut microbiome alterations may influence TAC PK. These findings highlight the need for close TAC monitoring during and after antibiotherapy.

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Keywords

Tacrolimus, antibiotherapy, anti-infective drugs, kidney transplantation, therapeutic drug monitoring, gut microbiome, pharmacokinetics

00258
Beware the Generic Immunosuppressants – Cheaper But Not Necessarily Safe!

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

In solid organ transplants (SOT) generic immunosuppression dominates sales. There is a growing concern that properties of generic vs brand immunosuppression in healthy volunteers may not reflect those in SOTs. We aimed to simultaneously assess the bioequivalence of generic formulations of tacrolimus (Ascend) and mycophenolate mofetil (Accord) in stable kidney transplant recipients (KTR), using Prograf (Astellas) and CellCept (Roche) as reference products.

Materials and methods

KTRs on Prograf (Tac) and CellCept (MMF) were randomized to one of four treatment sequences of original/generic Tac and MMF, using a single cross-over design. Two pharmacokinetic investigations were performed, collecting 14 blood samples for both Tac and MMF over 12 hours. The criteria for bioequivalence were achieved if the 90% confidence interval (CI) of the geometric mean of the ratio between generic and original was between 0.90 to 1.11 for tacrolimus $AUC_{0\text{-}12}$, and between 0.80-1.25 for MMF $AUC_{0\text{-}12}$ and C_{max} for both drugs.

Results

In total 36 KTR (61% males, 44% >60 years, 17% early posttransplant) were included, and provided two evaluable pharmacokinetic investigations. Generic Tac

was not bioequivalent, showing AUC_{0-12} and C_{max} ratios [90% CI] of 1.08 [1.02, 1.16] and 1.19 [1.1, 1.29], respectively. Importantly, the most extreme differences were seen in patients above 60 years old. Tac C_0 was similar with a ratio of 1.01 [0.94, 1.08]. Generic MMF was bioequivalent with AUC_{0-12} and C_{max} ratios of 1.07 [1.0, 1.13] and 1.12 [1.03, 1.21], respectively.

Discussion / Conclusion

This is the first simultaneous assessment of generic Tac and MMF in KTR. We were unable to demonstrate bioequivalence for the tested generic Tac, despite its EMA approval. Importantly, the discrepancy in Tac AUC_{0-12} and C_{max} was not detected by traditional pre-dose concentration monitoring. Current FDA/EMA requirements for generic immunosuppressants risk SOT patient safety. Our findings highlight the necessity of validating bioequivalence in actual clinical populations rather than healthy volunteers.

Keywords

generic drugs

bioequivalence

kidney transplantation

tacrolimus

mycophenolate

00320
Therapeutic Drug Monitoring of Tacrolimus in Liver Transplant Recipients with Post-Transplant Cholestasis: Accuracy of an Electrochemiluminescence Immunoassay

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

During episodes of cholestasis, blood concentrations of tacrolimus (TAC) metabolites may increase. Because immunoassays may exhibit antibody cross-reactivity with TAC metabolites, measured whole-blood TAC concentrations can potentially be overestimated. (1) The aim of this study was to evaluate the impact of post-transplant cholestasis on the analytical accuracy of tacrolimus measurement using an electrochemiluminescence immunoassay (ECLIA) in liver transplant recipients.

Materials and methods

A total of 160 whole-blood samples were included. Samples were stratified into four subgroups according to plasma conjugated bilirubin concentrations: < 3 µmol/L, 3-30 µmol/L, 30-150 µmol/L, and > 150 µmol/L (40 samples per subgroup). Tacrolimus

concentrations were measured using the Roche ECLIA immunoassay on a cobas e801 analyzer, following the manufacturer's instructions. A validated LC-MS/MS method (Xevo TQ-S micro, Waters) was used as the reference method. Method comparison was performed using Passing-Bablok regression and Bland-Altman analysis.

Results

Passing–Bablok regression and Bland-Altman analysis demonstrated strong agreement between the ECLIA immunoassay and LC-MS/MS (n = 160), with a slope of 1.00 (95% CI: 0.983-1.035) and an intercept of 0.20 (0-0.297). Post-transplant cholestasis had no significant impact on the analytical accuracy of the ECLIA assay. In the subgroup with plasma conjugated bilirubin concentrations >150 µmol/L (median: 326 µmol/L), the Passing-Bablok regression equation was: [TAC-ECLIA] = 1.03 (95% CI: 0.962-1.099) × [TAC-LC-MS/MS] + 0.11 (0.962-1.099).

Discussion / Conclusion

The ECLIA method is suitable for routine therapeutic drug monitoring of tacrolimus in liver transplant recipients, including patients with post-transplant cholestasis.

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Keywords

Tacrolimus - Electrochemiluminescence Immunoassay

00323
A Study on Tacrolimus Individualized Medication in Renal Transplant Patients Based on Transplantation Method and Gene Detection

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

To investigate the effects of CYP3A5*3, MDR1 G2677T/A, MDR1 C3435T, MDR1 C1236T gene polymorphisms and renal transplantation modality on tacrolimus(TAC) concentration in renal transplantation patients, to reveal the correlation between TAC concentration and blood, liver and kidney indexes.

Materials and methods

A quality control study was conducted for two TAC blood concentration monitoring methods, EMIT and CMIA. Patients were divided into ABOi-KT and ABOc-KT groups, and differences in C_0, D, C_0/D, and bio-chemical indices were analyzed. Pyrosequencing was used to genotype four single nucleotide polymorphisms (SNPs): CYP3A5*3, MDR1 G2677T/A, MDR1 C3435T, and MDR1 C1236T. The impacts of SNPs on postoperative TAC concentration and biochemical indices in kidney transplant recipients were compared.

Results

Quality control results indicated that the actual detection results of the quality control samples at all three levels were in control for both methods.302 kidney transplant patients were divided into the ABOi-KT group and the ABOc-KT group. In the ABOi-KT group, HGB, HCT, and RBC at 3 days were significantly positively correlated with TAC-C_0/D ($P<0.05$). In the ABOc-KT group, NE%, HGB, HCT, RBC, BG, and AST at 3 days, and WBC, NE%, and BG at 30 days were significantly positively correlated with TAC-C_0/D ($P<0.05$). To explore the impacts of SNPs, 187 patients were included. Only CYP3A53 polymorphism was significantly correlated with TAC-C_0/D, with the GG gen-otype being significantly higher than the AA and AG genotypes ($P<0.05$). MDR1C3435T and MDR1 C1236T polymorphisms were significantly correlated with AST values in kidney transplant recipients, with the TT genotype showing higher AST values than the CC genotype.

Discussion / Conclusion

EMIT and CMIA showed good consistency. The type of transplantation significantly affected postoperative TAC concentration and some biochemical indices, with differences observed at 3 and 30 days postoperatively. CYP3A5*3 polymorphism influenced TAC-C_0/D, while MDR1 C3435T and MDR1 C1236T polymorphisms affected AST values in kidney transplant recipients.

Keywords

Kidney Transplantation; Tacrolimus; Genetic Polymorphism; Drug Concentration

00364
Clinical safety of concomitant administration of immunosuppressive drugs and calcium supplementation in kidney transplant recipients using VAMS

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Kidney transplant (KTx) recipients have increased risk of bone-diseases and daily calcium supplementation is often warranted. Calcium interacts with mycophenolate mofetil (MMF) and a 2-3 hour time-shifted administration is therefore recommended. Theoretically, tacrolimus may experience the same interaction. We investigated the potential interactions between 500 mg calcium twice daily and these immunosuppressants in KTx recipients, to determine if a time-shifted administration is necessary.

Materials and methods

KTx recipients on twice daily MMF and tacrolimus at steady-state were included for two 12-hour pharmacokinetic (PK) investigations, both with and without a one-week twice daily 500 mg calcium carbonate. Samples were obtained by finger-prick using volumetric absorptive microsampling (VAMS). Each 12-hour PK profile consisted of supervised clinical samples followed by 7 self-collected VAMS samples at home at predefined intervals. The potential interactions on MMF and tacrolimus were assessed by with:without-ratios of area under the curve (AUC0-12) and maximum concentration (Cmax) per EMA’s guidelines for bioequivalence.

Results

Twenty-five included patients provided two 12-hour PK profiles. The mycophenolate AUC0-12 ratio was 0.91 (90 % confidence interval [CI], 0.80 – 1.03) and the Cmax ratio was 0.79 (90 % CI, 0.65 – 0.97). Additionally, the mycophenolate Tmax ratio was 1.21 (90 % CI, 0.84 – 1.76). For tacrolimus, the AUC0-12 and Cmax ratio was 1.02 (90 % CI, 0.94 – 1.11), and 0.97 (90 % CI, 0.86 – 1.08), respectively. Sampling success rates were >99% for supervised samples compared to >95% for self-collected samples by patients.

Discussion / Conclusion

Concomitant MMF and calcium supplementation showed a minor, but not clinically significant, decrease in AUC0-12. A moderate decrease in Cmax and increase in Tmax can be explained by a delayed absorption phase. No relevant alteration of tacrolimus PK was observed with concomitant calcium. Our findings support that concomitant administration of calcium supplementation and mycophenolate/tacrolimus is clinically applicable, and interaction studies are feasible using microsampling.

00376
Congestive hepatopathy after heart transplantation: The role of therapeutic drug monitoring in managing tacrolimus overexposure

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Tacrolimus presents the cornerstone of immunosuppressive therapy in heart transplantation. It is characterized by a narrow therapeutic index and marked pharmacokinetic variability, making therapeutic drug monitoring (TDM) essential. Its hepatic metabolism, mainly mediated by cytochrome P450 enzymes, exposes patients to a high risk of overexposure in the presence of impaired liver function.

Materials and methods

We report a single-center observational case of a heart transplant recipient at Sahloul Hospital, Sousse. Tacrolimus plasma concentrations were measured using immunoassay techniques. Clinical and biological data were collected from the hospital information systems.

Results

A 56-year-old patient underwent heart transplantation in October 2025. Initial immunosuppression consisted of tacrolimus (6 mg twice daily), mycophenolate mofetil, and corticosteroids. Following neurological toxicity symptoms, and a tacrolimus trough concentration (C0) peaking at 40 ng/mL, tacrolimus was discontinued and close biological monitoring was initiated, including TDM and assessment of hepatic and renal function leading to a progressive decrease in trough levels with neurological improvement. Liver tests showed abnormalities suggestive of hepatic injury, with mild transaminase elevation (AST 66 IU/L, ALT 73 IU/L), marked cholestasis (alkaline phosphatase 198 IU/L, γ-GT 482 IU/L), and impaired synthetic function (albumin 24.1 g/L). Renal function was preserved. No drug–drug interactions explaining the overdose were identified. Reintroduction of tacrolimus at a reduced dose (3 mg twice daily) resulted in re-accumulation (C0 = 29 ng/mL) confirming persistent hepatic metabolic impairment

Discussion / Conclusion

This case highlights the major impact of congestive hepatopathy on tacrolimus exposure. This condition can durably impair hepatic cytochrome P450 activity involved in tacrolimus metabolism following a heart transplantation. This case underscores the central role of TDM for early detection of tacrolimus overexposure and the need for heightened vigilance in heart transplant recipients at risk of congestive hepatopathy to prevent severe toxicities, that remains insufficiently documented in real-world clinical practice.

Keywords

Congestive hepatopathy

tacrolimus

therapeutic drug monitoring

00384
Drug-drug Interaction between Fluconazole and Tacrolimus: A Case report highlighting the role of Therapeutic Drug Monitoring in kidney transplantation

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Tacrolimus is a calcineurin inhibitor with a narrow therapeutic index and marked interindividual pharmacokinetic variability. It is mainly metabolized by cytochrome P450 3A4/5. Concomitant use of enzymatic inhibitors, such as azole antifungals, may significantly increase tacrolimus blood concentrations, leading to toxicity. This justifies their restricted use in kidney transplant recipients.

Materials and methods

We report a single-center observational case of drug interaction between tacrolimus and fluconazole highlighting the essential role of therapeutic drug monitoring (TDM) in a kidney transplant recipient at Sahloul Hospital, Sousse. Tacrolimus plasma concentrations were measured using immunoassay techniques. Clinical and biological data were collected from the hospital information systems

Results

A 22-year-old female kidney transplant recipient, transplanted in 2015, was receiving a stable tacrolimus regimen of 3 mg twice daily, with a mean trough concentration of 8.18± 1,68 ng/mL, within the therapeutic range for more than two years of monitoring. In December 2025, fluconazole therapy was initiated for neuro-meningeal cryptococcosis. To prevent toxicity, the tacrolimus dose was reduced to 0.5 mg twice daily. Despite the dose adjustment, tacrolimus trough concentrations increased markedly following the initiation of fluconazole, peaking at 26.38 ng/mL in the absence of further dose modifications. Tacrolimus was therefore discontinued in response to the persistent elevation in drug levels. A prolonged-release formulation of tacrolimus, which would have been preferable in this clinical context, was not available and immunosuppressive therapy was switched to cyclosporine taking into consideration the planned one-year duration of fluconazole treatment in this context.

Discussion / Conclusion

This case highlights the clinical significance of the fluconazole–tacrolimus interaction and emphasizes the critical role of TDM in preventing toxicity. When tacrolimus exposure remains difficult to control despite dose reduction and alternative formulations are unavailable, switching to another calcineurin inhibitor may represent a rational therapeutic option particularly when prolonged antifungal therapy is required.

Keywords

Drug interaction

tacrolimus

fluconazol

therapeutic drug monitoring

00391
Vitamin A Is Independently Associated with Tacrolimus Exposure and Predicts Short-Term Pharmacokinetics in Liver Transplant Recipients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Tacrolimus exhibits substantial pharmacokinetic variability in liver transplant recipients, necessitating therapeutic drug monitoring (TDM). Fat-soluble vitamins (A, D, E, K) share common pathways of intestinal absorption, hepatic metabolism, and transport with tacrolimus, suggesting potential pharmacokinetic interactions. However, the clinical relevance and temporal dynamics of these interactions remain unclear and have not been systematically evaluated in transplant populations.

Materials and methods

Plasma samples and corresponding demographic and clinical data were collected from adult liver transplant recipients. Tacrolimus dose-adjusted trough concentrations (C_0/D) were calculated. Vitamins A, D, E, and K were quantified using liquid chromatography–tandem mass spectrometry. Linear mixed-effects models with patient-level random intercepts were used to assess associations between vitamin concentrations and tacrolimus C_0/D, adjusting for clinically relevant covariates including demographics, concomitant medications, and liver and renal function. Hierarchical adjustment across predefined covariate levels and additional sensitivity

analyses were performed to confirm robustness. A time-lag analysis was conducted to assess whether vitamin levels predicted subsequent tacrolimus C_0/D.

Results

A total of 175 samples from 32 recipients were analyzed. Vitamin A showed a consistent negative association with tacrolimus C_0/D ($\beta = -0.311$, $p < 0.001$), remaining significant across hierarchical adjustment and sensitivity analyses. Vitamin K demonstrated a modest negative association in unadjusted analysis ($\beta = -0.071$, $p = 0.041$), which became nonsignificant after full adjustment. Time-lag analysis indicated that vitamin A levels predicted tacrolimus C_0/D within a median interval of 2 (2–4) days. A concurrent inverse association between tacrolimus C_0 and vitamin A was observed ($\beta = -0.161$, $p = 0.002$).

Discussion / Conclusion

This study suggests that vitamin A is independently associated with tacrolimus disposition. Its ability to predict short-term changes in drug exposure positions it as a readily available clinical biomarker to refine precision dosing. Incorporating vitamin A monitoring into routine practice could potentially reduce the risks of rejection or toxicity in liver transplant recipients

Keywords

Tacrolimus; Liver Transplantation; Vitamin A; Therapeutic Drug Monitoring; Mixed-Effects Modeling

00398
EVsDNA 5hmC Signatures Predict Infliximab Response Beyond Drug Exposure: A Multi-Omics Precision Therapeutics Strategy in IBD

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Despite therapeutic drug monitoring (TDM), up to 40% of patients with inflammatory bowel disease (IBD) exhibit primary non-response to infliximab (IFX). Our previous findings showed that adequate drug exposure alone does not fully explain treatment heterogeneity. We therefore investigated whether circulating epigenetic signatures could complement TDM and enable mechanism-informed precision therapeutics.

Materials and methods

In a prospective cohort of 54 IBD patients initiating IFX, pre-treatment plasma samples were collected. Genome-wide 5-hydroxymethylcytosine (5hmC) profiling of extracellular vesicle-derived DNA (EVsDNA) was performed using the 5hmC-SEAL liquid biopsy platform. Patients were randomly divided into training (n=32) and validation (n=22) cohorts. Lasso regression was used to construct a predictive model. Functional enrichment and multi-omics integration analyses were conducted to explore biological relevance.

Results

Eight 5hmC markers discriminated responders from non-responders. The predictive model demonstrated strong performance (AUC=0.94 in training; robust performance in validation), outperforming conventional clinical indicators and drug exposure metrics alone. GPD1L emerged as the most informative locus, with significantly higher 5hmC enrichment in responders (p=0.0026). Elevated GPD1L levels correlated with lower fecal calprotectin and systemic inflammation. Importantly, single-cell transcriptomic analysis of colonic tissue confirmed higher GPD1L expression in responders compared with non-responders, consistent with peripheral EVsDNA findings. Pathway analysis indicated enrichment in immune regulation and T-cell differentiation pathways, suggesting metabolism–epigenetic coupling via the α-KG–TET–5hmC axis.

Discussion / Conclusion

Circulating 5hmC profiling provides a minimally invasive biomarker framework that complements TDM by incorporating biological response heterogeneity. Integrating pharmacokinetics with epigenetic remodeling advances precision therapeutics and supports mechanism-based stratification of IFX therapy in IBD.

Keywords

Inflammatory bowel disease, infliximab, therapeutic drug monitoring, epigenetics, 5-hydroxymethylcytosine, extracellular vesicles, precision medicine.

00409
Chronic Kidney Disease After Lung Transplantation: Impact of Tacrolimus Exposure and Clinical Complications Post-Transplantation

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Lung transplant recipients (LTR) frequently develop chronic kidney disease (CKD). Risk factors for CKD after lung transplantation are often non-modifiable. A high tacrolimus metabolizing phenotype defined by a low predose concentration-to-dose ratio ([C0/D]), has been shown to negatively impact kidney function after heart, liver, and kidney transplantation. Our aim was to investigate the determinants of CKD in the lung transplant population and the [C0/D] ratio in particular.

Materials and methods

A retrospective study including all LTR transplanted between 2001 and 2025 at Erasmus MC Rotterdam. Patients had to be alive at 6 months and receive immediate-release tacrolimus. Variables on kidney function, known risk factors post-transplant, tacrolimus C0 and dose were collected. LTRs were categorized as fast, slow or intermediate metabolizers according to their median [C0/D] ratio.

Results

The analysis included 348 LTRs. Median age was 58.8 years and 179 were male (52%). The most common transplant indications were ILD (42%), COPD (40%). Median follow-up was 57.5 months. Sixty-eight LTR (22.5%) died during follow-up. Median baseline eGFR decreased from 95 ml/min/1,73m² to 44 ml/min/1.73m² during follow-up. 50/348 LTR (14.4%) progressed to CKD stage 5, of which 29 started dialysis (59%), while 13/49 were treated conservatively. A total of 17/49 (34.6%) of the CKD patients received a kidney transplant. Median time to CKD stage 5 was 50 months. Metabolizers were categorized slow with a [C0/D] ratio <1.16 ng/ml/mg, intermediate between 1.16-1.83 ng/ml/mg and fast >1.83 ng/ml/mg. Linear mixed-effects modelling showed that intermediate metabolizers (first 3 months) and fast metabolizers (at any timepoint) experienced greater kidney function decline after transplantation compared to slow metabolizers.

Discussion / Conclusion

CKD frequently complicates lung transplantation. This study demonstrates that LTRs with a higher tacrolimus metabolizing phenotype have a higher degree of CKD in the long-term. Faster metabolizers may benefit from dose reduction or switching tacrolimus formulation.

Reference(s)

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https://pubmed.ncbi.nlm.nih.gov/27003330/

Keywords

Tacrolimus Drug metabolism Lung transplantation

00452
Immunosuppressant therapeutic drug monitoring in whole blood on volumetric adsorptive microsamples: a development on i601 mass spec by Roche®

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Liquid chromatography coupled with mass spectrometry (LC-MS/MS) is the gold standard technique for immunosuppressant therapeutic drug monitoring (TDM). During the evaluation of the i601 Cobas by Roche®, which began in October 2025 at Saint-Louis Hospital in Paris, we aimed to adapt and validate locally the Ionify immunosuppressant technique (iISD) on whole blood to volumetric adsorptive microsamples (VAMS; Mitra® tips).

Materials and methods

i601 Cobas and Ionify immunosuppressant reagents and solvents were kindly provided by Roche (contract 2025-076-46/1). Calibrators (Clinical Whole Blood Calibrator Set Lyoph; Recipe Waters®) and quality control (Immunosuppressants Whole Blood Control; Chromsystem®) were loaded on 10 µL Mitra® tips, then dried

at ambient room temperature for at least 2 hours. The Mitra® tips were cut and mixed with 400 µL (iPTWB Roche®) plus 50 µL (iISD R0 Roches®) then shaken for 10min (3,000 RPM) followed by 10-min sonication. After 4-min centrifugation (10,000 RPM) 420 µL of the supernatant were discarded and loaded on i601 Cobas. Raw data were collected, and linear regression was used to plot the peak height ratio of cyclosporin, tacrolimus, everolimus and sirolimus to their stable labeled isotopes versus theorical concentrations. Linearity, repeatability and lower limit of quantification were assessed. Intermediate fidelity and accuracy are on-going.

Results

Preliminary results show good linearity (R^2>0.99) for the four molecules and satisfactory repeatability for cyclosporine and tacrolimus (CVs and relatives biases below 15%) and adapted LLOQ for cyclosporin (20 ng/mL) and tacrolimus (1.5 ng/mL). Due to wide analytical variability, an optimization of pretreatment is necessary for sirolimus and everolimus (data not shown).

Discussion / Conclusion

The i601 LC–MS/MS system (Roche®) showed robust analytical performance for immunosuppressant TDM while offering automated workflow. On-going development of immunosuppressant on 10 µL VAMS displays promising results for cyclosporin and tacrolimus, making it possible to implement this semi-automated method on a daily basis with significant clinical benefits.

00553
6-Thioguanine Nucleotide-Guided personalization of thiopurines in Tunisian inflammatory bowel disease patients

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The immunosuppressive therapy for inflammatory bowel disease (IBD) is based on thiopurines, particularly azathioprine (AZA) and 6-mercaptopurine. However, their narrow therapeutic window and marked inter-individual variability in metabolism create significant challenges in achieving optimal efficacy and safety. The active metabolites, 6-thioguanine nucleotides (6-TGN), mediate both therapeutic effects and meylotoxicity. Therapeutic drug monitoring (TDM) of 6-TGN provides a strategy to individualize treatment and improve patient outcomes.

Aim:To evaluate the clinical outcome of 6-TGN monitoring in optimizing thiopurines therapy in Tunisian patients with IBD.

Materials and methods

We conducted a retrospective cross sectional study including 140 Tunisian patients with IBD receiving thiopurine therapy. Blood samples were collected at steady state

(continuous treatment for at least three weeks), two hours after medication intake, and 6 -TGN peak concentrations were quantified using high-performance liquid chromatography; Dose adjustments were performed to target a 6-TNG levels between 235 and 450 pmol/8 × 10^8 red blood cells (RBCs). Associations between 6-TGN levels and hematological parameters (haemoglobin level, leukocyte and neutrophil count) were assessed using Pearson's correlation coefficient.

Results

Our study included 140 patients with IBD. The mean age was 38.6 ± 13.3 years with a sex ratio of 0.87. The mean 6-TGN concentration was 386.2 ± 258.9 pmol/8×10^8 RBCs. Following initial dosing, only 49% of patients achieved therapeutic target concentrations. TDM-guided dose adjustment significantly improved target attainment, increasing the proportion of patients within the therapeutic range to 69%. Furthermore, 6 - TGn concentrations demonstrated significant inverse correlations with hemoglobin levels, total leukocyte count, and neutrophil count.

Discussion / Conclusion

6-TGN monitoring enhances the optimization of thiopurine therapy in Tunisian IBD patients by improving target concentration attainment. Still, personalizing the treatment by combining TDM with pharmacogenetic testing for TPMT and NUDT15 variants, alongside pharmacokinetic modelling, could further improve both safety and effecacy for each patient.

Keywords

inflammatory bowel disease; azathioprine; 6-thioguanine nucleotides (6-TGN), Therapeutic drug monitoring

00637
Machine Learning-Based Model-Informed Precision Dosing for Tacrolimus in Patients Undergoing Kidney Transplantation

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Machine learning (ML)-based dosing strategies provide a promising tool to individualize recommendations and optimize therapeutic drug exposure. This is particularly important for drugs with a narrow therapeutic index and high inter- and intra-patient pharmacokinetic variability, such as tacrolimus. The aim of this study was to compare the predictive performance of different ML algorithms for tacrolimus dose prediction in a cohort of Tunisian kidney transplant recipients.

Materials and methods

This cross-sectional study was carried out in the Clinical Pharmacology Department at Fattouma Bourguiba-Monastir. Eligible participants were kidney transplant patients who received a tacrolimus and requiring therapeutic drug monitoring (TDM). Seven ML algorithms were assessed. The target variable was the dose-to-concentration ratio at the current visit (N). Input features included the dose-to-concentration ratio at the previous visit (N–1), clinical and demographic data. Model performance was assessed using mean square error (MSE), coefficient of determination R^2, and Pearson correlation coefficient and compared between the early (0–3 months; P1) and late (>3 months; P2) post-transplantation periods.

Results

A total of 1800 C0 from 263 adult kidney transplant recipients were included, with an average age of 34±11 years and an average body weight of 64±11 kg. In the early period, Bayesian Ridge regression showed the best performance (MSE = 0.27;Pearson r = 0.83) (Table I). During the late, only Bayesian Ridge and Decision Tree models retained acceptable predictive accuracy (MSE ≈ 0.82–0.83; Pearson r ≈0.73) (Table I).

Table I: Performance metrics for ML tested models

	P1 (0-3 months)			P2 (>3months)		
Model	MSE	R^2	Pearson Correlation	MSE	R^2	Pearson Correlation
Decision Tree	0.28	0.66	0.81	0.83	0.53	0.74
XGBoost	0.39	0.56	0.82	1.21	0.32	0.73
SVM	0.58	0.33	0.82	1.26	0.29	0.73
Bayesian Ridge	0.27	0.7	0.82	0.82	0.54	0.73
Lasso	0.28	0.66	0.82	0.83	0.53	0.73
Random Forest	0.28	0.66	0.81	0.83	0.53	0.74
Gradient Boosting	0.41	0.54	0.82	0.41	0.54	0.73

Discussion / Conclusion

This study demonstrated that Bayesian Ridge regression-based TDM of Tac provides accurate estimates of drug exposure during both periods. This ML model surpasses our previously published LSTM-based approach. Implementing model-informed precision dosing using ML-based approaches for TDM may significantly improve patient outcomes and reduce the risk of acute complications

Keywords

Machine Learning, tacrolimus; kidney transplant; dose prediction

00668
Analysis of 949 Immunosuppressant Therapeutic Drug Monitoring Samples: A Descriptive and Analytical Study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic Drug Monitoring (TDM) is essential in solid organ transplantation for optimizing immunosuppressive therapy, given the marked pharmacokinetic variability. This study aimed to characterize prescribing practices, dosing strategies and the extent of pharmacokinetic variability of immunosuppressant drugs.

Materials and methods

A retrospective and descriptive study was conducted to evaluate hospital TDM practices. Blood samples from kidney transplanted patients at a Tunisian hospital were collected over a twenty-month period. Whole-blood concentrations of tacrolimus, cyclosporine and sirolimus and plasma levels of Mycophenolic Acid (MPA) were measured using ElectroChemiLuminescence ImmunoAssay (ECLIA). MPA exposition was estimated using a Bayesian pharmacokinetic model. Data analysis were performed using Microsoft Excel and IBM SPSS 26.0.

Results

Our study included 281 patients with a mean age of 37±14.3 years. Tacrolimus was the most frequently monitored immunosuppressant, accounting for 73.1% (n=694) of all assays. The primary indication for TDM prescription was routine therapeutic monitoring (79.9%, n = 758). The mean daily dosage of tacrolimus was 0.085±0.06 mg/kg achieving an average trough concentration of 7.63±4.69 ng/mL, 12.0% of patients were under-dosed and 16.4% were above target concentrations, leading to 109 dosage adjustments (0.59 per patient). The mean trough concentration adjusted to daily dosage (C0/D) was 127.5 and was significantly correlated to post-transplant delay and haematocrit value ($p < 0.05$) but not to serum creatinine or CRP levels. Monitoring for other immunosuppressants showed an MPA AUC0-12h of 49.96±24.25 mg·h/L, a Sirolimus trough concentration of 9.3±4.4 ng/mL and Cyclosporine trough concentration of 129.56±70.9 ng/mL.

Discussion / Conclusion

Our study confirms that a considerable proportion of patients required dose adjustments to maintain an optimal balance between graft protection and the risk of drug-related toxicity. . These findings underscore the essential role of TDM in optimizing immunosuppressive therapy and improving long-term transplant outcomes through precision medicine.

00679
Absence of bioequivalence for generic formulations of mycophenolate mofetil if combined with proton pump inhibitor

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Since the patent of mycophenolate mofetil (MMF) expired, several generic versions have become available. MMF absorption depends on intragastric pH, with better tablet dissolution at lower pH. Many transplant recipients use proton pump inhibitors (PPIs) which increase gastric pH. Bioequivalence between generic MMF variants and the innovator in combination with a PPI has not been previously evaluated.

Materials and methods

In vitro dissolution of commercially available 500mg MMF tablets (innovator and generics A, B, C, D and E) was assessed at pH 1.0, pH 4.5 and pH 6.8. Subsequently, in vivo bioequivalence of the innovator and two generic variants (A and B) was studied in 12 healthy subjects pretreated with pantoprazole. Blood samples were collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours after a single 1000 mg MMF dose to determine pharmacokinetic parameters AUC(0-t), AUC(0-∞), Cmax and Tmax. This study was METC approved and CTIS registered under registration number 2024-517043-32-00 (IPCOM).

Results

Dissolution of MMF at pH 1.0 and 6.8 was similar across formulations. At pH 4.5, approximating gastric conditions during PPI use, generic A and C dissolved faster and generic B and D slower than the innovator. Similarity factors based on the dissolution data were below 50 for generic A (47.5), B (49.2) and D (46.3). The in vivo study showed that neither generic A nor generic B was bioequivalent to the innovator MMF. The 90% confidence interval of the geometric mean ratio (AUC generic/innovator) was 111.47% (98.45% -126.21%) for generic A, and 83.40% (73.66% - 94.43%) for generic B.

Discussion / Conclusion

In vitro dissolution and in vivo exposure to mycophenolic acid varies significantly between innovator and generic MMF formulations in an environment with a pH of 4.5. This lack of bioequivalence is clinically relevant for transplant recipients co-treated with a PPI.

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Keywords

bioequivalence, mycophenolate mofetil, pharmacokinetics, transplantation

00683
Prediction of Tacrolimus-Posaconazole Interactions in Renal Transplant Patients with Different CYP3A5 Genotypes Based on Physiological Pharmacokinetic Models

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Posaconazole, a second-generation triazole antifungal used for the prevention or treatment of invasive fungal infections, has been shown to markedly increase tacrolimus exposure in vivo when coadministered, potentially leading to clinically significant adverse events. A physiologically based pharmacokinetic (PBPK) model was developed to predict tacrolimus–posaconazole interactions in renal transplant recipients with different CYP3A5 genotypes, to inform tacrolimus dose adjustment in clinical practice.

Materials and methods

To obtain the critical inhibition parameters, in vitro enzyme kinetic studies were first conducted. Based on these data, a whole-body physiologically based pharmacokinetic (PBPK) model for TAC was developed and validated in PK-Sim. A published, validated posaconazole PBPK model was applied concurrently. Model performance was evaluated against published pharmacokinetic data in healthy volunteers receiving tacrolimus with posaconazole. Virtual Chinese renal transplant recipient was generated by incorporating population-specific physiological parameters, including CYP3A5 genotype–dependent enzyme expression.

Results

In vitro experimental results demonstrating that POSA acts as a potent reversible competitive inhibitor of CYP3A4/5-mediated TAC metabolism. The tacrolimus PBPK model adequately captured pharmacokinetics across CYP3A5 genotypes, and tacrolimus pharmacokinetics during coadministration with posaconazole were also predicted. Compared with CYP3A5 expressers, nonexpressers showed greater variability in tacrolimus whole-blood concentrations and greater susceptibility to posaconazole-mediated interactions. The CYP3A5*3*3 genotype was associated with higher Cmax and AUC. Dose optimization simulations suggested that after 6–7 days of posaconazole coadministration, nonexpressers were predicted to require reducing tacrolimus dosing frequency from every 12 h to every 24 h to maintain trough concentrations within 8–15 ng/mL, whereas a 50% dose reduction was predicted in expressers.

Discussion / Conclusion

A tacrolimus–posaconazole PBPK drug-durg interaction model was developed in renal transplant recipients and used to simulate tacrolimus trough concentrations across CYP3A5 genotypes and dosing regimens, supporting genotype-informed coadministration in clinical practice.

Keywords

physiologically based pharmacokinetic; CYP3A5; tacrolimus; posaconazole; drug–drug interactions

00695
Limited sampling strategy-based tacrolimus exposure assessment and CYP3A5 pharmacogenetics in pediatric kidney transplant recipients

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Tacrolimus shows high pharmacokinetic variability and requires therapeutic drug monitoring to optimize exposure in transplant recipients. At La Paz University Hospital, a limited sampling strategy (LSS) based on concentrations at 0, 1 and 3 hours post-dose is routinely used to estimate AUC_{0-24}. This model was developed from a cohort of pediatric kidney transplant recipients treated at our center (1). We aimed to characterize tacrolimus pharmacokinetics using LSS profiles and explore associations between concentration timepoints, systemic exposure, dose, apparent clearance and CYP3A5 genotype.

Materials and methods

A retrospective analysis of 38 tacrolimus pharmacokinetic profiles using LSS (C0, C1 and C3) in pediatric renal transplant recipients receiving twice-daily Prograf® was performed. Tacrolimus exposure (AUC_{0-24}) was estimated using the previously described LSS model. Apparent clearance was calculated as dose/AUC_{0-24}. Differences between sampling points (C1−C0 and C3−C1) characterized absorption dynamics. Associations between variables were assessed using Spearman

correlation and comparisons across CYP3A5 genotypes using Kruskal–Wallis and Dunn post-hoc tests.

Results

Mean tacrolimus concentrations were 7.6 ± 2.3 ng/mL (C0), 29.6 ± 13.4 ng/mL (C1) and 16.4 ± 5.4 ng/mL (C3). Moderate correlations were observed between sampling points (C0–C1 ρ=0.37, p=0.024; C1–C3 ρ=0.55, p<0.001; C0–C3 ρ=0.45, p=0.004). Dose correlated with tacrolimus exposure (ρ=0.41, p=0.010). The early absorption increment (C1−C0) was strongly associated with AUC (ρ=0.65, p<0.001), whereas a larger decline between C1 and C3 was associated with lower AUC (ρ=−0.44, p=0.006). Patients with C0 <5 ng/mL showed lower AUC values than those ≥5 ng/mL (median 184 vs 289 ng·h/mL, p=0.007). CYP3A5 genotype influenced dose requirements (p=0.0046) and clearance (p=0.0128), whereas AUC did not differ between genotypes, likely reflecting dose adjustments during routine TDM.

Discussion / Conclusion

In pediatric kidney transplant recipients receiving twice-daily tacrolimus, LSS profiles reveal relationships between absorption dynamics and systemic exposure. CYP3A5 genotype influences tacrolimus dose requirements and apparent clearance, supporting pharmacogenetics and LSS-based monitoring to optimize tacrolimus therapy.

Reference(s)

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Keywords

Tacrolimus; Limited sampling strategy; CYP3A5; Pediatric kidney transplantation; Therapeutic drug monitoring

00711
Modelling Enterohepatic Circulation to Explain Variability in Mycophenolic Acid Pharmacokinetics in Renal Transplant Recipients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Mycophenolic acid (MPA) demonstrates substantial interindividual pharmacokinetic variability. A major contributor to this variability is enterohepatic circulation (EHC), which produces a secondary concentration peak and complicates accurate exposure characterization. The conventional models often fail to adequately capture this phenomenon, potentially limiting predictive performance.

Materials and methods

A prospective pharmacokinetic study was conducted in 70 stable renal transplant recipients receiving tacrolimus-based immunosuppression. An intense steady-state

sampling was performed over one dosing interval (0 (pre-dose), 0.5, 1, 1.5, 2, 4, 6, 8, and 12 hours). A population pharmacokinetic model was developed in R using nlmixr2 and rxode2 packages. Five structural models were evaluated. The final model incorporated 3 transit-absorption compartments, 2-compartment disposition, and a time-triggered gallbladder pulse mechanism to represent EHC. EHC status (EHC+ vs EHC-) was determined from concentration-time profiles and evaluated as a binary covariate on the recirculation fraction (frc) using a logit scale. Interindividual variability was modelled exponentially, and residual variability included additive and proportional error components. Model evaluation included goodness-of-fit (GOF) diagnostics and visual predictive check (VPC) plots.

Results

The dataset contained 715 observation records after removing rows with missing concentration values. The final model showed a reduction in OFV by 609 as compared to the base model. The apparent clearance was 21.5 L/h, and the volume of distribution in the central compartment was 32.8 L. EHC was exhibited in 63% of subjects. The inclusion of EHC status as a covariate for fractional gall bladder recirculation (frc) and body weight as a covariate for clearance significantly improved model fit. GOF plots demonstrated minimal bias, and VPC plots confirmed accurate prediction.

Discussion / Conclusion

A population pharmacokinetic model incorporating pulse-based EHC and EHC-dependent recirculation fraction successfully characterised MPA disposition in renal transplant recipients. This framework improves the fidelity of the structural model and provides a robust foundation for exposure prediction in this population.

Keywords

Mycophenolate, MMF, Renal Transplantation, Enterohepatic Circulation, PoP_PK model, AUC

00717
Pharmacokinetic variability of once-daily tacrolimus in pediatric kidney transplant recipients: insights from AUC-based limited sampling analysis

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Tacrolimus has a narrow therapeutic index and marked interindividual pharmacokinetic variability. Therapeutic drug monitoring is usually based on trough concentrations (C0), although the relationship between C0 and systemic exposure may vary across patients. Limited sampling strategies allow estimation of tacrolimus exposure using a small number of samples and enable exploration of the relationship between early concentrations and overall drug exposure.

Materials and methods

We conducted a retrospective pharmacokinetic analysis of 110 pediatric kidney transplant patients (5–18 years) receiving once-daily tacrolimus (Advagraf). Variables included daily dose, concentrations at 0, 1 and 3 hours (C0, C1, C3), and estimated AUC_{0-24}. Age strata were defined as ≤12, 12–16 and >16 years. Additional clinical variables were derived to further characterize exposure patterns. Descriptive statistics, correlations and non-parametric tests were performed. Multivariable regression models explored predictors of AUC, and predictive performance of dose, clinical and demographic-based models was assessed using 10-fold cross-validation.

Results

Median AUC_{0-24} did not differ across age strata. Approximately 33% of profiles had C0 <5 ng/mL, which was associated with lower systemic exposure. Daily dose showed a modest correlation with AUC (ρ≈0.25) and a stronger correlation with early post-dose concentration (C1), whereas no meaningful correlation was observed with trough levels. The C1/C0 ratio was associated with higher exposure, indicating that early absorption dynamics contribute to variability in tacrolimus exposure, whereas lower exposure profiles tended to show lower C3 values. When AUC exposure ranges were considered, a substantial proportion of pharmacokinetic profiles fell outside proposed therapeutic windows, reflecting the variability of tacrolimus pharmacokinetics. These analyses support the role of non-pharmacokinetic variables in contributing to the observed variability.

Discussion / Conclusion

Tacrolimus exposure showed high variability and was poorly predicted by dose or age. Early concentrations, particularly C1 and the C1/C0 ratio, and adittion of clinical variables, better reflected systemic exposure than trough levels, supporting multipoint pharmacokinetic monitoring for individualized dosing.

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Keywords

Tacrolimus; Pharmacokinetics; Limited Sampling Strategy; AUC; Therapeutic Drug Monitoring; Pediatric Kidney Transplantation

00724
Tacrolimus Pharmacokinetics in Pediatric Liver Transplant Recipients Using Mitra™ Microsampling

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Tacrolimus is a key immunosuppressive agent used after pediatric liver transplantation and require careful therapeutic drug monitoring (TDM). In children shortly after transplantation, frequent blood sampling is often necessary to optimize tacrolimus therapy and prevent rejection or drug-related toxicity. Conventional venous sampling may be challenging due to limited blood volume and the invasive nature of repeated blood draws. Microsampling techniques such as Mitra™ volumetric absorptive microsampling (VAMS) enable collection of small, fixed blood volumes and represent a minimally invasive alternative for pharmacokinetic studies in pediatric patients. The aim of this study was to evaluate tacrolimus pharmacokinetics in pediatric liver transplant recipients using Mitra™ microsampling.

Materials and methods

Pharmacokinetic profiles were obtained in pediatric patients with recently transplanted liver grafts receiving oral Prograf® as part of standard immunosuppressive therapy. Whole blood samples were collected using Mitra™ (10µL) at predefined time points following tacrolimus administration (pre-dose,0.5,1,3,5,8, and 12-hours). Tacrolimus concentrations were determined using a

validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) method. Pharmacokinetic parameters were estimated using non-compartmental analysis (NCA). Calculated parameters included maximum concentration (Cmax), time to maximum concentration (Tmax), area under the concentration–time curve (AUC_{0-12}), elimination rate constant (k_{el}), and elimination half-life (t½).

Results

Sixteen pharmacokinetic profiles were analyzed. Tacrolimus reached peak concentrations within 0.5–3 hours after oral administration. Maximum concentrations (Cmax) ranged from approximately 19.6 to 53.9 ng/mL. The area under the concentration–time curve (AUC_{0-12}) ranged from approximately 95.8 to 274.1 ng·h/mL, indicating substantial inter-individual variability in tacrolimus exposure in the early post-transplant period. Estimated elimination rate constants ranged from 0.0097 to 0.1287 h^{-1}.

Discussion / Conclusion

Mitra™ microsampling using 10 µL-VAMS devices enabled reliable pharmacokinetic profiling of tacrolimus in pediatric patients shortly after liver transplantation. This minimally invasive approach allows dense pharmacokinetic sampling while minimizing blood loss and represents a valuable tool for individualized dosing and therapeutic drug monitoring in pediatric transplant recipients.

Reference(s)

Tacrolimus; Pediatric liver transplantation; Microsampling; Mitra™ VAMS; Pharmacokinetics; Therapeutic drug monitoring; LC–MS/MS.

00733
Optimization of tacrolimus therapeutic drug monitoring using microsampling in solid organ transplantation: experience of a hospital centre

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Background: Tacrolimus monitoring usually relies on trough concentration (Cmin), although the area under the curve (AUC) provides a more accurate estimate of exposure. Microsampling devices allow mini-invasive and repeated AUC assessment in solid organ transplant (SOT) patients.

Materials and methods

Methods: From 2019 to 2026, 554 pharmacokinetic profiles were obtained using microsampling in 470 transplant recipients (69% kidney, 31% liver). Correlations between Cmin and AUC were assessed according to organ, formulation, and post-transplant period. Apparent clearance (CL/F) was estimated to classify patients as fast or slow metabolizers. Intra-patient variability was evaluated for patients with repeated AUCs for different pharmacokinetic indices.

Results

Results: The Cmin and AUC correlation was weak to moderate depending on organ and formulation, r^2 ranging from 0.37 to 0.66, highlighting the limited predictive value of Cmin for tacrolimus exposure measurement. About 7 % of kidney and 17 % of liver

recipients displayed fast clearance with lower systemic exposure at equal doses, suggesting higher risk of graft rejection for these patients. Intra-patient variability reached 24.7–30.2% for Cmin and AUC, but was reduced for the AUC/Cmin ratio (13.3%) meaning that this index is probably more relevant for patients monitoring. Early use of microsampling enabled individualized dosing within the first 3 months post-transplant, a high-risk period for rejection.

Discussion / Conclusion

Conclusions: Micosampling proved to be a reliable, routine - applicable tool for tacrolimus AUC estimation. It is particularly valuable to identify fast metabolizers and patients with high discrepancies between AUC and Cmin and finally individualize immunosuppression in SOT recipients using the AUC/Cmin ratio.

00737
Comparative Analysis of NFAT-Residual Gene Expression in Patients with End-Stage Renal Disease and Healthy Controls

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Nuclear factor of activated T-cells residual gene expression (NFAT-RGE) is a biomarker reflecting T-cell activation and calcineurin pathway activity. Understanding baseline NFAT signaling in end-stage renal disease (ESRD) patients is essential for interpreting NFAT-based immune monitoring in transplantation. This study compared NFAT-RGE levels between ESRD patients and matched healthy controls and evaluated NFAT activation after stimulation.

Materials and methods

This cross-sectional study involved 30 pre-transplant patients with end-stage renal disease (ESRD) and 30 healthy controls matched for age and sex. All participants' baseline demographic and biochemical data were collected. Blood samples were separated into unstimulated and stimulated groups, with stimulation using phorbol 12-myristate 13-acetate (PMA) and ionomycin. RNA was extracted and reverse transcribed to cDNA, and NFAT-RGE was measured by real-time PCR. The target genes studied included interleukin-2 (IL-2), tumor necrosis factor-alpha (TNF-α), granulocyte-macrophage colony-stimulating factor (GM-CSF), and interferon-gamma (IFN-γ), with β-actin and GAPDH serving as housekeeping genes.

Results

Baseline demographic and biochemical characteristics were similar between the groups. The mean age was comparable in ESRD patients and healthy controls (47.6±9.8 vs. 48.8±9.5 years). Serum creatinine levels were higher in the ESRD group compared to controls (3.2±0.3 vs. 1.01±0.4 mg/dL), indicating kidney dysfunction. In healthy controls, NFAT-RGE increased markedly after stimulation, from 0.028 (0.007–0.079) to 0.269 (0.13–0.32), a tenfold rise (p = 0.0001). ESRD patients also showed a significant increase, from 0.04 (0.007–0.12) to 0.21 (0.02–0.33), about fivefold (p=0.001). While baseline and stimulated NFAT-RGE levels were similar, ESRD patients had more variability and a reduced fold response.

Discussion / Conclusion

Both healthy controls and ESRD patients show significant NFAT activation after stimulation. However, ESRD patients exhibit a reduced and more variable NFAT-RGE response, indicating altered immune activation processes in advanced kidney disease. These results may influence the interpretation of NFAT-based immune monitoring in renal transplant recipients.

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Keywords

NFAT-Residual Gene Expression; End-Stage Renal Disease; T-cell Activation; Calcineurin Signaling; Immune Biomarkers; Immune Monitoring

00740
Kidney function does not differ across tacrolimus C0/dose metabolizer phenotypes under AUC-guided therapeutic drug monitoring

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Previous studies suggest that kidney transplant recipients with a low tacrolimus trough concentration/dose (C_0/dose) ratio, indicative of a fast metabolizer phenotype, may be at increased risk of worse kidney outcomes[1]. These findings largely originate from centers where therapeutic drug monitoring (TDM) is guided by tacrolimus C_0, despite variability in peak and total drug exposure. As tacrolimus dosing at our center is routinely guided by area under the curve (AUC), we investigated whether kidney function differs according to C_0/dose metabolizer status under AUC-guided monitoring.

Materials and methods

In 1,041 kidney transplant recipients followed for up to 13 months and managed with AUC-guided tacrolimus dosing, metabolizer status was defined using the last

C_0/dose ratio measured ≥3 months post-transplantation (median ~10 months) and categorized as fast (<1.05 ng/mL/mg; n=293), intermediate (1.05–1.54; n=264), or slow (≥1.55; n=484). Kidney function was assessed as change in eGFR relative to Month 6 (ΔeGFR) and compared between metabolizer groups using linear mixed-effects models.

Results

Median eGFR at month 6 was 55 (IQR 44–70) mL/min/1.73m² in slow metabolizers, 53 (43–69) in intermediate, and 53 (41–63) in fast metabolizers. In linear mixed-effects models, ΔeGFR relative to month 6 did not differ between metabolizer groups. At month 12, the mean ΔeGFR difference was −0.54 mL/min/1.73m² (95% CI −2.59 to 1.51; p=0.811) for fast versus slow metabolizers, and −1.71 (−3.98 to 0.57; p=0.185) at month 24. Differences for intermediate versus slow metabolizers were similarly non-significant.

Discussion / Conclusion

In kidney transplant recipients managed with AUC-guided tacrolimus dosing, C_0/dose metabolizer status was not associated with differences in renal function over 12 and 24 months. This suggests that AUC-guided TDM may offset potential adverse effects of pharmacokinetic variability in tacrolimus peak and total exposure among fast metabolizers.

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Keywords

tacrolimus, transplantation, kidney, pharmacokinetics, therapeutic drug monitoring

00751
Population Pharmacokinetic Modeling of Cyclosporine in Algerian Renal Transplant Recipients : A Monocentric Study from Sétif

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Ciclosporine (CsA) is a key immunosuppressive drug used in renal transplantation, but its narrow therapeutic index and high interindividual pharmacokinetic variability require therapeutic drug monitoring (TDM) to ensure efficacy and limit toxicity. Population pharmacokinetic (PopPK) modeling is a useful tool to characterize this variability and support individualized dosing. However, pharmacokinetic data on immunosuppressive drugs in Algerian patients remain scarce, and no PopPK studies have been conducted in Algeria to date. This study aimed to develop a PopPK model of CsA in Algerian renal transplant recipients to support dose individualization and optimize TDM

Materials and methods

A prospective monocentric study conducted at the Toxicology Laboratory of the University Hospital of Sétif (Algeria) included 55 renal transplant recipients receiving oral cyclosporine therapy. The mean daily dose was 175 mg administered in two divided doses. Population pharmacokinetic analysis was performed using Monolix® 2024R1 with the stochastic approximation expectation–maximization algorithm. Covariate analysis was conducted to identify patient characteristics influencing pharmacokinetic parameters.

Results

CsA pharmacokinetics were best described by a one-compartment model with first-order absorption and linear elimination. The absorption rate constant (ka) was fixed at 1 h^{-1}.

The estimated mean apparent volume of distribution (V/F) was 82.61 L (relative standard error [RSE] 8.49%), and the apparent clearance (CL/F) was 16.08 L/h (RSE 5.86%). Interindividual variability was estimated at 0.37 for ka, 0.11 for V/F, and 0.17 for CL/F.

Triglyceride levels were identified as a significant covariate influencing CsA clearance. The final model showed satisfactory predictive performance, and a dosing adjustment equation incorporating triglyceride levels was proposed.

Discussion / Conclusion

A PopPK model of CsA was developed in Algerian renal transplant recipients. The identification of triglyceride levels as a significant determinant of CsA clearance highlights the potential importance of metabolic factors in dose optimization. This model may contribute to improved individualized dosing and better attainment of therapeutic target concentrations in routine TDM.

Keywords

Cyclosporine, Population pharmacokinetics, Monolix modeling,Therapeutic drug monitoring, Renal transplant recipients

00753
Real-world tacrolimus exposure during the first year after liver transplantation using abbreviated sampling and Bayesian estimation

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Tacrolimus dose individualization after liver transplantation is usually guided by trough concentrations (C0), although the area under the concentration–time curve (AUC) better reflects systemic exposure. Within a Model-Informed Precision Dosing (MIPD) framework, Bayesian forecasting combines abbreviated pharmacokinetic sampling with a population PK model to estimate individual AUC.

We aimed to characterize tacrolimus systemic exposure during the first year after liver transplantation in a real-world cohort using abbreviated sampling and Bayesian estimation.

Materials and methods

We performed a single-centre retrospective study (2014–2026) including de novo liver transplant recipients aged >18 years receiving prolonged-release tacrolimus (Advagraf®) with ≥1 abbreviated profile within the first year. Profiles (C0, 2 h, 3 h post-dose) were obtained at protocol timepoints (7, 15, 30, 90 days; 6, 9, 12 months). Individual tacrolimus AUC0–24 was estimated by Bayesian forecasting (MIPD

approach). Creatinine (Cr), estimated GFR (eGFR), total bilirubin and GGT from the same visits were extracted.

Results

Overall, 349 recipients met inclusion criteria. Bayesian AUC0–24 was available for 1334 profiles. Median (IQR) AUC0–24 declined from 276.9 (233.0–326.8) ng·h/mL (n=134) to 180.2 (147.5–218.2) at 12 months (n=195), a −35% change; median C0 decreased similarly from 7.9 (6.4–10.1) ng/mL (n=142) to 5.5 (4.5–6.7) (n=202), a −30% change. C0 correlated moderately with AUC0–24 (Spearman ρ=0.50; n=1334). Using tertile-based categories, concordance between C0 and AUC was 50.7%, adjacent-category disagreement 41.6%, and extreme discordance 7.6%. Liver biochemistry improved (bilirubin 1.33 [0.85–2.75] to 0.56 [0.39–0.76] mg/dL; GGT 218 [118–415] to 32 [21–59] U/L), while renal function remained broadly stable (Cr 0.89 [0.72–1.22] to 0.99 [0.81–1.17] mg/dL; eGFR 89.5 [61.9–90.0] to 76.4 [60.0–90.0] mL/min; frequent “>90” reporting).

Discussion / Conclusion

This study provides one of the few real-world descriptions of tacrolimus exposure throughout the entire first year after liver transplantation using Bayesian pharmacokinetic estimation within an MIPD strategy, supporting Bayesian AUC estimation from abbreviated sampling to strengthen routine management beyond trough-only targets.

Keywords

Tacrolimus; liver transplantation; Model-Informed Precision Dosing; Bayesian forecasting; AUC; renal function.

00761
TDM of hydroxychloroquine (HCQ) in Systemic Lupus Erythematosus (SLE): a systematic review and meta-analysis of PK-PD evidence

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Although HCQ is widely used in patients with SLE, the implementation of its TDM lags behind, and inconsistencies persist in the literature regarding its PK and PD characteristics. Our objective was to review the current data supporting the recommendation for HCQ TDM and to develop guidelines for its practice in patients with SLE, in accordance with model-based precision dosing (MIPD) principles.

Materials and methods

We conducted a systematic literature review to identify publications describing (1) the population PK of both plasma and whole blood HCQ in adults, and (2) the exposure-response relationship of HCQ in the treatment of SLE.

Results

(1) Eleven studies provided 13 usable population PK models, 6 for plasma and 7 for whole blood HCQ, 10 one-compartment and 3 two-compartment. Average parameter values varied widely between the studies (e.g. CL 10.9 to 68.2 L/h, V 437 to 73’540 L), only partly accounted for by the blood/plasma ratio of 3.7 to 4. Large interindividual PK variability was generally observed. Most analyses found an effect

of body weight on CL and sometimes on distribution volumes, while age and sex were never retained as covariates. (2) Eighteen studies collectively reported consistent exposure-response relationships for preventing SLE flare-ups and improving the SLE activity index, converging towards a trough concentration target of 750 to 1’500 ng/mL in whole blood, the preferred sample type for HCQ TDM. Published exposure-toxicity relationships are more elusive and less well documented.

Discussion / Conclusion

HCQ meets the classic criteria defining a drug as a candidate for TDM, even though randomized controlled intervention trials are rare. Observational studies suffer from biases induced by both compliance issues and empirical increase in HCQ dosage by prescribers in patients poorly responding to treatment. The evidence gathered in our review supports the development of a rational TDM and MIPD strategy for SLE patients.

Keywords

Hydroxychloroquine, Systemic Lupus Erythematosus, Meta-analysis

Other

00030
A Pharmacokinetic Evaluation and External Validation of a Pediatric Lacosamide popPK model in Japanese Children Aged One Month to Four Years

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

A published population pharmacokinetic (PopPK) model for lacosamide has been developed using 666 pediatric subjects aged 1 month to <18 years, identifying body weight, race, and enzyme inducers as covariates of apparent clearance (CL/F). Japanese subjects were limited (n=46) and all were ≥4 years. Although lacosamide is not approved for children <4 years in Japan, it is used off-label for seizures. This study evaluated model predictability and potential pharmacokinetic differences in Japanese children <4 years.

Materials and methods

Children <4 years receiving oral lacosamide between 2016 and 2024 with ≥2 plasma concentrations (including ≥1 at maintenance/final dose) were retrospectively included. Age, dose per weight (Dw), number of doses/blood draws, and plasma

concentration (C) were extracted from an integrated medical record across 14 hospitals. Predictive performance for the second concentration from the first was assessed using bias, mean absolute error (MAE), root mean square error (RMSE), and concordance correlation coefficient (CCC). Apparent CL/F was also estimated.

Results

Among 280 cases, 132 met inclusion criteria. No patients had hepatic/renal impairment or dialysis. Monotherapy was used in 6 (4.6%), and enzyme inducers in 26 (19.7%). Median age (95%CI) was 1.6 (0.3–3.9) years, and median maintenance dose (95%CI) was 5.4 (1.1–9.6) mg/kg/day. Median plasma concentration (95%CI) was 6.8 (2.5–12.4) μg/mL with no age-group differences. Median C/Dw ratio (95%CI) was 1.06 (0.3–2.7), and younger age groups tended to have lower values. Overall prediction performance for the second concentration was excellent (bias: +0.38, MAE: 0.63, RMSE: 0.82, CCC: 0.98) without significant age-related differences. Estimated median CL/F increased with decreasing age (0.04–0.07 L/kg/hr) and was within reported non-Japanese ranges.

Discussion / Conclusion

The pediatric lacosamide PopPK model accurately predicted concentrations in Japanese children <4 years and provided CL/F estimates consistent with non-Japanese populations. The model may support maintenance dosing to prevent under- or overdosing. Further analyses assessing PK equivalence, efficacy, and safety are warranted.

Reference(s)

U.S. Food and Drug Administration. Office of Clinical Pharmacology Review: Lacosamide Population Pharmacokinetic Analysis (CL0447-Part IV). FDA; Oct 15, 2021.

Keywords

lacosamide, pediatric, Japanese, population pharmacokinetics, model validation, therapeutic drug monitoring

00052
LogP/LogD to artificial neural networks to elucidate blood extraction of low-molecular-weight pharmaceutical compounds: application to PST II and Barricor tubes for therapeutic drug monitoring and toxicology

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Plasma drug extraction for TDM is influenced by drug lipophilicity and the collection tube type. Previous research has demonstrated significant variations in drug recovery, with PST II gel separator tubes often affecting the extraction of lipophilic drugs. While logP and logD are traditionally used to predict this behavior, they are sometimes insufficient. A neural network predictive model was developed to better understand and anticipate drug-matrix interactions during pre-analytical phases.

Materials and methods

A total of 167 compounds were analyzed. A 20 ng/mL mixture of these drugs was prepared in whole blood, then divided into tubes of various types. Following

centrifugation, plasma was crushed with methanol, and 50 µL of the supernatant was injected into a reversed-phase UPLC-MS/MS system, operating in positive mode with multiple reaction monitoring. Six samples were prepared for each condition. A comprehensive set of molecular descriptors was calculated for each analyte using MOE (Molecular Operating Environment) software.

Results

To build predictive models, data were first normalized using Z-scores. After multilinear approaches failed, neural networks were successfully employed, using 463 molecular descriptors as input to predict extraction yields in two tube types. Iterative refinement identified a dozen significant descriptors. Redundant descriptors were then eliminated with a 65% similarity threshold. The final model, validated by training on 80% of the data, achieved a regression of 0.6 with 16 parameters and a 0.8 threshold. The most influential descriptors included the number of aromatic rings, sp3 carbon position, basic functions, electronic surface area, and $logD_{pH9}$.

Discussion / Conclusion

A validated neural network model successfully explains the extraction performance of 167 therapeutic drugs. This confirms that plasma extraction is a multidimensional process where Log D is a contributing factor, but not the sole determinant. In clinical laboratories, these models can predict extraction yields in different tubes enabling the immediate analysis of valuable samples (such as pediatric’s or interhospital’s).

Keywords

Therapeutic drug monitoring (TDM), Toxicology, Plasma sampling, Drug stability, Blood collection tube, separator gel, Artificial neural network, Molecular descriptors

00164
Optimizing Elexacaftor/Tezacaftor/Ivacaftor Therapy: When Biological "Over-Response" Triggers Toxicity

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The triple combination elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) is a highly effective therapy for cystic fibrosis, but its clinical use is limited by marked interindividual variability and adverse drug reactions (ADRs), particularly neuropsychiatric events (anxiety, depression, and insomnia) which can result in treatment modification. This study aimed to investigate, through Therapeutic Drug Monitoring (TDM), the relationship between drug exposure, biological response (sweat chloride), and ADR occurrence to support a personalized treatment approach.

Materials and methods

Data from 84 patients (47 adults, 37 children) were analysed. Trough plasma concentrations (Cmin) of ELX/TEZ/IVA and their metabolites were measured using LC-MS/MS. Clinical and biological efficacy was assessed by changes in forced expiratory volume in one-second (FEV1) and sweat chloride levels. “Asymptomatic” patients were statistically compared with those experiencing “ADRs” (neuropsychiatric or hepatic).

Results

Among 50 patients with ADRs, 84% reported neuropsychiatric symptoms and 16% experienced hepatic events. A significantly greater relative reduction in sweat chloride was observed in the ADR group compared with asymptomatic patients, in both adults ($p = 4.05\times10^{-8}$) and children ($p = 1.59\times10^{-6}$). Although plasma concentrations were generally comparable between groups, patients with ADRs achieved lower absolute sweat chloride levels. No correlation was found between sweat chloride reduction and FEV1 improvement, suggesting a “plateau effect,” whereby some patients reach maximal biological efficacy at lower exposure levels. In these individuals, standard dosing may result in systemic overexposure without additional clinical benefit, increasing the risk of toxicity. No significant impact of CYP3A4/5 genotypes was observed on plasma concentrations or toxicity occurrence.

Discussion / Conclusion

Patients experiencing neuropsychiatric or hepatic adverse drug reactions appear biologically more sensitive to ELX/TEZ/IVA, reaching maximal efficacy earlier than others. Combining TDM with sweat chloride assessment may identify patients who could benefit a dose reduction. This personalized approach could reduce toxicity while maintaining optimal therapeutic efficacy and improving long-term treatment adherence.

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Keywords

CFTR modulators, Cystic fibrosis, therapeutic drug monitoring, adverse drug reactions

00205
Evaluating Antipsychotic Adherence Using Therapeutic Drug Monitoring: A Japanese Real-World Study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Medication adherence to antipsychotics is frequently suboptimal in patients with psychiatric disorders, including schizophrenia (SCZ). Although medication adherence to antipsychotics is often assessed by self-report, we tried to evaluate the utility of therapeutic drug monitoring (TDM) in Japanese patients receiving antipsychotics.

Materials and methods

Patients diagnosed with SCZ or other psychiatric disorders at the Department of Psychiatry, Gifu University Hospital, registered in the Cognitive Genetics Collaborative Research Organization (COCORO) project, were enrolled. Eligible patients were prescribed at least one of seven measurable antipsychotics (haloperidol, levomepromazine, aripiprazole, paliperidone, risperidone, olanzapine, or quetiapine). Based on the 2018 consensus guidelines for TDM in neuropsychopharmacology [1)], patients whose plasma concentrations of all currently prescribed antipsychotics were within the guideline reference ranges were classified as the “good adherence” group. Factors associated with adherence were analyzed,

and results were compared with Drug Attitude Inventory-10 (DAI-10) scores. The institutional ethics committees approved the study.

Results

Forty-seven patients receiving any of the seven antipsychotics were included; 35 had SCZ. The proportion classified as having good adherence was 59.6% in the overall cohort and 51.4% among SCZ patients. Compared with the poor adherence group, the good adherence group showed significantly higher chlorpromazine-equivalent doses. In both antipsychotic polypharmacy and monotherapy users, concomitant prescriptions (e.g., antiparkinsonian agents and anxiolytics) were significantly more frequent in the good adherence group. DAI-10 scores did not differ significantly between adherence groups. Patient enrollment is still ongoing. Thus, additional data will be presented at the meeting.

Discussion / Conclusion

TDM-based classification revealed substantial discordance with self-reported DAI-10, suggesting that questionnaire-based assessment alone may miss clinically meaningful nonadherence. Concomitant medications may be associated with better adherence. Overall, TDM may offer a more objective method for assessing antipsychotic adherence in clinical practice.

Reference(s)

1) Hiemke et al., Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017. Pharmacopsychiatry 2018 Jan;51(1-02):9-62.

Keywords

therapeutic drug monitoring; antipsychotics; adherence; schizophrenia; DAI-10; Japan

00250
Accurate Measurement of Iohexol in Human Serum Using the Nephrolyx IVDx Kit (UHPLC-UV): Comparison with a Laboratory-Developed LC MS/MS Method

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Measured glomerular filtration rate (mGFR) using exogenous markers such as iohexol is the reference method for kidney function according to the KDIGO 2024 CKD guideline. The Nephrolyx CE-marked IVD kit enables a standardized, rapid, and user-friendly implementation of iohexol quantification and mGFR calculation in clinical routine. We evaluated the transfer of the Nephrolyx CE-marked IVD kit workflow, originally developed for (U)HPLC-UV, to LC-MS/MS (Shimadzu Nexera X3 with LCMS-8050) and performed a CLSI compliant method comparison.

Materials and methods

Nephrolyx matrix-matched calibrators (C1–C6), QCs (QC1–QC3), and clinical serum samples were prepared and analyzed according to kit instructions, using the kit chromatographic gradient and Nephrolyx UHPLC column. LC-MS/MS acquisition employed ESI+ MRM transitions for iohexol and iopromide (internal standard). In a comparison study in accordance with CLSI EP09-A3, 135 samples (8–500 µg/mL) were evaluated using scatter and difference plots and Passing–Bablok regression.

Results

130 paired measurements were analyzed, showing excellent correlation (R^2 = 0.9966); four samples outside the measuring range of Nephrolyx IVDx Kit (UHPLC-UV) and one statistical outlier (ESD, $\alpha = 0.05$) were excluded from the analysis. Difference plots demonstrated concentration-dependent variability consistent with constant CV. Passing–Bablok regression showed no significant constant or proportional bias (intercept: 0.0538; slope: 1.0203). The mean inter-method bias was 2.13%.

Discussion / Conclusion

The Nephrolyx LC-MS/MS method demonstrated high accuracy and robust analytical performance, showing strong concordance with the UHPLC-UV reference procedure across the evaluated range. This allows rapid and reliable iohexol quantification for routine mGFR assessment in alignment with the KDIGO 2024 CKD guideline. Validation of the method is required for implementation in clinical laboratories.

Keywords

iohexol, mGFR, LC-MS/MS, UHPLC-UV, Nephrolyx IVDx, method comparison.

00327
Discovery of novel CYP3A5 biomarker candidates by non-targeted metabolomics in Japanese general population and patient cohorts

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Cytochrome P450 (CYP)3A5 shares considerable substrate overlap with CYP3A4 and contributes to the metabolism of many clinically used drugs. Notably, tacrolimus is strongly influenced by CYP3A5 expression status and exhibits a narrow therapeutic window, requiring therapeutic drug monitoring. Interindividual variability in tacrolimus pharmacokinetics is largely attributed to differences in CYP3A5 activity. Plasma 4β-hydroxycholesterol is an established endogenous biomarker of overall CYP3A activity; however, a biomarker that specifically indicates CYP3A5 activity is needed when evaluating drugs with highly CYP3A5-dependent disposition, such as tacrolimus. This study aimed to comprehensively explore novel endogenous

biomarkers of CYP3A5 activity in Japanese general population and patient cohorts using a non-targeted metabolomics approach.

Materials and methods

Non-targeted metabolomics was performed in 448 individuals from the Japanese general population and 295 patients. Participants carrying *CYP3A5*1/*1* or *CYP3A5*1/*3* were classified as expressers, whereas those with *CYP3A5*3/*3* as non-expressers. Plasma samples were prepared using two solid-phase extraction methods and a liquid–liquid extraction method. Extracted analytes were quantified by ultra-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry. Candidate biomarkers were selected using volcano plots and S-plots derived from orthogonal partial least squares discriminant analysis. Selected compounds were subjected to database-based identification.

Results

In the general population cohort, six compounds were extracted as candidate biomarkers by volcano plot, whereas 36 were extracted by S-plot. In the patient cohort, one compound was extracted by volcano plot and 69 by S-plot. One compound (compound A) was detected by both plots in the general population cohort. Another compound (compound B) was detected by both plots in the general population cohort, and was also detected by the volcano plot in the patient cohort. Compound B was putatively identified as austalide-L.

Discussion / Conclusion

Austalide-L was identified as a novel candidate endogenous biomarker for CYP3A5 activity. Further investigations are required to evaluate its clinical utility as a biomarker.

00343
Elucidation of inflammasome activation in proton pump inhibitors-induced interstitial nephritis

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Proton pump inhibitors (PPIs) are known to be relatively safe medications with few side effects. However, in recent years, their association with the development of interstitial nephritis as severe adverse events has become evident. PPIs-induced interstitial nephritis is characterized by immune cell infiltration into the interstitium and renal tubules, supporting the possibility that PPI-induced interstitial nephritis involves immune mediated mechanisms. On the other hand, we have reported that drugs and their reactive metabolite induces the release of damage-associated molecular patterns（DAMPs）that activate immune cells, which causes the idiosyncratic drug-induced serious adverse effects.

We tested the ability of the culture supernatants from human renal proximal tubule epithelial cells (RPTECs) incubated with PPIs to activate human macrophage cell line (THP-1 cell).

Materials and methods

Human RPTECs were respectively cultured in three dimensions for 28 days with omeprazole, lansoprazole, esomeprazole, rabeprazole, and vonoprazan. The supernatants from the RPTECs were added to differentiated THP-1 cells and incubated for 24 hr. IL-1β concentration of the supernatants and caspase-1 activity of THP-1 cells were measured. DAMPs in the culture supernatant were measured by the western blotting.

Results

The supernatant from an incubation of RPTECs with omeprazole, lansoprazole, esomeprazole, rabeprazole, and vonoprazan increased the IL-1β production and caspase-1 activity of THP-1 cells. Regarding omeprazole, HSP60 was significantly increased in the supernatants from RPTECs.

Discussion / Conclusion

These results demonstrated that the PPIs activated the inflammasome in THP-1 cells treated with the culture supernatant. Moreover, HSP60 may be potential biomarkers for omeprazole-induced interstitial nephritis.

Keywords

proton pump inhibitor, idiosyncratic drug induced serious adverse effects, DAMPs, inflammasome, interstitial nephritis

00348
Sex differences in risperidone and aripiprazole exposure between the age of 40 and 60

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Physiological and hormonal changes during the menopause may alter the exposure of antipsychotic medications. We aimed to compare risperidone and aripiprazole exposure between males and females aged 40–60 years.

Materials and methods

Retrospective serum concentration data for aripiprazole and risperidone (including active metabolites) from a therapeutic drug monitoring service were analyzed in patients aged 40–60 years. For each antipsychotic, the main outcomes were the dose-adjusted serum concentration (C:D ratio) and the metabolite-to-parent ratio (MPR). Sex-related differences were visualized by plotting C:D ratio versus age with sex-specific smoothing lines. Planned statistical analyses include linear mixed models to account for repeated measurements per patient.

Results

For aripiprazole, 1799 serum concentration measurements from 647 males and 2141 from 796 females were included. For risperidone, 1617 measurements from 565 males and 1611 from 603 females were included. Mean doses were slightly lower in females than in males for both aripiprazole (14.8 mg vs 13.6 mg) and risperidone (3.6 mg vs 3.0 mg). Preliminary analyses suggest that the risperidone C:D ratio (parent

plus active metabolite) is similar in males and females at age 40, but increases more steeply in females from 45 to 60 years compared to males. For aripiprazole (parent plus active metabolite), sex differences in C:D ratio were smaller, but concentrations remained slightly higher in females.

Discussion / Conclusion

Preliminary findings indicate that sex-related differences in risperidone and aripiprazole exposure emerge in the 40s, consistent with a possible impact of menopausal changes. These observations will be further explored by statistical analyses of the C:D ratios, as well as analyses of the MPRs to investigate metabolism via CYP2D6/CYP3A4 for aripiprazole and CYP2D6 for risperidone.

00359
Therapeutic Drug Monitoring of Lurasidone in Clinical Practice: Evaluation of Therapeutic Ranges and the Impact of Patient-Specific Factors on Plasma Concentrations

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Lurasidone is a second-generation antipsychotic approved for schizophrenia and bipolar depression. Lurasidone exhibits substantial interindividual pharmacokinetic variability, largely driven by differences in CYP3A4-mediated metabolism. A reference plasma concentration range was proposed by the AGNP[1], but recent real-world evidence in Asian[2-3] populations have challenged its applicability. This study aimed to evaluate the factors influencing lurasidone plasma concentrations and to explore the relevance of the current therapeutic reference range.

Materials and methods

This retrospective observational study included 453 lurasidone plasma concentrations from 274 adult patients from Switzerland. Concentration-to-daily dose ratios (CDR) were calculated. Intrinsic factors (e.g., sex, age, body weight, diagnosis) and extrinsic factors (e.g., co-medications) were extracted from routine TDM request forms. Multivariable linear mixed-effects models were used to identify the relevant covariates. Time-adjusted trough concentrations were calculated, and ROC curve analyses assessed association with clinician-reported therapeutic response or adverse events.

Results

Compared to schizophrenia (n=68, 34%), diagnoses of bipolar depression (n=60, 30%) were associated with 28% lower prescribed doses. Body weight was associated with an increase in CDR. CYP3A4 inhibitors and inducers were associated with 57% higher and 49% lower CDR values, respectively. The median lurasidone concentration was 7.6 ng/ml [IQR=4.0-14.0] for a median dose of 60 mg/d [IQR=40-80]. Overall, 88% of lurasidone plasma concentrations fell below the recommended therapeutic range of 15-40 ng/mL[1]. Using ROC curve analyses, no trough concentration threshold was identified in relation to clinical response. However, trough concentrations above 8.2 ng/ml were associated with higher risk of severe adverse events.

Discussion / Conclusion

We found substantial interindividual variability in lurasidone concentrations. Most measured plasma concentrations were below the currently recommended therapeutic reference range and plasma levels as low as 8 ng/mL could already be associated with severe adverse events, demonstrating that the current reference range needs to be adjusted.

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Keywords

Lurasidone, antipsychotic, Therapeutic drug monitoring, Pharmacokinetics, therapeutic range

00414
Reprocessing high-resolution mass spectra from TDM samples of escitalopram reveals comedication with proton pump inhibitors causing significant phenoconversion of escitalopram metabolism

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Escitalopram is a frequently prescribed antidepressant drug. CYP2C19 genotype is a major determinant of escitalopram metabolism and treatment outcome. However, real-life studies show a high degree of genotype-phenotype mismatch in escitalopram metabolism. The present study aimed to identify comedication with proton pump inhibitors (PPIs) and quantify phenoconversion of escitalopram metabolism in genotyped patients by reprocessing high-resolution mass spectra from escitalopram therapeutic drug monitoring (TDM) analyses.

Materials and methods

Patients were included from a combined TDM/pharmacogenetics (PGx) laboratory facility in Oslo, Norway. TDM profiles and genotypes were available in the laboratory database. Reprocessing of high-resolution mass spectra by exact mass (5ppm mass window) and fragment detection identified possible comedication with pantoprazole, esomeprazole/omeprazole or lansoprazole using mzCloud reference library. Patients were subgrouped as normal metabolizers (NMs), intermediate metabolizers (IMs),

poor metabolizers (PMs), rapid metabolizers (RM) or ultrarapid metabolizers (UM). Primary outcome measure was N-desmethylescitalopram-to-escitalopram metabolic ratio (MR; CYP2C19 metric) in UMs vs. PMs.

Results

2,816 patients were included, constituting 2,373 without and 443 (15.7%) with PPIs. Most patients were females (64.4%). CYP2C19 phenotype distribution showed 39.2% NMs, 29.4% IMs, 2.6% PMs, 24.6% RMs, and 4.2% UMs. Escitalopram MR was 4.5-fold higher in CYP2C19 UMs vs. PMs without PPIs ($p<0.001$), while this difference was 2.8-fold in pantoprazole users ($p<0.001$) and 1.8-fold in esomeprazole/omeprazole users ($p=0.2$).

Discussion / Conclusion

PPIs show significant phenoconversion of CYP2C19-mediated escitalopram metabolism with esomeprazole/omeprazole exhibiting a stronger effect than pantoprazole. The novel method for identification of interacting comedications in blood samples illustrate the innovative power of high-resolution mass spectrometry in translational and precision medicine.

00434
Impact of age on serum concentrations of lurasidone in female and male patients

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Lurasidone is among the newest antipsychotic medications, and knowledge about the impact of age on the exposure of this medication is limited. The aim of the present study was to investigate the effect of age on lurasidone serum concentrations in female and male patients separately.

Materials and methods

Retrospective serum concentration measurements for lurasidone were extracted from a therapeutic drug monitoring service for a 10-year period and analyzed in females and males separately. Patients aged 50-69 years and patients aged ≥70 years were compared with patients aged 18-49 years. The main outcome was the dose-adjusted serum concentration of lurasidone. The effect of age was analyzed by linear mixed model to account for repeated measurements per patient.

Results

Lurasidone serum concentration measurements were included for 276 females (537 samples) and 240 males (474 samples). Mean lurasidone doses were slightly lower in females than in males (75.3 vs 81.0). The mean dose-adjusted serum concentration of lurasidone was 20% higher in female patients aged 50-69 years compared to females aged 18-49 years (*p=0.027*). There was no statistically significant difference in the mean dose-adjusted serum concentration for females

aged ≥70 years compared to females aged 18-49 years. Among males there were no statistically significant differences between the age groups.

Discussion / Conclusion

This study suggests that the impact of age on dose-adjusted serum concentrations of lurasidone is greater among females than males. The non-significant difference between females aged ≥70 years compared to females aged 18-49 years may be due to few samples in the oldest age group.

00478
Pop-PK modeling enables the bidirectional prediction for exposure levels or individualized dosing of atomoxetine in children with ADHD within real-world clinical scenarios

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Personalized dosing of atomoxetine remains an unmet clinical need. This study aimed to develop a population pharmacokinetic (Pop-PK) model based on real-world data to enable bidirectional prediction of atomoxetine exposure or individualized dosing in children with ADHD.

Materials and methods

Medical records and CYP2D6 genotype data were retrospectively collected, and Pop-PK modeling was performed using a nonlinear mixed-effects modeling program (NONMEM). The absorption rate constant of atomoxetine was set at 0.71. Models were evaluated across multiple clinical scenarios, and Monte Carlo simulations were conducted to examine different dosing regimens.

Results

This study included 306 atomoxetine concentrations from 256 children with ADHD. Body weight (BW) and CYP2D6 polymorphisms, retained in the final Pop-PK models, affected the pharmacokinetics of atomoxetine. In four scenarios, the dosing for lower BW children [15-40 kg) was slightly higher than that for higher BW group [40-70 kg]. Pop-PK models (MODELs II-IV) were constructed using gene polymorphisms of CYP2D6*10, activity scores (ASs; based on CYP2D6*2, *10, and *14), or phenotypes as covariates along with covariate BW, which demonstrated better predictive performance compared to model constructed with BW alone (MODEL I). Notably, models constructed with CYP2D6*10 or AS showed better predictive performance than that based on CYP2D6 phenotype. Such differences might be related to our reliance on the genotyping of only CYP2D6*2, *10, and *14 to define phenotype or calculate the AS value. For cases carrying CYP2D6*10 CC (rs1065852) or with an AS score of 2, the predicted dosing when BW was in the range of 40-70 kg reached the maximum indicated dose of 1.4 mg/kg, while for those weighing 15-40 kg, the required dose was 1.5 mg/kg, which falls into off-label use.

Discussion / Conclusion

These findings support using BW-based or BW-plus-CYP2D6–based Pop-PK models to guide individualized atomoxetine dosing in children with ADHD, helping reduce variability in exposure and improve therapeutic safety and efficacy.

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Keywords

Atomoxetine, ADHD, children, CYP2D6, population pharmacokinetics, dosage optimization

00482
Dysfunction of Intestinal Barrier in Rats with Pulmonary Arterial Hypertension

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Pulmonary arterial hypertension (PAH) is a progressive pulmonary vascular disease that leads to right heart failure and systemic venous congestion, which may affect the intestine through portal hypertension. Elevated circulating endotoxin levels have been reported in patients with PAH, and we previously reported increased intestinal permeability of polyethylene glycol 400 in rats with PAH.[1)] However, how PAH affects intestinal permeability at sites relevant to drug absorption remains unclear. This study aimed to evaluate the effect of PAH on duodenal and jejunal permeability, the major sites of drug absorption, in rats.

Materials and methods

PAH was induced in rats by two subcutaneous injections of monocrotaline (20 mg/kg). The duodenal and jejunal permeability were quantitatively evaluated using the Ussing chamber technique by measuring cumulative permeability of 3H-lactulose, a marker of paracellular pathway, over 120 minutes. The protein expression levels of the tight junction (TJ) protein, claudin-1, were assessed.

Results

The established PAH model showed an increase in plasma brain natriuretic peptide levels and right ventricular hypertrophy. In controls, the cumulative permeability of

lactulose over 120 minutes was 2.9-fold higher in the jejunum than in the duodenum, indicating different baseline permeability between the two intestinal segments. The PAH model showed similar increases in lactulose permeability in the duodenum (2.0-fold) and the jejunum (1.9-fold). Claudin-1 protein expression was decreased by 56% in the duodenum and 44% in the jejunum of the PAH model compared with controls. In addition, plasma angiopoietin-2 concentrations increased 2.9-fold in the PAH model.

Discussion / Conclusion

These findings suggest that PAH induces intestinal barrier dysfunction with disruption of TJ. Angiopoietin-2 may be involved in the regulation of TJ integrity.

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Keywords

Pulmonary arterial hypertension; Right heart failure; Intestinal permeability; Claudin-1; Angiopoietin-2

00487
Defining the therapeutic range of levetiracetam for personalized treatment in pediatric epilepsy: insights from a large real-world study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

This study sought to define the therapeutic drug monitoring (TDM) range and assess the efficacy-safety profile along with its determinants for levetiracetam (LEV) in Chinese children with epilepsy.

Materials and methods

We conducted a retrospective study (2021-2023) at Children's Hospital of Nanjing Medical University in children with epilepsy taking LEV therapy with routine TDM. The LEV therapeutic range was defined by the generalized additive models for location, scale, and shape (GAMLSS) analysis. A linear mixed-effects model identified concentration determinants. Efficacy was assessed via propensity score matching (PSM)-adjusted logistic regression, time-to-failure via Kaplan-Meier/Cox regression (monotherapy), and adverse events (AEs) temporal patterns via Weibull distribution analysis.

Results

This study (n = 1,174) defined a LEV TDM range of 2.82−24.37 μg/mL. Predictors of LEV levels included age, body weight, oxcarbazepine (OXC)/topiramate use, and developmental delay. OXC lowered concentration-to-dose (C0/D) (β = −0.1824, P = 0.0012). The 12-month response rate was 81.01% (90.89% monotherapy vs. 70.78% polytherapy). Concentration-response correlation was significant only in focal epilepsy. Protective factors for response were female sex, generalized epilepsy, and longer treatment; risk factors were polytherapy and infectious etiology. Comorbid attention deficit and hyperactive disorder improved, but developmental delay did not affect, response. Neuropsychiatric AEs were most frequent (median onset: 196.5 days); gastrointestinal and systemic reactions showed early failure patterns.

Discussion / Conclusion

This real-world study confirmed the efficacy and safety of LEV in Chinese children with epilepsy, and revealed relevant drug interactions. By proposing a therapeutic LEV reference range (2.82−24.37 μg/mL), it provides a critical evidence base for TDM and guides the personalized treatment.

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Keywords

Levetiracetam (LEV); children with epilepsy; efficacy; adverse events (AEs); therapeutic drug monitoring (TDM); personalized treatment.

00491
Stratified therapeutic drug monitoring could potentially improve efficacy and safety of oxcarbazepine in children with epilepsy: Novel insights from a single-center, large-sample, retrospective real-world study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

This study aimed to characterize the population exposure, efficacy, and safety profiles of oxcarbazepine (OXC) in Chinese children with epilepsy using real-world data, to define its optimal therapeutic range and inform individualized therapy.

Materials and methods

This single-center retrospective cohort study included pediatric patients (< 18 years) who received OXC therapy between September 2021 and August 2024, with follow-up continuing until February 2025. The plasma active metabolite 10,11-dihydro-10-hydroxycarbamazepine (MHD) concentration was monitored. A mixed-effects model identified factors influencing MHD exposure. Logistic regression and Cox proportional hazards models analyzed the concentration-efficacy relationship, while Kaplan-Meier and time-to-onset analyses characterized adverse events.

Results

Among 824 included patients (1,976 concentration samples), body weight, age, treatment duration, and epilepsy type significantly influenced MHD's exposure levels. The 12-month overall response rate was higher in monotherapy than add-on therapy (82.9% vs. 60.4%). A plasma MHD concentration ≥ 10 μg/mL was identified as a critical "risk transition point" for treatment failure (PSM-adjusted OR = 2.42, $P < 0.001$). Multivariate logistic analysis confirmed higher concentrations, specific etiologies, and polytherapy as risk factors for inefficacy. Cox regression further revealed that concentration ≥ 10 μg/mL and specific etiologies were predictors of reduced long-term treatment persistence. Adverse events occurred in 30.5% of patients; for most, the risk did not change over time.

Discussion / Conclusion

This study tentatively proposed a therapeutic reference range (3.0−20.0 μg/mL) of MHD for Chinese children with epilepsy and identified a concentration ≥ 10 μg/mL as a "risk transition point". The findings provided a practical, evidence-based insights for tailoring OXC therapy and managing potential risks.

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Keywords

Oxcarbazepine (OXC); 10,11-dihydro-10-hydroxycarbamazepine (MHD); Epilepsy; Children; Therapeutic drug monitoring (TDM); Real-world study; Individualized therapy.

00503
A comparative analysis of clozapine metabolite profiles in treatment-resistant schizophrenia patients who discontinue versus maintain clozapine treatment

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Clozapine (CLZ) is the gold standard for treatment-resistant schizophrenia, but a considerable proportion of patients discontinue treatment, which is associated with poorer clinical outcomes. Discontinuation is often related to adverse drug reactions, non-adherence, inadequate response, and/or the stringent monitoring practices of blood counts and therapeutic drug monitoring (TDM). This retrospective study examines whether interindividual differences in CLZ metabolism, including recently identified metabolites, are associated with clozapine discontinuation by comparing metabolite profiles in patients who discontinue versus those who maintain CLZ treatment.

Materials and methods

TDM data from patients who discontinued CLZ between March 2019 and December 2025 will be compared with those who maintained treatment throughout the same period. Routine TDM will provide serum CLZ and N-desmethylclozapine levels, whereas clozapine-N-oxide and the other CLZ metabolites will be obtained by reprocessing full-scan UHPLC–HRMS data files from CLZ TDM. Mixed model linear regression analyses will be used to compare CLZ concentration-to-dose ratios and

metabolic ratios, with covariate adjustments for age, sex, sampling time and smoking status.

Results

In total, 1215 CLZ patients have been identified in the database before exclusion criteria are applied, providing a robust sample for comparative analyses. Data processing and statistical analyses are currently underway, and final results will be presented at the congress.

Discussion / Conclusion

This study will explore whether metabolic factors are associated with CLZ discontinuation, using laboratory data from Norway’s largest TDM facility. The findings are expected to provide insights that may inform optimization of CLZ therapy and monitoring practices.

Keywords

Clozapine metabolism, treatment-resistant schizophrenia, discontinuation

00508
Validation of a Novel Raman-based Therapeutic Drug Monitoring Platform for ß-Lactam Antibiotics

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Half of the patients admitted to an intensive care unit (ICU) receive a ß-lactam antibiotic. However, suboptimal dosing leads to avoidable mobidity and mortality. Therapeutic drug monitoring (TDM) of ß-lactams could improve patient outcomes, but the lack of actionable results prevents effective implementation in clinical practice, since the gold standard is restricted to large central laboratories and has a long turnaround time. This study validates Axithra's novel TDM-platform allowing real-time dose adjustments at the point-of-need. This 'enhanced Raman spectroscopy on chip'-method allows to detect and quantify specific molecular fingerprints in a sample-in to result-out manner, hereby not requiring any complex sample preperation steps. This solution could resolve a large unmet clinical need by delivering actionable results with a short turnaround time to effectively guide clinical decision-making.

Materials and methods

This validation study evaluates samples obtained from adult ICU patients from the University Hospital of Ghent treated with ceftazidime, piperacillin, or meropenem. Drug concentrations measured with Axithra's TDM solution are compared to those obtained with a gold standard, validated LC-MS/MS method to assess overall accuracy. In addition, precision of this novel methodology was assessed by comparing repeated measurements.

Results

The Raman-based platform effectively identifies the spectral signatures of all three target antibiotics from plasma and shows an accuracy of x%, y%, and z% relative to the gold standard for ceftazidime, meropenem, and piperacillin, respectively. In addition, high precision (<a%CV) was shown across relevant therapeutic ranges for all three antibiotics.

Discussion / Conclusion

This study demonstrates the performance of Axithra's platform for TDM of ß-lactams through a head-to-head comparison with a gold standard clinical method like LC-MS/MS. This novel TDM solution allows for a rapid turnaround time at the point-of-need, providing actionable results to clinicians in minutes, hereby paving the way for precision dosing strategies that are currently impossible with standard laboratory workflows.

Keywords

Therapeutic drug monitoring, ß-lactams, Raman spectroscopy, Biosensor, Point-of-need, Near-patient testing, LC-MS/MS

00510
Therapeutic drug monitoring of Clozapine in Tunisian schizophrenic patients: a longitudinal analysis

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Clozapine is an atypical antipsychotic drug that is commonly used in the treatment of refractory schizophrenia. Given its large inter-individual pharmacokinetic variability, therapeutic drug monitoring (TDM) is highly required to optimize the effectiveness and tolerance of this treatment. The aim of this study is to analyze the results of clozapine concentrations (C0) and deduce the interest of the TDM of this drug in patients with schizophrenia

Materials and methods

We conducted a 5-year longitudinal study, performed in Clinical Pharmacology Department of Monastir, including Tunisian patients with schizophrenia. Clozapine levels were measured using a liquid-phase chromatographic method. Analysis of trough concentrations (C0) was performed based on clinician adherence to our recommendations, comparing the 'TDM group' and the 'Control group'

Results

A total of 104 patients with a sex-ratio of 4.2 were included in our study. The median age was 35±13 years with a mean weight of 78.4±12 kg. The overall analysis showed that among 232 analyzed C0, 30% were within the therapeutic range, while 51% were below and 19% were above this range. We demonstrated the absence of a significant correlation between C0 and the dose of clozapine (absolute or weight-adjusted). The study of the influence of demographic data and tobacco consumption on the variation of C0/D showed a significant implication of sex ($p<0.001$). The comparative longitudinal analysis demonstrated a significant improvement in C0 in the therapeutic range in the "STP group" (19% vs 44%; $p=0.003$).

Discussion / Conclusion

Our results demonstrate the undeniable interest of TDM of clozapine in patients with schizophrenia, through a global and longitudinal analyses based on clinician adherence to our recommendations. Therefore, it is recommended to systematically perform TDM to optimize the clinical response to clozapine and minimize its toxic side effects.

00528
Impact of body mass index and body surface area on perampanel concentration-to-dose ratio in children with epilepsy: A real-world study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Perampanel (PER) dosing in children is typically based on actual body weight (mg/kg). However, the influence of body composition (obesity, leanness) on PER pharmacokinetics remains unclear. This study aimed to compare the associations of various anthropometric indices with PER concentration-to-dose (C/D) ratio.

Materials and methods

Children on PER maintenance therapy (≥4 weeks) with steady-state trough concentrations were enrolled. C/D ratio was calculated as concentration (μg/L) divided by daily dose per kg body weight. Anthropometric indices included weight, height, BMI, BMI z-score, and body surface area (BSA). Patients were classified as underweight (BMI <5th percentile), normal (5th-85th), or overweight/obese (≥85th) based on WHO growth charts. Correlations were analyzed using Spearman's test, and comparisons among groups used Kruskal-Wallis test.

Results

①305 children included (median age 8.75 years). ② C/D ratio correlated most strongly with BMI (r=0.654, p<0.001), followed by weight (r=0.536) and BSA (r=0.533). ③ Overweight/obese children (n=105) had significantly lower C/D ratio than normal-weight children (6221.31±4861.83 vs 3163.98±1492.62, p<0.001). ④ Underweight children (n=102) had higher C/D ratio (1846.33±993.39 vs 3163.98±1492.62, p<0.001). ⑤ Multivariate regression identified BMI (β=0.654, p<0.001) as independent predictors.

Discussion / Conclusion

BMI predicts peramphenol C/D ratio better than body weight in children. Obese children require higher weight-based doses; underweight children may need lower doses. BMI should be considered in pediatric perampanel dosing algorithms.BMI predicts peramphenol C/D ratio better than body weight in children. Obese children require higher weight-based doses; underweight children may need lower doses. BMI should be considered in pediatric perampanel dosing algorithms.

00531
Evaluation of FDA Label–Recommended Digoxin Dosing Using Therapeutic Drug Monitoring in Korean Clinical Practice

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Digoxin is commonly used for atrial fibrillation and heart failure; however, its narrow therapeutic index and pharmacokinetic variability necessitate therapeutic drug monitoring (TDM). Reflecting its predominant renal excretion and limited tissue distribution, the FDA-approved prescribing information recommends maintenance dosing based on creatinine clearance (CrCL) and lean body weight (LBW). This study evaluated whether these recommendations achieve appropriate therapeutic exposure in Korean patients using real-world TDM data.

Materials and methods

This retrospective single-center study included patients treated with digoxin at Seoul National University Hospital between January 2024 and December 2025. Patients were included if they had at least one serum digoxin concentration (SDC) measurement with available demographic data and serum creatinine values. The maintenance dose was defined as the regimen maintained for at least 2 weeks at the time of TDM. The therapeutic SDC range was defined as 0.5–0.9 ng/mL. Patients were categorized by concordance between prescribed and label-recommended dosing as lower, concordant, or higher.

Results

Among 1,977 screened patients, 210 met the inclusion criteria. Lower-than-recommended doses were prescribed in 103 patients (49.0%), concordant doses in 82 patients (39.0%), and higher-than-recommended doses in 25 patients (11.9%). Mean SDCs were 0.400 ± 0.353, 0.621 ± 0.476, and 1.520 ± 1.076 ng/mL for the lower, concordant, and higher groups, respectively. In the lower-dose group, 20.4% achieved therapeutic and 74.8% had subtherapeutic concentrations. In the lower-dose group, 20.4% achieved therapeutic concentrations and 74.8% were subtherapeutic. In the concordant group, 25.6% were therapeutic, 51.2% subtherapeutic, and 23.2% supratherapeutic. In the higher-dose group, 12.0% were therapeutic and 69.2% were supratherapeutic.

Discussion / Conclusion

FDA label–concordant dosing was associated with a substantial proportion of subtherapeutic concentrations. These findings suggest that LBW- and CrCL-based label recommendations alone may not ensure optimal digoxin exposure in Korean patients and support routine TDM to guide individualized dosing.

Keywords

digoxin, therapeutic drug monitoring, maintenance dose, renal function, lean body weight

00538
Exploring therapeutic drug monitoring of CFTR modulator therapy in cystic fibrosis

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Cystic fibrosis transmembrane conductance regulator (CFTR) modulators have transformed cystic fibrosis (CF) management by restoring CFTR function, resulting in improved pulmonary function and overall clinical outcomes. The triple-combination therapy ivacaftor/tezacaftor/elexacaftor (IVA/TEZA/ELEX) is administered at weight-based standard doses. However, substantial interindividual pharmacokinetic variability and numerous potential drug–drug interactions may lead to inconsistent therapeutic response or toxicity (particularly hepatotoxicity and neuropsychiatric side-effects). Therapeutic drug monitoring (TDM) may therefore support individualized dosing and optimize treatment safety and efficacy. Additionally, as IVA/TEZA/ELEX must be taken with fat-containing food to ensure adequate absorption, TDM may help assess correct administration. Currently, no established therapeutic or toxic reference ranges are available. This study aimed to characterize trough plasma concentrations of IVA/TEZA/ELEX in clinically stable patients.

Materials and methods

Trough plasma samples were collected during routine follow-up visits from patients with CF receiving IVA/TEZA/ELEX. Drug concentrations were quantified using an in-house developed LC-HRMS method. Data analysis focused on patients weighing ≥30 kg receiving the standard morning dose (150/100/200 mg IVA/TEZA/ELEX) with

presumed good therapeutic response and no evident toxicity. Concentrations below the limit of quantification (LOQ) were imputed as half the LOQ (0.0625 mg/L) for calculation of medians and interquartile ranges (IQRs). In a subsequent phase, trough concentrations will be correlated with clinical parameters (e.g., sweat test and fecal elastase).

Results

Trough concentrations from 34 patients (≥30 kg) were available at interim analysis. Median (IQR) concentrations were 0.391 mg/L (0.165–0.618) for IVA, 1.58 mg/L (0.777–2.01) for TEZA, and 3.05 mg/L (0.539–4.09) for ELEX. For now there is too little data available to make calculations on 75/50/100 (<30 kg) and 60/40/80 (<14 kg) dosing regimens.

Discussion / Conclusion

TDM of IVA/TEZA/ELEX shows promise in CF management. Pending the establishment of definitive therapeutic ranges, targeting observed median trough concentrations may provide clinical guidance.

Keywords

CFTR modulators - cystic fibrosis - therapeutic drug monitoring - reference values

00655
Impact of Unannounced Plasma Drug Monitoring in Specialized Hypertension Consultation: A Retrospective Real-Life Study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Medication non-adherence is a major barrier to blood pressure (BP) control. While indirect methods often overestimate adherence, unannounced plasma drug monitoring (PDM) provides an objective "snapshot" of patient behavior.

Materials and methods

We devopped a simple, rapid and sensitive quantification method for 21 anti-hypertensive or diuretic drugs in plasma for clinical applications using liquid chromatography with tandem mass spectrometry (LC-MS/MS) (Boudin et al, 2025). We conducted a retrospective study of our first 24 patients who underwent unannounced PDM immediately following a specialized hypertension consultation at Grenoble University Hospital. Patients were categorized into three groups based on PDM results: Observant (100% of prescribed drugs detected), Non-Observant (0% detected), and Partially Observant (some drugs detected). Statistical analysis was performed using Kruskal–Wallis test and Fisher’s exact test.

Results

The PDM revealed that only 21% (n=5) of patients were fully observant, while 46% (n=11) were partially observant and 33% (n=8) were totally non-compliant. Systolic Blood Pressure (SBP) was significantly higher in the Non-Observant group (189.0 ± 19.4 mmHg) compared to the Observant group (174.5 ± 17.3 mmHg) ($p < 0.05$). There was a clear correlation between the complexity of the regimen and non-adherence. Observant patients had significantly fewer prescribed treatments (2.4 ± 1.2) compared to Non-Observant (4.5 ± 2.1) and Partially Observant (3.7 ± 1.3) patients ($p < 0.05$). Non-adherence was more frequent in women (73.6% of the non/partially observant groups) and older patients (Mean age 53.0 in Non-Observants vs 41.0 in Observants).

Discussion / Conclusion

In patients referred in Specialized Hypertension Consultation for suspected resistant hypertension, unannounced plasma antihypertensive drug measurements revealed a high prevalence of pseudo-resistance due to poor adherence, often involving multiple missing treatments. This strategy provides valuable objective information to avoid futile treatment escalation and may significantly impact clinical decision-making and patient management

Reference(s)

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Keywords

Hypertension, Adherence, LC-MS/MS

00659
Carbon Emission Reduction Through Microsampling for Therapeutic Drug Monitoring in Remote Kidney Transplant Care

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Background:
Healthcare accounts for 4–5% of the world's carbon footprint(1). Therapeutic drug monitoring (TDM) of immunosuppressants is essential for kidney transplant recipients to prevent rejection and drug-related toxicity(2). This presents logistical challenges in geographically remote regions of Australia where large distances separate patients from laboratories(3). Venous blood sampling requires cold-chain transport, insulated packaging, and courier transport. Mitra® microsampling device (VAMS™) enables ambient transport and may reduce transport-related carbon emissions. This study calculates carbon emission savings associated with replacing cold-chain fresh whole blood transport with ambient temperature transport of microsampling devices.

Aims:
To calculate the carbon emissions from cold transport of fresh blood sample vs. ambient temperature transport of Mitra® VAMS™ microsample.

Materials and methods

A limited comparative carbon footprint analysis was performed for fresh blood cold-chain transport and ambient Mitra® microsample devices. Fresh venous sampling included an EDTA blood tube, secondary biohazard packaging, insulated polystyrene box, and ice packs. Microsampling consisted of VAMS™ device in a plastic

clamshell, absorbent sleeve and express post plastic sleeve envelope. Emissions were calculated using Australian freight emission factors (g CO_2e/tonne-km), proportionally allocated by shipment weight over 1km. Additional emissions from packaging, manufacture, and ice pack freezing were included for cold-chain samples.

Results

Cold-chain transport generated approximately 605.3 g CO_2e per sample per km, driven by weight and packaging. Microsampling transport generated 8.96 g CO_2e per sample per km. This represents a 98.5% reduction in transport-related emissions per test.

Discussion / Conclusion

Ambient microsampling for immunosuppressant monitoring substantially reduces transport-associated carbon emissions by 98.5% compared with conventional cold-chain venous sampling. Integration of VAMS™ into remote transplant care offers both clinical accessibility for remote patients and measurable environmental benefit, aligning TDM practice with healthcare decarbonisation and sustainable laboratory practice goals. Further studies are required to establish a comprehensive dry blood spot monitoring program for kidney transplant recipients.

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Keywords

Therapeutic Drug Monitoring; Immunosuppressants; Kidney Transplantation; Volumetric Absorptive Microsampling; Rural and Remote Healthcare; Healthcare Carbon Footprint; Sustainable Laboratory Practice

00677
The Evolving Role of Levetiracetam TDM in Critical Care: Real-World Evidence from a Five-Year Single-Center Experience

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

In convulsive status epilepticus (SE), rapid seizure control within the first two hours is a critical determinant of clinical outcome. While levetiracetam is increasingly utilized as a second-line treatment for established SE, the AGNP guidelines score the therapeutic drug monitoring (TDM) of levetiracetam as "potentially useful"; particularly in critical care. This study evaluates the real-world impact and routine management of levetiracetam TDM in critical care and emergency settings.

Materials and methods

We performed a retrospective analysis of routine levetiracetam TDM requests processed by the Pharmacology Unit of ASST Spedali Civili (Brescia, Italy) between 2021 and 2025. Drug concentrations were determined using a validated LC-MS/MS method and classified as "under", "in", or "above" the reference range (10–40 mg/L) according to AGNP guidelines.

Results

A total of 5,651 TDM requests from 2,527 patients were analyzed. While overall volume remained stable, TDM requests originating specifically from intensive and emergency units saw a nearly threefold increase, rising from 6.7% in 2021 to 17.5% in 2025. By selecting first-time requests in critical care units (n=387), we found that most concentrations were within range (n=270, 69%). Patients were more at risk to be underdosed (18%) than overdosed (13%) like the total population. Pediatric requests represent the 9.8% of the total. A significant positive correlation was identified between levetiracetam concentrations and age ($p < 0.0001$). Older patients demonstrated a significantly higher probability of exceeding the reference range compared to younger cohorts ($p < 0.05$).

Discussion / Conclusion

Our findings reflect the growing integration of levetiracetam into emergency treatment protocols. The significant correlation between age and plasma levels underscores the necessity of TDM for personalizing doses in vulnerable populations, such as the elderly and neonates. These data suggest that TDM is transitioning from a supplemental tool to an essential component of precision medicine in the emergency management of SE.

Keywords

Levetiracetam, TDM, emergency

00678
Therapeutic Drug Monitoring of Brivaracetam: Real-World Exposure Variability and Clinical Implications

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Brivaracetam (BRV) is a third-generation antiseizure medication approved as adjunctive therapy for focal seizures in patients aged ≥16 years. Although its pharmacokinetic profile is considered predictable, currently proposed therapeutic reference ranges are largely derived from registrative studies rather than real-world data. Evidence linking BRV serum concentrations with clinical outcomes and drug-drug interactions remains limited. This study aimed to characterize BRV trough concentrations in clinical practice and evaluate the impact of enzyme-inducing antiseizure medications (ASMs) on exposure.

Materials and methods

We conducted a retrospective analysis of routine BRV TDM requests processed by the Pharmacology Unit of ASST Spedali Civili (Brescia, Italy) between 2020 and 2024. Demographic and clinical variables were collected. Concentration variability was assessed using coefficients of variation (CV), including dose-normalized

concentrations to explore exposure variability independent of prescribed dose. Associations between BRV levels and clinical covariates were also evaluated.

Results

A total of 121 BRV trough measurements from 58 patients (mean age 47 years) were included. Most patients (81%) had drug-resistant epilepsy and were receiving more than one drug; 43% were co-treated with enzyme-inducing ASMs. Concentrations ranged from 0.2 to 5.5 mg/L (mean 1.3 mg/L). Marked interindividual-variability was observed (CV 63.5%), which increased after dose-normalization (CV 141%), suggesting substantial variability in BRV apparent clearance. No sex-related differences were observed (p=0.704), whereas age showed a significant positive correlation with serum concentrations (p=0.007). Co-treatment with enzyme-inducing ASMs was associated with significantly lower BRV levels (1.0 vs 1.5 mg/L, p=0.001) consistent with increased metabolic clearance. Adverse events were infrequent and not related BRV plasma trough concentrations.

Discussion / Conclusion

In real-life setting BRV exhibited considerable real-world exposure variability, which was mainly driven by concomitant enzyme inducing ASM. These findings support the clinical utility of TDM to identify altered clearance and optimize individualized dosing. Furthermore, the absence of toxicity at high concentrations suggests that existing reference ranges may be widened.

00692
Association Between Risperidone Plasma Concentrations, D2 Receptor occupancy and Treatment Response: A Systematic Review, Meta-analysis and Individual Participant Data Meta-analysis

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Individual variability in response to antipsychotic therapy remains a significant challenge in clinical psychiatry. This study investigates the association between active moiety concentrations of risperidone and 9-hydroxyrisperidone, dopamine D2 receptor occupancy, and clinical improvement, aiming to establish a basis for optimized dosing strategies that can be tailored to individual patient profiles.

Materials and methods

A meta-analytic approach was applied to analyze data from studies examining risperidone and paliperidone treatment outcomes in relation to active moiety concentration and D2 receptor occupancy. Sensitivity analyses were conducted on studies employing high-quality therapeutic drug monitoring (TDM) methodologies to mitigate methodological heterogeneity. Positron emission tomography (PET) imaging data were included to assess D2 receptor occupancy, with a therapeutic target range of 60-78% occupancy identified as the efficacy threshold.

Results

Clinical responders had significantly ($p<0.01$) higher active moiety concentrations than non-responders when stringent TDM protocols were applied, although this finding was tempered by methodological variability. The relationship between concentration and D2 receptor occupancy was stronger than that between dose and occupancy, suggesting that plasma concentration is a more accurate pharmacodynamic predictor ($p<0.05$). A therapeutic range of 12-45 µg/L was proposed, aligning with the D2 receptor occupancy target for optimal efficacy and safety.

Discussion / Conclusion

This study supports the clinical value of TDM for risperidone and paliperidone in guiding individualized therapy. Monitoring plasma concentration, rather than relying on dose alone, may improve therapeutic outcomes by better predicting efficacy and tolerability, reinforcing the value of concentration-based strategies in personalized antipsychotic management.

Reference(s)

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Keywords

risperidone, treatment response, plasma concentrations, D2 occupancy, schizophrenia, meta-analysis, therapeutic drug monitoring

00694
Interest of Therapeutic Drug Monitoring (TDM) of Valproic Acid in Tunisian Critically Ill Patients

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Valproic acid (VPA), a widely used anticonvulsant, exhibits highly variable pharmacokinetics in critically ill patients due to organ dysfunction, hypoalbuminemia, and drug interactions, which may increase the risk of toxicity or subtherapeutic dosing. Therefore, therapeutic drug monitoring is essential to ensure both safety and efficacy in the ICU

Materials and methods

A retrospective case series was conducted on plasma valproic acid (VPA) concentrations collected from intensive care unit patients and sent to the Monastir Clinical Pharmacology Department. Dose adjustments were made as needed to maintain VPA concentrations within the therapeutic range of 50–100 µg/mL.

Results

A total of 34 plasma valproic acid (VPA) concentrations were collected from 29 men and 5 women, with a median age of 26.7 years (range: 16–41). VPA was indicated for status epilepticus in all cases. Twenty patients received VPA as a continuous infusion, while the remaining patients received it via a gastric tube. VPA concentrations were below the therapeutic range in 35.2% of patients, within the

therapeutic range in 52.9%, and above the therapeutic range in 12.5%. Therapeutic drug monitoring identified drug interactions in 6 patientsof the patients with subtherapeutic levels: four with Tienam and two with Meropenem. Dose adjustments were proposed, resulting in controlled VPA concentrations within the therapeutic range. For the remaining six patients with subtherapeutic levels, administration methods were revised to optimize exposure. For the remaining six patients with persistently subtherapeutic levels, administration methods were carefully reviewed and revised, such as switching from intermittent to continuous infusion, optimizing gastric tube delivery, or adjusting timing relative to concomitant interacting drugs, in order to maximize drug absorption and maintain adequate plasma concentrations.

Discussion / Conclusion

Therapeutic drug monitoring is essential for valproic acid in critically ill patients due to variable pharmacokinetics and drug interactions. Dose adjustments and optimized administration ensure safe and effective treatment in the ICU.

00699
Are Large Language Models Ready for Therapeutic Drug Monitoring? A Multi-Dimensional Performance Evaluation Across Real-World Clinical Scenarios

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic drug monitoring (TDM) requires precise pharmacokinetic reasoning, individualized dose adjustment, and strict adherence to safety standards. Although large language models (LLMs) have demonstrated strong performance in general medical examinations and documentation tasks, their reliability in high-risk pharmacotherapeutic decision-making remains unclear. This study evaluated whether contemporary LLMs are ready for clinical application in TDM.

Materials and methods

In this cross-sectional benchmarking study, four mainstream LLMs (ChatGPT-5, Gemini-3 Pro, Qwen3-Max, and DeepSeek-R1) were evaluated using a standardized 60-item TDM test set derived from OSCE cases, real-world consultation records, case reports, and current guidelines. Each item was submitted three times per model (total responses: n=720) to assess reproducibility. Responses were independently scored by clinical pharmacists across six domains: accuracy, logical coherence, comprehension, reproducibility, reliability, and clinical safety. Performance was compared across models and stratified by task complexity (knowledge recall, concentration interpretation, dose adjustment).

Results

Mean overall accuracy ranged from 76.3% to 81.8% across models, while safety scores remained consistently low (59.4%–61.2%). Comprehension scores were uniformly high (98.1%–100%), and logical coherence ranged from 85.2% to 92.7%. Accuracy declined significantly with increasing task complexity (knowledge recall: 88.5% vs. concentration interpretation: 74.2% vs. dose adjustment: 68.9%, $p<0.01$). Reproducibility analysis demonstrated moderate response variability, with intra-model score fluctuations of 6–9% across repeated submissions. Clinically relevant safety deficiencies were identified in 38% of dose-adjustment scenarios, including inappropriate dose modifications and incomplete monitoring recommendations.

Discussion / Conclusion

Despite advanced linguistic and reasoning capabilities, current LLMs exhibit substantial limitations in safety and reliability for TDM-related clinical decision-making. Their performance degradation in complex pharmacokinetic tasks highlights the need for domain-specific training, guideline grounding, and robust validation frameworks before integration into individualized pharmacotherapy practice.

Keywords

Therapeutic Drug Monitoring; Large Language Models; Clinical Decision-Making; Individualized pharmacotherapy

00703
From Identifiability Screening to Meta-Model Development: A Simulation Study of Clozapine–Norclozapine Pharmacokinetics

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Clozapine is a second-line antipsychotic for treatment-resistant schizophrenia, typically administered twice daily. In a previous study, population pharmacokinetic (popPK) models of clozapine and norclozapine were reviewed, and structural identifiability was evaluated using PFIM. Of 33 screened models, only five could be assessed—the rest were excluded due to non–parent–metabolite modeling, insufficient data, animal studies, or language limitations. Among these, only two met predefined criteria of relative standard errors (RSE) below 30%. This study extends that work through simulation-based analyses to evaluate model robustness and develop a unified meta-model.

Materials and methods

Six thousand virtual pharmacokinetic (PK) profiles were simulated per selected model using Simulx (SimulationPlus), with repeated dosing to ensure steady-state conditions. Sampling times were set at 0.75, 1.5, 3.5, 5, and 11.75 hours post-dose, following the original studies. The simulated datasets were merged, and 300 virtual patients were randomly selected and divided into three splits. Doses reflected minimum, median, and maximum reported values, accounting for covariates such as smoking status or sex. Split 1 was used to develop a new model in Monolix; splits 2

and 3 were used for re-estimation and reproducibility assessment. Structural identifiability was reassessed using PFIM.

Results

The meta-model included lag time, first-order absorption, a two-compartment structure for clozapine, a one-compartment structure for norclozapine, complete metabolic conversion (kpm), and metabolite elimination (Clm). It was successfully fitted across splits with consistent parameter estimates. PFIM confirmed good identifiability (RSE < 30%). Body weight was retained as a covariate on the central volume. Although smoking status influenced metabolism, no covariate effect could be reliably estimated on Kpm or Clm.

Discussion / Conclusion

Simulation-based evaluation enabled development of a structurally identifiable and reproducible clozapine–norclozapine popPK meta-model. External validation with independent clinical datasets is required before routine therapeutic drug monitoring implementation.

00715
Analysis of the Efficacy and Safety of Glucocorticoids Combined with Mycophenolate Mofetil in the Treatment ofSevere Henoch-Schönlein Purpura in Children

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

To investigate the efficacy and safety of glucocorticoids combined with mycophenolate mofetil in the treatment of children with severe Henoch-Schönlein purpura (HSP)

Materials and methods

A retrospective analysis was conducted on 70 pediatric cases of severe HSP hospitalized at the First Affiliated Hospital of the University of Science and Technology of China from January 2020 to December 2025. Patients were divided into an observation group (42 cases, glucocorticoids + mycophenolate mofetil) and a control group (28 cases, glucocorticoids alone). All children received basic treatments, including dietary management, gastric protection, anticoagulation, vitamin D supplementation, and fluid therapy. Clinical effectiveness, readmission rates, recurrence rates, and adverse reactions were compared between the two groups.

Results

During hospitalization, the observation group showed significantly higher clinical effectiveness than the control group ($P < 0.05$). After discharge, the observation group had a significantly lower readmission rate compared to the control group ($P < 0.05$). No severe adverse reactions were observed in either group

Discussion / Conclusion

Glucocorticoids combined with mycophenolate mofetil significantly improve clinical outcomes and reduce readmission rates in children with severe HSP, with a high safety profile.

Keywords

Children; Henoch-Schönlein purpura; Mycophenolate mofetil Glucocorticoids

00728
Assessment of the pharmacokinetic profile of continuous subcutaneous apomorphine infusion in stable patients with Parkinson's disease

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Continuous subcutaneous apomorphine infusion (CSAI) is indicated for patients with advanced Parkinson's disease (PD) and (non)motor fluctuations. While the drug has been known since a very long time, limited data exists on its pharmacokinetics. Moreover, to date, there is no established exposure – response relationship for apomorphine in PD.

The aim of this study was to describe CSAI pharmacokinetics and evaluate the plasma exposure in patients with stable PD.

Materials and methods

Eighteen stable patients, treated with diurnal CSAI (portable infusion pump CRONO-PAR), have been included in this phase II pharmacokinetic study. Steady-state concentrations (Css) before CSAI discontinuation and 180 min after infusion restart on mornings were evaluated. Area under the curve (AUC) of CSAI were also compared between patients.

Results

The mean CSAI Css before discontinuation of the pump was 36.8 ± 7.5 ng/mL, while it was 26.4 ± 12.7 ng/mL three hours after pump restart. AUC was 107.1 ± 33.8 ng.h/mL. These pharmacokinetic parameters presented a low to moderate variability: coefficient of variability of 20.5, 48.2 and 31.5% for Css before discontinuation, Css after discontinuation and AUC.

Discussion / Conclusion

To our knowledge, this is the first study aiming at documenting the pharmacokinetics of diurnal CSAI in stable PD patients. Given the relatively close value of the parameter in a population where the treatment is effective, these results highlight the possibility to inform the therapeutic range of the drug and offer a pathway to therapeutic drug monitoring, supporting the concept of closed-loop systems in PD.

Keywords

Neurology ; Therapeutic range ; Dopaminergic agonist

00735
From Pain to Treatment: Plasma Concentration of Cannabinoids in Patients Treated with Cannabis Oil Extracts

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Chronic and neuropathic pain represents a major therapeutic challenge, often inadequately managed with conventional treatments. Medical cannabis (MC), particularly standardized oil-based preparations, has emerged as a promising adjunct therapy in pain management. Despite its growing use, real-world pharmacokinetic (PK) data on cannabinoids and their metabolites in treated patients are lacking.

The present study evaluated steady-state plasma concentrations of Δ9-tetrahydrocannabinol (THC), cannabidiol (CBD), and six major metabolites, including 11-hydroxy-THC, 11-nor-9-carboxy-THC (COOH-THC), COOH-THC-glucuronide, and 7-hydroxy-CBD, in patients with chronic or neuropathic pain treated with MC.

Materials and methods

31 patients treated with MC oil extract at concentrations of 5 mg/mL THC + 5 mg/mL CBD were enrolled. The blood withdrawn was obtained before the new dose assumption at the steady state and metabolites plasma concentrations were measured with a validated UHPLC-MS/MS method.

Results

All analytes were quantifiable, supporting the feasibility of therapeutic drug monitoring (TDM) in this population. Inactive elimination metabolites exhibited the highest plasma levels, followed by active intermediates and parent compounds, reflecting known oral PK pathways. A significant sex-related difference was observed for CBDA concentrations ($p = 0.011$), while age and BMI showed no correlation with plasma exposure. A correlation between vitamin D plasma levels and normalized COOH-THC ($p=0.008$) plasma levels (ng/mL/mg) was suggested.

Discussion / Conclusion

These findings underscore the clinical utility of plasma cannabinoid quantification to optimize individual dosing, avoiding toxicity. TDM may play a pivotal role in the safe and effective personalization of MC therapy in chronic pain management. This study provides PK data to guide future clinical protocols and supports the integration of TDM in routine MC prescribing.

Keywords

THC; CBD; pharmacokinetics; therapeutic drug monitoring

00744
Nephrolithiasis During Adalimumab and Vedolizumab Therapy in Inflammatory Bowel Disease Patients: Emerging Post-Marketing Safety Signals

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Adalimumab (ADA, anti-TNFα) and Vedolizumab (VDZ, anti-integrin) are cornerstone inflammatory bowel disease (IBD) therapies. While clinical trials established their initial safety, real-world evidence is critical for identifying rare adverse events (AEs) and long-term risks. Recent post-marketing data have reported emerging signals, including nephrotoxicity.

Materials and methods

This analysis integrates findings from a retrospective real-world cohort study and a large-scale disproportionality analysis using the FDA Adverse Event Reporting System (FAERS) database. Exposure-adjusted incidence rates (per 100 patient-

years [PYs]), Reporting Odds Ratios (ROR), and Proportional Reporting Ratios (PRR) were calculated.

Results

In the cohort study, 217 ADA and 107 adult VDZ patients were monitored at a tertiary center in Serbia between 2021 and 2022. Crohn's disease was overrepresented with 74%. Median ADA exposure was 903 days (interquartile range, IQR 365-1466) and VDZ exposure 605 days (IQR 209-860). The exposure-adjusted incidence rate of nephrolithiasis in the ADA group was 0.67/100 PYs and in the VDZ group 2.46/100 PYs. Nephrolithiasis was identified as a significant unlisted safety signal for VDZ through disproportionality analysis (ROR/PRR > 1). None of the patients with nephrolithiasis had concurrent mesalazine. There were no ADA or VDZ therapy discontinuations due to AEs.

Discussion / Conclusion

Nephrolithiasis incidence was nearly fourfold higher with VDZ than with ADA. In the FAERS database, nephrolithiasis met the statistical thresholds for a VDZ signal of disproportionate reporting, confirming it as an unlisted AE in the current U.S. Prescribing Information (USPI). While IBD itself is a known risk factor for nephrolithiasis, these findings suggest an added drug-specific association. Emerging signals like nephrolithiasis necessitate continued clinical vigilance, especially in patients with existing risk factors. Further prospective, multicenter studies and pharmacogenomic research are required to validate these findings and clarify the underlying mechanisms of these emerging risks.

Reference(s)

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Keywords

pharmacovigilance; kidney stones; nephrotoxicity; biologics; inflammatory bowel disease.

Pharmacogenetics

00020
Exploratory Pharmacogenetic and Pharmacokinetic Study of Bulevirtide in Patients with Chronic Hepatitis D

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Bulevirtide is an HDV entry inhibitor targeting the sodium taurocholate co-transporting polypeptide (NTCP). Despite its efficacy, substantial inter-individual variability in pharmacokinetics and treatment response was reported. This study evaluated bulevirtide plasma levels and clinical parameters over time and explored the influence of *NTCP* genetic variants on drug exposure and clinical outcomes.

Materials and methods

Patients with HDV infection treated with bulevirtide were enrolled. Clinical, biochemical and virological parameters, together with bulevirtide plasma concentrations (liquid chromatography), were assessed at baseline and at weeks (W) 4,12,24,36,48 and 60. *NTCP* genetic polymorphisms (rs8011311/rs2296651) were analyzed using real-time PCR.

Results

Of the 17 enrolled patients, four were excluded due to suboptimal treatment adherence. In the analyzed cohort, 76.9% were male, with median age of 50 years and BMI of 24.4 kg/m²; 46.2% had cirrhosis. At W60, significant differences were observed in AST (p=0.049), ALT (p=0.023) and INR (p=0.049). Lipid profile was unaffected, while a non-significant increase in bile acids was noted. No treatment-related adverse events occurred. Liver stiffness decreased at W48/W60 compared with baseline. At W60, virological, biochemical and combined responses were achieved in 27.3%, 46.2% and 27.3% of patients, respectively.

Median bulevirtide plasma concentrations increased over time, ranging from 0.4 ng/mL at W4 to 1.1 ng/mL at W60. BMI and concomitant medications did not influence drug exposure, whereas female sex was associated with higher bulevirtide concentrations. Patients with liver stiffness>12kPa showed reduced early drug exposure, which increased at later time points in parallel with stiffness improvement. The *NTCP* rs8011311 GG genotype was associated with higher bulevirtide concentrations and a trend toward a higher combined response rate compared with GC/CC genotypes.

Discussion / Conclusion

This study provides bulevirtide plasma concentrations in patients treated up to 60 months and highlights the potential role of liver stiffness and pharmacogenetics in modulating drug exposure. Larger studies are needed to confirm these findings.

Reference(s)

Toniutto et al. Sodium taurocholate cotransporting polypeptide (NTCP) polymorphisms may influence HDV RNA load and early response to bulevirtide. J Hepatol., 2024.

Keywords

Chronic Hepatitis D; Drug exposure; NTCP polymorphisms; personalized therapy; treatment outcome

00040
Evaluation of the first Vancomycin dose using model informed precision dosing software

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The value of therapeutic drug monitoring is no longer in doubt. It is strongly recommended, particularly in the case of vancomycin treatment. Objective: comparing the dosage recommended by the NextDose® software with the dosage actually administered to a group of adult patients treated with vancomycin

Materials and methods

We conducted a retrospective study at department of Clinical Pharmacology of National Pharmacovigilance Center. We included 33 Tunisian patients with normal renal function, for whom we had information on gender, weight, height and the date of vancomycin treatment initiation. We compared the actual maintenance doses with those predicted by the NextDose software, as well as the actual plasma concentrations with the predicted ones. Then we compared patients according to vancomycin concentrations.

Results

Initial doses of vancomycin only were evaluated. No significant differences between the initial prescribed and predicted maintenance doses, nor between the measured and predicted concentrations. The comparison according to vancomycin concentrations, showed no significant differences. Assessment based on plasma concentrations showed measured vancomycin concentrations significantly lower than

the concentration predicted among the subtherapeutic patient group, (12.64 mg/l vs 16.7 mg/l; p< 0.0001), and was borderline significant among the group within the therapeutic range (18.18mg/l vs 16.7mg/l; p= 0.056).

Discussion / Conclusion

Discussion: These results suggest that prescription accuracy may be improved through the use of prediction software. It should be noted that this study's major limitations are the small sample size and lack of clinical data.

Conclusion: The validity of this software, or others, could be verified through prospective or real-time work.

Keywords

Monitoring, Vancomycine, Dose Prediction, Bayesian software, NextDose, Therapeutic interval, Prescription, Plasma concentration.

00079
Voriconazole as an alternative oral treatment in fluconazole-resistant urinary candidiasis: the Rennes University Hospital experience

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Urinary candidiasis increasingly involves *Candida* isolates with reduced susceptibility to fluconazole (FLZ) that complicates therapeutic strategy. The minimum inhibitory concentrations (MICs) of *Candida* spp. for voriconazole (VRZ) are usually low, making it a potential alternative oral treatment. The aim of this work was to evaluate urinary and plasma exposure in patients treated with VRZ for FLZ-resistant urinary candidiasis, and to assess their clinical outcome.

Materials and methods

VRZ concentrations were measured by liquid chromatography-tandem mass spectrometry. Urine was collected over a 12-hour period between two VRZ administrations. Demographic, mycological and clinical data were prospectively gathered, as well as information on treatment dosage and co-treatment with flucytosine. MICs were determined by gradient strip method (E-test®, Biomérieux). A positive clinical outcome was defined by the improvement or disappearance of urinary functional signs, apyrexia, and overall improvement in clinical condition.

Results

Twelve patients were treated with VRZ for a median duration of 21 days [14-100]. *C. glabrata* strain was found in 75% of cases (*C.krusei*: n=2; *C.parapsilosis*: n=1). Median VRZ MIC, excluding *C.parapsilosis*, was 0.25 µg/mL [0.09 ;0.50]. Median VRZ urinary concentration was 2.6 µg/mL (range: 0.3 -5.5), and VRZ plasma trough concentration was 3.4 µg/mL (range: 0.3 -6.7), with good correlation between the two parameters (R^2= 0.94). VRZ urinary exposure was good and above MIC in 91.6% of cases. Six patients were treated with adjunctive flucytosine. Clinical improvement was observed for 91.6% of patients, one patient not improved probably related to the presence of a kidney stone.

Discussion / Conclusion

VRZ seems to be an interesting option in FLZ-resistant urinary candidiasis treatment, despite its low urinary excretion as an unchanged compound, ≤1.5% according to Schulz (Schulz Drug Metab Rev 2019). The majority of patients showed clinical improvement. Therapeutic drug monitoring allows the optimization of VRZ treatment for uncomplicated urinary candidiasis due to fluconazole-resistant strains.

Reference(s)

Schulz J, Kluwe F, Mikus G, Michelet R, Kloft C. Novel insights into the complex pharmacokinetics of voriconazole: a review of its metabolism. Drug Metab Rev 2019;51(3):247–65.

00115
From Evidence to Practice: Identifying Determinants of Pharmacogenomics Implementation in Paediatric Oncology

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Adverse drug reactions (ADR) significantly impact children with cancer: 80% experience ADRs, which are fatal for up to 10%, and 30% are left with life-long health complications at a cost of 1.2 billion to the Australian healthcare system. Up to 75% of ADRs may be avoided through pharmacogenomics (PGx), which enables genetically informed prescribing. Despite its potential to improve medication safety and effectiveness in paediatric oncology, PGx implementation remains limited. Education is frequently cited as a key enabler, however there is limited synthesis of educational gaps, barriers, enablers, and strategies supporting PGx implementation. This study aims to identify the key determinants influencing PGx implementation in paediatric practice and inform development of a theory-informed educational intervention.

Materials and methods

A systematic review of eligible studies focused on paediatric health care professional's knowledge, attitudes, and PGx education or implementation strategies. Barriers and enablers were deductively mapped to the Capability, Opportunity, Motivation–Behaviour (COM-B) framework.

Results

Of 1,728 records screened, 23 studies met inclusion criteria. Educational interventions commonly improved clinician capability, particularly PGx knowledge and confidence; however, implementation was constrained by opportunity and motivation barriers, including lack of decision-support tools, funding constraints, and poor workflow integration. A second phase of this study will involve stakeholder interviews at a tertiary paediatric hospital.

Discussion / Conclusion

PGx education improves knowledge but insufficiently addresses system-level barriers limiting implementation. A theory-informed, behaviourally grounded approach is required to support sustainable integration into paediatric oncology practice.

00127
Clinical Implementation and Outcome Evaluation of DPYD Pharmacogenomic Testing for Fluoropyrimidine Dosing

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Fluoropyrimidines, including 5-fluorouracil (5-FU) and capecitabine, are widely used in the treatment of solid tumours, such as colorectal, breast, pancreatic, and gastrointestinal cancers. While treatment with fluoropyrimidines is generally well-tolerated, severe toxicity remains a significant issue, particularly in patients with dihydropyrimidine dehydrogenase deficiency caused by *DPYD* variants. Pre-treatment pharmacogenomic testing has been recommended to guide dosing and improve patient safety. This study describes the clinical implementation of *DPYD* genotyping and evaluates outcomes following genotype-guided fluoropyrimidine dosing in a provincial Canadian healthcare system.

Materials and methods

An in-house *DPYD* genotyping assay using the Elucigene DPYD kit (Yourgene Health, UK) was implemented to detect four clinically actionable variants (*DPYD *2A*, **13*, c.2846A>T, *HapB3*). Analytical validation assessed sensitivity, specificity, accuracy, and reproducibility. Clinical workflow integration ensured results were available for treatment planning. Six months post-implementation, a retrospective

review evaluated genotype distribution, chemotherapy regimens, dose modifications, toxicity, and demographics. Data were de-identified prior to analysis.

Results

Analytical validation demonstrated 100% sensitivity, specificity, accuracy, reproducibility, and repeatability. The testing workflow was successfully integrated into routine oncology care with turnaround time compatible with treatment planning. From July to December 2024, 299 patients underwent *DPYD* testing; 22 (7.4%) carried variants, including 20 (6.7%) with reduced DPD function and 2 with normal-function variants. *HapB3* (n=18) was the most frequent risk allele. Among 233 patients receiving fluoropyrimidine-based chemotherapy, 13 were variant carriers. Genotype-guided dosing enabled early dose optimization; all completed at least three treatment cycles. One severe adverse event occurred and was attributed to oxaliplatin rather than fluoropyrimidine therapy.

Discussion / Conclusion

Implementation of in-house *DPYD* genotyping enabled timely genotype-guided fluoropyrimidine dosing and was feasible, safe, and effective in reducing treatment-related toxicity. High analytical performance and rapid turnaround supported clinical integration, demonstrating the value of pharmacogenomic-guided precision dosing to improve chemotherapy safety in routine oncology practice.

Reference(s)

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drug interaction of DPYD and fluoropyrimidines, Eur J Hum Genet 28(4) (2020) 508–517.

Keywords

DPYD, pharmacogenomics, fluoropyrimidine, precision dosing, chemotherapy toxicity

00133
6-Mercaptopurine metabolics profiles and Clinical outcome in TPMT and NUDT15 phenotype during maintenance therapy for paediatric acute lymphoblastic leukaemia

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Thiopurine S-methyltransferase (TPMT) and nucleoside diphosphate-linked moiety X-type motif 15 (NUDT15) are crucial for 6-MP metabolism and linked to myelosuppression. However, clinical markers for treatment monitoring during maintenance are limited. We aimed to investigate the real-world profiles of 6-MP treatment in various TPMT/NUDT15 phenotype groups among paediatric patients with ALL.

Materials and methods

We conducted a prospective cohort study of 104 paediatric patients with ALL during the maintenance phase, collecting baseline data and 5-month follow-ups at 1-month intervals. Patients were genotyped, and we classified their phenotypes for the TPMT and NUDT15 genes. Additionally, we assessed TPMT activity and concentrations of 6-thioguanine nucleotides (6-TGN) and 6-methylmercaptopurine nucleotides (6-MMPN).

Results

The patients were categorized into five phenotype groups: NM/NM (73.08%), NM/IM (17.31%), NM/PM (1.92%), IM/NM (3.85%), and IM/IM (3.85%). The incidence of myelosuppression was about 31% (32/104), and hepatotoxicity was around 16% (17/104). The tolerated 6-MP dose was lowest in the NM/PM group (18 mg/m²) and highest in the IM/IM group (25 mg/m²), which also had the highest rate of early neutropenia (75%). TPMT activity remained stable, while patients with NM/PM had the lowest 6-TGN and 6-MMPN levels, with increases observed in the IM/NM and IM/IM groups after 3 months of treatment.

Discussion / Conclusion

NM/PM and IM/IM patients showed lower tolerance to 6-MP, with IM/IM patients at higher risk for myelotoxicity. The differing mechanisms of toxicity between TPMT and NUDT15 variants indicate a need for a new DNA-TG concentration monitoring method for patients with NUDT15 variants, enabling better dose adjustments.

Keywords

TPMT, NUDT15, ALL, 6-Mercaptopurine, 6-TGN, 6-MMPN

00134
Genotype–Phenotype Associations Between DPYD Polymorphisms and Uracil/Dihydrouracil Metabolic Profiles in Healthy Thai Individuals

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Fluoropyrimidines continue to serve as cornerstone chemotherapeutic agents; however, their clinical application is frequently limited by severe interindividual toxicity associated with dihydropyrimidine dehydrogenase (DPD) deficiency. Although DPYD genotyping and phenotyping strategies are increasingly implemented to optimize dose individualization, population-specific reference data remain limited in Southeast Asia. This study aimed to characterize DPYD genetic variability, establish Thai-specific reference intervals for plasma uracil, dihydrouracil (DHU), and the DHU/uracil (DHU/U) ratio, and investigate genotype–phenotype correlations in healthy Thai adults.

Materials and methods

A total of 135 healthy Thai volunteers were enrolled. Participants were genotyped for clinically relevant and Asian-enriched DPYD variants using targeted assays. Plasma uracil and DHU concentrations were quantified by ultra-performance liquid chromatography–tandem mass spectrometry (UPLC–MS/MS). Reference intervals were derived according to CLSI EP28-A3 guidelines. Genotype–phenotype associations were assessed using nonparametric tests and multivariable Gamma generalized linear models adjusting for age and sex.

Results

No high-risk European DPYD variants (DPYD*2A, *13, c.2846A>T) were detected. In contrast, Asian-predominant variants—DPYD*5, DPYD*9A, and c.1896T>C—were observed at moderate frequencies. The derived reference intervals were 7.23–17.34 ng/mL for uracil, 87.39–176.83 ng/mL for DHU, and 6.75–17.53 for the DHU/U ratio. Among the evaluated variants, DPYD*5 showed a significant genotype–phenotype association, with G/G carriers exhibiting lower uracil concentrations and higher DHU/U ratios, indicating enhanced DPD activity. No significant metabolic effects were observed for DPYD*9A or c.1896T>C. Age and sex independently influenced the DHU/U ratio.

Discussion / Conclusion

This study provides the first population-specific reference intervals for DPD activity markers in Thailand and demonstrates distinct genotype–phenotype patterns for Asian-enriched DPYD variants. The findings underscore the limitations of extrapolating Western toxicity markers to Southeast Asian populations and support the development of regionally tailored pharmacogenomic strategies to improve the safety and precision of fluoropyrimidine therapy.

Keywords

DPYD gene, Uracil and Dihydrouracil, 5-Fluorouracil, Pharmacogenetics

00144
Implementation of pharmacogenetics in kidney transplantation: a national survey among nephrologists

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Pharmacogenetics (PGx) is routinely used in kidney transplantation to individualize tacrolimus dosing and to guide azathioprine therapy through CYP3A5 and TPMT genotyping, respectively. The use of multi-gene panel testing offers the opportunity to optimize additional treatments in these patients who are often exposed to polypharmacy both prior and after the transplantation. Despite these potential benefits, the integration of PGx in nephrology remains largely limited to single-gene testing. This study therefore aimed to assess nephrologists' perceptions, knowledge, and expectations regarding the implementation of PGx in kidney transplantation.

Materials and methods

We conducted a national survey with the support of the Société Francophone de Transplantation (SFT). A questionnaire was sent by email to 1,038 nephrologists and relayed via the SFT website. It included 35 items and was structured into four sections: respondent demographics (7 items), general questions on PGx (3 items), a kidney transplantation clinical case (12 items), and barriers, facilitators, and perspectives (13 items). The clinical case was designed to assess participants' level of knowledge in PGx.

Results

A total of 105 responses were collected (response rate: 10.1%). Only 9.5% of respondents achieved a high PGx knowledge level (≥66% correct responses). 42.9% of them had received training in PGx, and 77.1% reported having been exposed to PGx at least once. The main barriers identified were the cost and reimbursement of tests (62.5% of responses), as well as turnaround time and lack of training, each reported by 50% of respondents. A semi-preemptive approach was favored by 54.3% of respondents, while an acceptable turnaround time between two weeks and one month was reported by 81.9%.

Discussion / Conclusion

French nephrologists are generally favorable toward PGx, but insufficient training still limits its application. The increasing availability of PGx data supports moving beyond immunosuppressants to broader use of PGx in transplant patients' therapeutic management.

00156
Severe toxicity risk of UGT1A1 intermediate metaboliser genotype and other baseline characteristics in patients treated with irinotecan-containing chemotherapy

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Approximately 1 in 3 irinotecan-treated patients experiences severe toxicity. Irinotecan tolerability may differ between UGT1A1 intermediate metabolisers (IMs) and normal metabolisers (NMs), yet both groups are currently recommended the

same standard dose [1]. We assessed irinotecan toxicities and dose intensities in IMs vs NMs, and investigated baseline characteristics predictive of high severe toxicity risk.

Materials and methods

Patients who received systemic irinotecan and *UGT1A1* genotyping between 2017-2024 at six Dutch hospitals were eligible. IMs and NMs with a full irinotecan dose in at least cycle 1 were included in the primary analysis. The primary endpoint was overall, early-onset, severe toxicity (cycles 1-3, grade ≥3, CTCAEv5.0). Other endpoints included neutropenia, diarrhoea and dose modifications. Associations between variables and endpoints were assessed with univariable and multivariable logistic regressions.

Results

A total of 320 IMs and 350 NMs were included. Baseline characteristics were comparable between groups. Overall, early-onset, severe toxicity occurred in 39% of IMs *vs* 26% of NMs (adjusted Odds Ratio (aOR) 1.77 [95%CI 1.24-2.51]; *P*=0.002), severe diarrhoea in 19% of IMs *vs* 13% of NMs (*P*=0.03), and severe neutropenia in 20% of IMs *vs* 14% NMs (*P*=0.002). IMs were dose-reduced more often in subsequent cycles (51% *vs* 42%; *P*=0.02). WHO performance score 2, type of treatment regimen, and abnormal alkaline phosphatase were significantly associated with higher severe toxicity risk, whereas G-CSF prophylaxis was significantly associated with a lower risk. Subgroup analyses revealed that higher overall, early-onset, severe toxicity rates in IMs *vs* NMs were only observed in those treated with standard FOLFIRINOX (51% *vs* 35%; *P*=0.02) or FOLFOXIRI (46% *vs* 22%; *P*=0.03), but not with mFOLFIRINOX, FOLFIRI or monotherapy.

Discussion / Conclusion

UGT1A1 IMs are at increased risk of severe toxicity and may benefit from additional monitoring, G-CSF prophylaxis, and/or initial dose reductions, especially in the presence of additional risk factors. Prospective studies are warranted to confirm this.

Reference(s)

[1] Hulshof et al. Dutch pharmacogenetics working group (DPWG) guideline for the gene-drug interaction between UGT1A1 and irinotecan. Eur J Hum Genet. 2023 Sep;31(9):982-987.

Keywords

UGT1A1, pharmacogenetics, toxicity, irinotecan, precision dosing, oncology

00158
A descriptive case series of pharmacogenetic polymorphisms and drug-induced liver injury associated with CFTR modulators in cystic fibrosis patients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Cystic fibrosis transmembrane conductance regulator (CFTR) modulators are widely used in patients with cystic fibrosis. They can have a significant impact on respiratory function and quality of life, but their effectiveness is hampered by liver damage, which has been well documented in clinical trials and has led to treatment discontinuation in clinical practice (1-4). The hepatotoxic mechanisms are not yet known. In this case series, we investigated the presence of functional genetic polymorphisms in the enzymes and transporters involved in the pharmacokinetics of CFTR modulators (CYP3A4/CYP3A5/SLCO1B1/ABCB1), and in glutathione S-transferases, responsible for detoxification mechanisms.

Materials and methods

All patients experienced liver damage, adverse events reported to the French Network of Regional Pharmacovigilance Centers (RF-CRPV) were genotyped (CYP3A4/CYP3A5/SLCO1B1/ABCB1/GST P1 /GST M1 /GST T1). The RECAM score was assessed individually to diagnose drug-induced liver injury (DILI).

Results

The seven patients (4 children and 3 adults) who experienced liver toxicity, had a highly possible or probable RECAM score. In this case series, among the nine genetic polymorphisms evaluated, only the decreased function allele *CYP3A4*22* (rs35599367) had a higher allelic frequency compared in the general population or in any GnomAD ethnic group. The other genetic polymorphisms as *CYP3A5*3, SLCO1B1*5* or *ABCB1* (c.2677G>T/A and c.3435C>T) had the same allelic frequencies that described in the general population or in any GnomAD ethnic group. One patient with *ABCB1* mutated genotype (c.2677G>T/A and c.3435C>T) and heterozygous for *SLCO1B1*5* allele experienced hepatotoxicity with ivacaftor/lumacaftor combination, which is the most clinically well-tolerated CFTR modulator. We cannot exclude the influence of non-functional alleles of OATP1B1 or P-glycoprotein transporters on hepatotoxicity induced by CFTR modulators.

Discussion / Conclusion

We hypothesize that the presence of *CYP3A4*22* allele, by reducing CYP3A4 enzyme activity, could decrease the clearance of CFTR modulators and increase the risk of DILI. Further studies are needed to confirm these pharmacogenetic findings.

Reference(s)

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Keywords

Cystic Fibrosis; Pharmacogenetics; CFTR modulators; drug-induced liver injury

00166
From Summary of Product Characteristics (SmPC) recommendations to clinical practice: Is pharmacogenetics documented in serious adverse drug reactions to psychotropic drugs?

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Pharmacogenetics (PGx) is increasingly integrated into personalized treatment strategies in psychiatry. For several psychotropic drugs, regulatory documents (Summary of Product Characteristics, SmPC) describe the clinical implications of specific phenotypes (e.g., poor metabolizer status) or genotypes (e.g., HLA variants), sometimes recommending dose adjustments. We aimed to assess the extent to which PGx information is used in the context of serious adverse drug reactions (ADRs) involving psychotropic drugs using French pharmacovigilance reports.

Materials and methods

We identified psychotropic drugs with SmPC information related to a PGx profile and the date these mentions were introduced, using public databases and dictionaries

(VIDAL) over a 23-year period. We extracted serious ADR reports from the French National Pharmacovigilance Database (BNPV) for January 2024 to December 2025, for selected drugs. We searched for text suggesting that a PGx test was performed or that results were available, using a regular-expression (regex) approach, supported by large language models (llama3.1.8b and mistral-memo), after validating these tools on the first 50 reports.

Results

Of the 68 psychotropic drug SmPCs, 18 contained PGx information. Among them, dose adjustment recommendations were provided for amitriptyline, escitalopram, vortioxetine, clobazam and long-acting injectable aripiprazole. For this study, we focused on the three antidepressants. A total of 482 serious ADRs were identified. After excluding cases of overdose, interactions, pregnancy, breastfeeding, medication error, withdrawal, and pharmacodependence, 308 reports were analyzed. None of the reports documented the use of PGx testing.

Discussion / Conclusion

Despite regulatory recommendations highlighting the impact of PGx profiles on drug exposure and dosing, PGx information was not reported in serious ADR cases involving three commonly used psychotropic drugs. These data raise questions about the clinical implementation of these recommendations and the traceability of PGx information in pharmacovigilance reports.

Keywords

Pharmacogenetics, pharmacovigilance, psychotropic drugs, personalized medicine

00173
Isoform-specific metabolic impairment in fatal olanzapine toxicity

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Interindividual variability in drug disposition is a major determinant of adverse drug reactions and unexpected drug-related deaths. Although pharmacogenetics is increasingly incorporated into clinical practice, acquired modifiers of metabolic activity—particularly systemic inflammation—remain insufficiently integrated into toxicological interpretation. We report a fatal case of olanzapine toxicity occurring despite therapeutic dosing, highlighting isoform-specific inflammation-induced phenoconversion and the need to consider both oxidative and conjugative pathways.

Materials and methods

Medico-legal investigation was conducted in a 57-year-old woman hospitalized in a psychiatric unit for bipolar disorder with psychotic features. Olanzapine was initiated and titrated to therapeutic doses under strict supervision. The investigation included a review of the medical file. An autopsy was performed. Comprehensive toxicological analyses were conducted in both femoral blood and urine using LC-HRMS. Pharmacogenetics analyses of CYP1A2, CYP2D6, CYP2C8, CYP2C9, and UGT1A4 genes were performed by NGS.

Results

Medical record review demonstrated evidence of an acute systemic inflammatory state, characterized by neutrophilic leukocytosis (16 × 10^9/L) and elevated C-reactive

protein (62 mg/L). Toxicological analyses revealed a toxic femoral blood olanzapine concentration (172 µg/L). Concentrations of other drugs were within therapeutic ranges. No other substances were detected. Pharmacogenetics analysis revealed CYP1A2*30/*30, CYP2C8*1/*3, CYP2D*62/*5 and UGT1A4*1B/*1 genotypes, none of which alone accounted for the observed olanzapine accumulation.

Discussion / Conclusion

The selective accumulation of olanzapine, contrasted with preserved exposure to drugs predominantly metabolized by CYP3A4, CYP2D6 or alternative UGT isoforms, supports isoform-specific metabolic inhibition rather than global hepatic dysfunction. CYP1A2, a principal pathway for olanzapine oxidative clearance and particularly sensitive to inflammatory downregulation, was the most plausible target of suppression. Although the impact of inflammation on UGT activity is less well characterized and appears isoform- and substrate-dependent, selective modulation of UGT1A4 cannot be excluded. This case emphasizes that inflammation may differentially affect metabolic isoenzymes, and that both CYP- and UGT-mediated pathways should be considered when interpreting unexpected psychotropic drug overexposure.

00176
Implementing quality in a pharmacotoxicology department: a five year-experience of ISO 9001:2015 certification at Lyon University Hospital

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The Pharmacotoxicology Department of Lyon University Hospital (SHUPT) comprises three vigilance units (pharmacovigilance, addictovigilance, toxicovigilance) and the antipoison call center. In 2018, Quality Management System (QMS) aligned with ISO 9001:2015 was initiated, in the context of national reorganisation of vigilance networks, enhanced regulatory expectations, and the need to harmonise surveillance practices. We report the design, deployment, monitoring, and five-year outcomes of this QMS across two certification cycles.

Materials and methods

A PDCA (Plan–Do–Check–Act) approach guided QMS development. The Plan phase included SWOT-based context analysis, identification of interested parties, process mapping, and definition of metrics. The Do phase covered deployment of human resources (HR) tools, communication workflows, non-conformity management, implementation of an electronic document management system (EDMS), and formalisation of partnership agreements. The Check phase included internal/cross audits, satisfaction surveys, annual process and management reviews. The Act

phase involved corrective actions, improvement plans, and adjustments based on audit findings and regulatory changes.

Results

Initial certification was obtained in March 2021, followed by surveillance audits (2021, 2022) and recertification in February 2024. Over five years, six internal audits were conducted, 111 non-conformities reported, and 214 improvement actions initiated. The EDMS enabled document traceability and processes harmonisation. HR tools professionalised onboarding and competency management, including Objective Structured Clinical Examination (OSCE) assessments. Satisfaction surveys showed high requester satisfaction and positive staff feedback. The QMS facilitated major organisational transitions, including deployment of a secure request-tracking system and a comprehensive continuity plan.

Discussion / Conclusion

Implementing an ISO 9001:2015 QMS in a vigilance department is feasible, sustainable, and transformative. It strengthens governance, harmonises practices, supports digital integration, enhances regulatory compliance, and reinforces resilience—even under crisis conditions such as COVID-19. Although its deployment requires financial investment and significant staff engagement, the SHUPT model offers a transferable framework for other vigilance structures seeking enhanced performance, reliability, and institutional alignment.

Keywords

ISO 9001:2015, Quality Management System, pharmacovigilance, toxicovigilance, addictovigilance, EDMS, audits, continuous improvement.

00181
Use of Therapeutic Drug Monitoring of Antipsychotics in Routine Clinical Practice: A Retrospective Study from a French University Hospital

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The prescription of antipsychotics has markedly increased over recent decades. This expansion is associated with a higher risk of insufficient efficacy and dose-related adverse effects, partly due to substantial inter- and intraindividual pharmacokinetic variability[1]. Therapeutic drug monitoring (TDM) is recommended / highly recommanded for several antipsychotics[2] but remains insufficiently implemented in routine clinical practice[3]. Objectives were to describe the real-world use of antipsychotic TDM in a French university hospital and to analyse plasma concentration results in relation to therapeutic reference ranges and sampling conditions.

Materials and methods

We conducted a monocentric retrospective observational study including all requests for antipsychotic plasma concentration measurements performed by the clinical pharmacology laboratory of Nantes University Hospital during 2024[4]. For each measurement, data were collected on the antipsychotic analysed, plasma concentration, dosing regimen, timing of last intake and blood sampling, and concomitant treatments. Sampling conditions were considered optimal when performed at pharmacokinetic steady state and at trough concentration. Plasma concentrations were classified as within, below, or above the therapeutic range[2].

Results

A total of 364 samples corresponding to 206 patients were included (mean age 41.9 years; 65% men). Clozapine accounted for 87.6% of all TDM requests, followed by olanzapine (6.6%), while other antipsychotics (aripiprazole, risperidone, haloperidol, quetiapine) each represented less than 5%. Overall, 71.1% of samples were obtained under optimal conditions. Among optimally sampled measurements, 32.6% of plasma concentrations were within the therapeutic range, whereas 47.5% were below and 19.9% above. In most cases, concentrations outside the therapeutic range could not be explained by inappropriate dosing or identified pharmacokinetic drug–drug interactions.

Discussion / Conclusion

In routine clinical practice, antipsychotic TDM is largely restricted to clozapine and frequently reveals plasma concentrations outside therapeutic ranges. These findings highlight the marked pharmacokinetic variability of antipsychotics and support more systematic use of TDM for antipsychotics to optimise individualised treatment.

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Keywords

therapeutic drug monitoring ; antipsychotics ; clozapine ; observationnal study

00212
Carbon footprint assessment of tacrolimus blood quantification

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Healthcare activities significantly contribute to greenhouse gas emissions. Assistance Publique Hôpitaux de Paris estimates its annual emissions at 1.8 million tonnes of CO2, of which 14% are issued from laboratories. However, the impact of individual laboratory tests remains poorly characterized. Our objective was to determine the carbon footprints of two analytical techniques and identify opportunities for decarbonization.

Materials and methods

This study applied bottom-up approach by a life cycle assessment to tacrolimus assay performed using tandem mass spectrometry (LC-MS/MS) (AltisPlus, ThermoFisher) and an immunoassay on Cobas8000 (Roche) used only on weekends. Carbon footprint determination was carried out using the in-house tool Carebone® by collecting data during pre-analytical, analytical and post-analytical phases, as well as human resources, waste management, building energy consumption, digital data, and storage. After data collection and verification, emission factors were applied before result analysis.

Results

The carbon footprint of the tacrolimus assay was estimated at 2.213 and 3.925 kg CO_2e per test for LC-MS/MS and immunoassay techniques, respectively. In both cases, the analytical step accounted for the primary contributor (89% and 91%, respectively). These emissions primarily arose from the reagents (30.9% and 61.5% respectively), including calibrators and quality controls, as well as from the equipment (33.5% and 15.8%, respectively) and human resources (18.3% and 17.0% respectively). Blood collection tubes, refrigerated storage containers and digital data were the most CO2 emissive sources during the pre-analytical and post-analytical steps.

Discussion / Conclusion

Equipment and reagents account for a significant portion of CO2 emissions (46% and 70% respectively for LC-MS/MS and immunoassay). Regarding LC—MS/MS, reducing equipment costs is difficult; possible solutions include increasing the analysis volume or decreasing reagent, and consumables consumption. Regarding Cobas 8000, reagent consumption was twice higher than LC-MS/MS. Therefore, the routine use of Cobas8000—particularly during weekends—should be considered. Alternatives such as prioritizing LC-MS/MS or using a Cobas i601 module may represent lower-carbon options.

Keywords

Carbon footprint; Decarbonization; Immunoassay; Tandem mass spectrometry

00218
RNPGx recommendations for gene panel analysis in Pharmacogenetics: from consensus to pilot implementation.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Pharmacogenetics (PGx) is increasingly implemented through multigene panels, creating a need for harmonized recommendations on gene selection and variant prioritization. The French-Speaking Network of Pharmacogenetics (RNPGx) recently published a consensus-based list of genes and prioritized variants for multigene PGx panels. Here, we summarize these recommendations and report preliminary results from a pilot analytical implementation.

Materials and methods

RNPGx combined a structured scoring approach with expert consensus to define a core gene panel and target regions classified as Class 1 (clinically actionable

variants), Class 2 (optional extension) and, for selected genes, Class 3 (deep sequencing). Fifteen patients were analyzed using the SOPHiA GENETICS SOPHiA DDM™ Community Extended Pharmacogenomics Solution on an Illumina MiSeq platform. Class 1 and Class 2 variants were curated and summarized by patient and by gene. Results are reported as median (interquartile range, IQR).

Results

The RNPGx core panel comprises 28 genes: 25 with prioritized Class 1 and/or Class 2 variants, and 3 eligibles for Class 3 only. The recommendations include 76 Class 1 variants in 20 genes and 62 Class 2 variants in 14 genes, with nine genes overlapping between the Class 1 and Class 2 lists. In this pilot series, at least one Class 1 or Class 2 variant was detected in 21/25 genes (≥1 Class 1 variant in 17/20 genes; ≥1 Class 2 variant in 8/14 genes). At the patient level, the median number of Class 1-2 variants was 20 (IQR 17-22). Variants were predominantly Class 1, with a median of 15 Class 1 variants per patient (IQR 13-17), most frequently in NAT2, *SLCO1B1 CYPD6*, *UGT1A1*, *2C19* and *2B6*, actionable in 15, 13, 12, 12, 10 and 10 patients, respectively.

Discussion / Conclusion

This pilot implementation supports the feasibility of applying RNPGx recommendations to next-generation sequencing data in a clinical workflow.

Reference(s)

Picard et al. RNPGx recommendations for gene panels in pharmacogenetics. Fundamental & Clinical Pharmacology. 2026.

Keywords

Pharmacogenetics; multigene panel; RNPGx; next-generation sequencing; clinical implementation

00220
Exploring the contribution of CYP pharmacogenetics to methadone enantiomeric distribution in postmortem setting

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Methadone is administered as a racemic mixture of R- and S-enantiomers that differ in pharmacodynamics activity, metabolic pathways and safety profile. R-methadone primarily mediates μ-opioid receptor effects, whereas S-methadone contributes to hERG channel inhibition. Methadone pharmacokinetics is characterized by pronounced interindividual variability, partly attributed to polymorphic cytochrome P450 (CYP) enzymes, especially CYP2B6 and CYP2C19, which exhibit stereoselective involvement in methadone clearance. However, the extent to which pharmacogenetics variability influences enantiomeric balance remains unclear. This study aimed to assess the relationship between predicted CYP phenotypes and stereoselective methadone distribution in femoral blood and vitreous humor.

Materials and methods

Eight adult cases with documented methadone exposure were included. Enantioselective quantification of R- and S-methadone was performed in femoral blood and vitreous humor using a validated LC-MS/MS method with chiral chromatographic separation. Enantiomeric distribution was characterized using S-methadone/total methadone, R-methadone/total methadone and S-methadone/R-methadone ratios. Genotyping of CYP2B6, CYP2C19, CYP2D6, CYP2C9, CYP3A4 and CYP3A5 was performed using the Agena MassARRAY® platform, and predicted

metabolic phenotypes were assigned according to international consensus recommendations. Analyses were descriptive.

Results

In femoral blood, total methadone concentrations ranged from 233 to 1940 µg/L, with S-methadone/R-methadone ratios between 0.635 and 1.178. In vitreous humor, total concentrations ranged from 52 to 737 µg/L, with S/R ratios between 0.667 and 1.000. Enantiomeric proportions were comparable between matrices within individuals despite differences in absolute concentrations. Interindividual variability was observed across all enantiomeric metrics; no consistent or directional association was identified between predicted CYP phenotypes and stereoselective distribution.

Discussion / Conclusion

In this exploratory series, inherited CYP variability did not appear to be the principal determinant of methadone enantiomeric balance. The relative stability of enantiomeric proportions across matrices suggests that stereochemical distribution may be more robust than absolute concentrations. These findings indicate that determinants beyond genotype, including phenoconversion, may substantially influence stereoselective methadone disposition and should be considered in pharmacokinetic interpretation.

00231
Mavacamten therapeutic drug monitoring by HPLC-MS/MS for the real-life follow-up of patients with obstructive hypertrophic cardiomyopathy: what's the use ?

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The objective of the study was to validate a HPLC-MS/MS method to investigate the relevance of mavacamten therapeutic drug monitoring (TDM) in the real-life follow-up of patient with obstructive hypertrophic cardiomyopathy (oHCM).

Materials and methods

The analytical method was validated according to ISO-15189 standards. Mavacamten TDM was performed at the time of clinical examination in 28 patients

with oHCM treated for at least 6 months. Clinical efficacy was assessed by echocardiographic parameters (maximal left ventricular outflow tract gradient [mLVOTg] below 30 mm Hg with left ventricle ejection fraction [LVEF] above 55%) and classical functional indices. Dose titration was performed on the basis of cardiac function and obstruction, as recommended by EMA and FDA.

Results

Using a deuterated analogue, mavacamten level was measured from 5 to 2000 µg/L with satisfactory performances. Pre-analytics showed more stable mavacamten levels in plasma than in whole blood, even after successive freeze/thawn cycles. Ex-vivo mavacamten blood/plasma ratio was lower than anticipated from in-vitro experiment. Six months mavacamten reduced mLVOTg by 71%, NT-proBNP and troponin-I levels by 63% and 59%, respectively. A stronger correlation was found between mLVOTg decrease and mavacamten plasma concentration (r=-0.68), than with NT-proBNP (r=0.34) or Tn-I (r=0.46) levels decrease, respectively. Efficacy started from the first month of treatment with a plasma level above 350 µg/l being associated with the best probability of good clinical response at 6 months. When considering the therapeutic range of 350 to 700 µg/l, 54 to 75% of patients met the clinical objective at 6 months depending on the concentration interval.

Discussion / Conclusion

Mavacamten therapeutic drug monitoring may be helpful to provide early clinical efficacy then to track possible drug under- or over-exposure during echocardiography-guided drug titration.

Keywords

Mavacamten, TDM, oHCM, HPLC-MS/MS, mLVOTg, real life

00243
Genotype informed Bayesian dosing of tacrolimus in paediatric solid organ transplant patients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Tacrolimus is essential for preventing rejection in solid organ transplantation but exhibits complex pharmacokinetics with substantial interindividual variability driven by genetic polymorphisms (particularly CYP3A5), age, organ type, and drug interactions. Current weight-based dosing with therapeutic monitoring often results in significant time outside therapeutic target ranges, associated with rejection, graft loss, and toxicity. While genotype-informed and Bayesian dosing has shown to improve outcomes in adults, paediatric data is limited. Given children's unique physiology and ongoing development, there is a critical need for paediatric evidence characterising time outside target range and its clinical impact to enable more precise, personalised tacrolimus dosing in this vulnerable population.

Materials and methods

Participants (n=45) of this prospective single-arm cohort study receive initial dosing informed by CYP3A4 and CYP3A5 genotypes, with Bayesian dose optimization using NextDose software from day 4 through week 8 post-transplant. The study assesses and compares tacrolimus target range attainment and clinical outcomes including rejection and toxicity with the retrospective standard-of-care cohort.

Results

To date, 26 patients have been enrolled with pharmacogenetic results available for 25 patients; 9 have completed the 8-week study period. CYP3A5 genotype distribution includes 10 expressers (*1/*3, 40%), 1 extensive expresser (*1/*1, 4%), and 15 non-expressers (60%). The prospective genotype-informed Bayesian dosing group demonstrated significantly higher time in therapeutic range over retrospective standard of care (71.3% [SD 11.4] vs 59.3% [SD 15.4], $p < 0.05$), while coefficient of variation was similar between groups (27.7% [SD 5.3] vs 28.3% [SD 9.9], respectively).

Discussion / Conclusion

Preliminary results suggest using genotype-informed Bayesian dosing can improve tacrolimus concentration control in paediatric transplant recipients. This first-of-kind study will provide essential paediatric-specific evidence on whether precision dosing strategies combining pharmacogenetics and Bayesian optimisation can improve tacrolimus dosing and clinical outcomes in the critical early post-transplant period.

Keywords

Pharmacogenomics, Bayesian Prediction, Transplant, Paediatrics, Genotype

00244
Genetic variants associated with anthracycline-induced cardiotoxicity in paediatric oncology: a case-control study

Oral or Poster

J. Netylko[1], A. Halman[1], J. Stolper[1], L. Collier[1], C. Moore[1], T. Stenta[1], B. Williams[1], R. Dyas[1], R. Conyers[1]

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Anthracyclines are widely used in cancer treatment and improve patient survival, however they are also known to cause anthracycline induced cardiotoxicity (ACT). Genetic susceptibility has been reported for several genes and variants, but results remain inconclusive. In this study, ACT associated variants in an Australian paediatric survivor cohort using a matched case control design were investigated.

Materials and methods

Fifty-two participants formed 26 matched case-control pairs. Cases had echocardiographic cardiotoxicity (EF <53% or FS <28%) ≥21 days post-anthracycline. Controls were matched on treatment era, diagnosis, age, sex, and cumulative dose. Whole exome (n=18) and genome sequencing (n=34) were performed. Previously reported variants were tested and discovery analyses were undertaken on gene and variant level.

Results

Mean age at diagnosis was 7.4 years, with 44.2% male. A total of 16 literature curated variants were analysed. TTN rs2303838 was enriched in controls and

associated with reduced toxicity odds, while SLC28A3 rs7853758 was enriched in cases. For the latter, a meta-analysis was conducted showing high heterogeneity in results with minor odds for risk. Gene-based discovery analysis prioritised six genes (SLC12A4, REG3A, TRIM34, HTR3D, HPS5 and SERPIND1), within which several rare risk-associated variants were identified. In SLC12A4, which has been linked to the cardiovascular system, the rs770789419 variant was enriched in cases (~26%) and were found in none of the controls.

Discussion / Conclusion

This matched case control study replicated a protective association for TTN rs2303838 and observed case enrichment for SLC28A3 rs7853758. Discovery analyses highlighted additional candidate loci, including variants in previously unreported K-Cl cotransporter 1 gene, supporting larger studies for validation and mechanistic follow up.

Keywords

Pharmacogenomics, paediatrics, anthracyclines, oncology, cardiotoxicity

00282
When the veins fail : therapeutic drug monitoring of subcutaneous Cefazolin in frail elderly patients

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Subcutaneous (SC) administration of antibiotics represents an emerging therapeutic alternative, particularly in elderly patients with difficult vascular access and in strategies promoting outpatient antimicrobial therapy. However, pharmacokinetic data on subcutaneous cefazolin (CZ) remain limited. This study describes our experience with therapeutic drug monitoring (TDM) of SC CZ and pharmacokinetic/pharmacodynamic (PK/PD) targets in frail geriatric patients.

Materials and methods

We conducted a single-center retrospective 4-years observational study (01/2022-02/2026) including adult patients treated with SC CZ at Groupe-Hospitalier-Paris-Saint-Joseph. Demographic, clinical, and pharmacological data were collected. Steady-state plasma concentrations were measured using ultra-high-performance-liquid chromatography-coupled with high-resolution-mass-spectrometry and were compared with predefined PK/PD targets. The PK/PD target for CZ was defined as trough total concentration >40mg/L, whereas concentrations >80mg/L were considered indicative of overexposure.

Results

Eight elderly patients were included (median 89 years [IQR:80-91years]). Indications for treatment were primarily for Staphylococcus aureus osteoarticular infections or bacteremia. The cohort was markedly frail, with a median Charlson comorbidity index of 6±2 and exhibited severe hypoalbuminemia (23.2±3g/L). The median daily CZ dose was 4g (IQR:3-6g). The median total plasma concentration following SC administration was 66.7mg/L (IQR:23.7-92.1mg/L). Substantial interindividual variability was observed, likely related to heterogeneity in renal function (median creatinine 67µM [IQR:50-97µM]). Five of eight achieved the predefined PK/PD target, whereas three exhibited concentrations consistent with overexposure. TDM directly influenced clinical management in four patients, leading to dosage adjustments (three dose reductions for overexposure and one dose increase for insufficient exposure). Clinical outcomes were favorable in seven of eight patients.

Discussion / Conclusion

Cefazolin administered subcutaneously achieved plasma concentrations comparable to those observed with intravenous administration and compatible with therapeutic targets. However, marked pharmacokinetic variability in frail geriatric patients underscores the importance of TDM to prevent both accumulation-related toxicity and underexposure. The main limitations of this study include small sample size and incomplete data collection, which may affect the generalizability of the findings.

Keywords

Cefazolin, Subcutaneous administration, Geriatrics, Pharmacokinetics, Therapeutic drug monitoring (TDM)

00312
Functional evaluation of the ABCC2 1249 G>A variant in a recombinant cell system to support anticancer drug transport studies

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

ABCC2 (ATP-binding cassette sub-family C member 2) is an efflux transporter involved in the transport of xenobiotic and endogenous substrates. It plays a role in the disposition of anticancer agents, contributing to interindividual variability in drug exposure and response. The 1249G>A (rs2273697) SNP, resulting in a Val417Ile substitution, has been associated with altered transport activity. However, how this SNP modulates transport activity remains insufficiently characterized, limiting anticipations of its potential impact on drug pharmacokinetics.To address this, we developed and functionally validated a recombinant cell model expressing either the wild-type (1249G) or the variant (1249A) ABCC2 transporter.

Materials and methods

HEK293 cells were stably transfected with ABCC2 plasmid coding the wild-type or the variant alleles. ABCC2 expression in the recombinant cell models were assessed by immunofluorescence (IF) and confocal microscopy and confirmed at the protein

level by Western blot. To validate these models functionally, an accumulation assay using 5,6-Carboxyfluorescein Diacetate (5,6-CFDA) was performed with or without MRP inhibitors.

Results

IF and confocal microscopy confirmed the expression of ABCC2 wild-type and 1249A in recombinant cell models. Western blotting confirmed ABCC2 overexpression in all cell lines. Functional validation using 5,6-CFDA accumulation assays showed that cells overexpressing ABCC2 (wild-type and 1249A) accumulate significantly lower amounts of 5,6-CFDA compared with non-transfected HEK293 cells. Similar 5,6-CFDA accumulation was observed in cells overexpressing the 1249A when compared to 1249G cells. Additionally, incubating with ABCC2 inhibitor, restored 5,6-CFDA accumulation in the overexpressing models like non-transfected HEK293 cells, confirming that the differences observed in the absence of inhibition were due to ABCC2-mediated transport, validating the functionality.

Discussion / Conclusion

ABCC2 wild-type and 1249A recombinant cell models were developed and validated using structural and functional approaches. These models constitute an in vitro tool to investigate substrate-specific transport differences and will support studies exploring the impact of ABCC2 1249G>A SNP on anticancer drug transport.

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00318
Easy use of a Shiny application based on posologyr for Model-Informed Precision Dosing: illustration with a clinical case of cefotaxime

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

As Therapeutic Drug Monitoring (TDM) is increasingly associated with Model-Informed Precision Dosing (MIPD), tools such as NONMEM, Monolix, BestDose or mapbyr allow using locally developed as well as published models. Posologyr (1) is a recently developed open-source R package that proposes a full Bayesian approach in dosing individualization compared to the Maxium A posteriori Bayesian Estimation used by most existing solutions. We developed a Shiny (2) application on top of posologyr to facilitate the routine use of MIPD by colleagues not familiar with the R language. The application currently covers 29 molecules, including antibiotics, antifungals, neuroleptics, and antiepileptics, and we illustrate its practical use through a real-world case focused on an antibiotic.

Materials and methods

A 45-year-old man was hospitalized in the Intensive Care Unit of the Versailles Hospital Centre for an acute hypoxemic respiratory distress. An infectious pneumonia was suspected and, on a probabilistic basis, treatment with cefotaxime, rovamycin, and linezolid was initiated. TDM was used for cefotaxime, blood concentrations were measured by a validated liquid chromatography-tandem mass spectrometry method

and MIPD used the model of Swartling *et al.* (3) validated on our own patient population.

Results

An initial intravenous dose of 1g every 4h for 4 days led to a blood concentration of 10 mg/L. A switch to a 6g/24h continuous administration was proposed to get a steady-state concentration of 25-30 mg/L. After 24h of this new regimen, a concentration of 23.1 mg/L was achieved. The concentration dropped to 16 mg/L after 10 days and needed an 8g/24h increase to achieve a concentration of 27 mg/L. The identified germ was a *Klebsiella pneumoniae*.

Discussion / Conclusion

The Shiny application facilitated rapid attainment of the effective concentration after initial underexposure, improving patient management and limiting the risk of resistance. This tool exemplifies how user-friendly MIPD interfaces can help move precision medicine from concept to clinical reality.

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Keywords

population pharmacokinetics, antibiotics, posologyr, R software

00322
Individualized Dosing Study of Lamotrigine Based on Blood Concentration Monitoring and Genetic Testing

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

This study aims to investigate the impact of the UGT1A4 142T＞G metabolizing enzyme gene polymorphism on the blood concentration and therapeutic effect of lamotrigine (LTG), and to construct blood concentration prediction equations for the drug, thereby providing a scientific reference for the individualized medication of LTG in this patient population.

Materials and methods

A HPLC method for LTG blood concentration was established, with methodological validation and internal quality control per Westgard multi-rule theory. Sanger sequencing detected the UGT1A4 142T＞G genotype and analyzed its distribution in Anhui epileptic patients. Enrolled patients were grouped into wild-type and mutant by UGT1A4 142T＞G genotyping; LTG concentration and therapeutic efficacy were compared between groups, with stratified analysis by polypharmacy and age. Multiple linear regression analyzed the effects of genotype, gender, dosage, age and polypharmacy on LTG concentration, and a LTG blood concentration predictive equation was constructed.

Results

HPLC was used to determine LTG blood concentration, LTG showed a good linear relationship in the range of 0.2~20μg/mL (r=0.9991), and its precision, recovery and stability met the requirements with all RSD < 15%. The UGT1A4 142T>G genotype was detected in 102 patients, with a mutation frequency of 25.49%. 99 epileptic patients were enrolled, and the LTG-C/D in patients with UGT1A4 142TT was significantly higher than that in TG+GG carriers (P=0.041). Multiple linear regression analysis indicated that genotype, polypharmacy and dosage had significant effects on LTG concentration (P<0.05), and the predictive equation for LTG blood concentration was C=1.840-1.152*UGT1A4 142T>G +1.580*medication regimen +0.021*dosage(UGT1A4 142T>G: TT=1, TG+GG=2; medication regimen: monotherapy=0, combination therapy=1).

Discussion / Conclusion

The established HPLC method passed validation with compliant performance. UGT1A4 142T>G polymorphism affected LTG blood concentrations, polypharmacy and age significantly modified the genetic effect on LTG levels. A LTG concentration prediction equation was constructed to guide its individualized dosing.

Keywords

Epilepsy; Lamotrigine; UGT1A4; Blood concentration; Biochemical index

00339
Impact of early CYP2C19 genotyping on escitalopram treatment failure

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Escitalopram is primarily metabolised by the polymorphic enzyme CYP2C19. It was previously shown that switching from escitalopram to a different antidepressant occurs more frequently in poor and ultrarapid metabolisers compared with normal metabolisers, suggesting that early genotyping of *CYP2C19* could improve treatment outcomes. The aim of this study was to investigate the frequency of escitalopram treatment failure, using drug switching as a proxy, in relation to timing of *CYP2C19* genotyping.

Materials and methods

Patients with detectable escitalopram serum concentrations and available information on *CYP2C19* genotypes were retrospectively included from the routine therapeutic drug monitoring (TDM) and pharmacogenetics service at Diakonhjemmet Hospital in Oslo, Norway during the period 2010-2025. Patients were grouped based on whether genotyping was performed before or during escitalopram treatment (early), at the same time as the last escitalopram TDM, or at a later time point (reactive). Escitalopram treatment failure was defined as switch to another antidepressant within 1 year following the last TDM of escitalopram. The switch frequencies were compared using the chi-square test.

Results

The study population consisted of 11,466 *CYP2C19*-genotyped patients treated with escitalopram. The overall switch frequency was 12.4% (n=1,423). Switch frequencies were 11.1% among the patients with early genotyping (n=4,714) compared to 17.2% among the patients with reactive genotyping (n=2,811) and 10.6% among the patients genotyped at the same time as the last escitalopram TDM (n=3,941) ($p<0.001$).

Discussion / Conclusion

The frequency of switching was lower in patients with early genotyping compared with reactive genotyping, which may suggest that early *CYP2C19* genotyping facilitates precision dosing and hence prevents treatment failure of escitalopram, either due to insufficient clinical response or side effects. Further studies are needed to verify if the findings can be translated into real clinical observations and not only drug switch, as a surrogate endpoint of failure.

00371
Mycophenolic acid in systemic sclerosis-related interstitial lung disease patients: exposure and efficacy assessment

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Interstitial lung disease (ILD) can affect up to 50% of systemic sclerosis (SSc) patients, with a high mortality. Mycophenolic acid (MPA) is indicated as an oral immunosuppressive treatment for ILD management. Therapeutic drug monitoring allows patient exposure assessment, but the therapeutic range is poorly defined in this population. The aims of the study were in ILD patients: i) to assess mycophenolic acid exposure and compare it to a composite efficacy endpoint, ii) to assess the impact of a dosage reduction.

Materials and methods

Forty-five SSc-ILD patients receiving MPA were included in this retrospective study. MPA concentrations were measured by LC-MS/MS and area under the curve (AUC) was estimated. A composite efficacy criterion included assessment of the stability of

forced vital capacity and diffusion capacity for carbon monoxide, unaltered clinical condition and radiological stability for 24 months.

Results

Most patients were female (60%) with a mean age of 64 years. Median MPA AUC_{0-12} was 44.4 h.mg/L [range: 11.4-121.8], with a median 1000 mg BID dosage. Efficacy rate at 12 and 24 months was seen in 91.7% and 79.1%. A trend towards lower efficacy with an AUC<30 (24.4% of patients) was observed at 12 months (p=0.09). A dosage ≥ 2000 mg/day tended to be associated with greater efficacy at 24 months (p=0.07), whereas a reduction in dosage at 6 months tended to be associated with a loss of efficacy at 24 months (p = 0.06).

Discussion / Conclusion

Lowering MPA dosage could be detrimental to clinical outcome. AUC<30 could be linked to reduced efficacy but was not statistically significant for insufficient power. Our study had broader evaluation criteria compared to literature: exposure assessed by AUC, extended period of 24 months, a composite efficacy criterion. In cases of high exposure with good safety, the dosage should be maintained to promote continued clinical efficacy.

Reference(s)

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00377
Analytical Feasibility of Linezolid Quantification by LC–MS/MS Using Dried Plasma Spots (DPS)

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Linezolid is indicated for infections caused by multidrug-resistant Gram-positive bacteria and for drug-resistant tuberculosis. Its high interindividual pharmacokinetic variability[1] and risk of hematological toxicity[2] support the use of therapeutic drug monitoring (TDM). Dried plasma spots (DPS) represent a less invasive alternative to conventional plasma sampling and may facilitate access to TDM.

Materials and methods

DPS were prepared from 80 µL of whole blood. Linezolid was rapidly extracted using methanol-assisted sonication. After centrifugation, the supernatant was analyzed by LC–MS/MS. Chromatographic separation was performed on a C18 column with a

total run time of 4.5 minutes.
The method was applied to samples from four adult patients receiving linezolid, and concentrations measured in DPS were compared with those obtained in plasma.

Results

The method demonstrated analytical performances consistent with FDA bioanalytical validation guidelines. Three-day validation confirmed linearity over the range 1–100 µg/mL ($r^2 > 0.99$). Accuracy and precision, assessed at multiple quality control levels under intra- and inter-day conditions, remained within acceptance criteria (±15% and <15%, respectively). The lower limit of quantification (LLOQ) was established at 1 µg/mL. Linezolid remained stable in DPS for three days at both 5 °C and 22 °C. Comparison of concentrations obtained from DPS and plasma in treated patients showed satisfactory agreement between matrices.

Discussion / Conclusion

This LC–MS/MS method appears reliable and promising for linezolid quantification using DPS microsampling. DPS may represent a valuable alternative to plasma for TDM, particularly in pediatric populations and resource-limited settings. Clinical validation in a larger cohort is required to confirm interchangeability.

Reference(s)

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Keywords

Linezolid, dried plasma spots, LC–MS/MS, therapeutic drug monitoring (TDM)

00387
Automated Thiopurine S-Methyltransferase (TPMT) Activity Profiling using Volumetric Absorptive Microsampling: Enhancing Efficiency and Precision

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Thiopurines are purine antimetabolites used for Crohn's disease and other oncologic and autoimmune disorders that may cause severe myelosuppression. Thiopurine S-methyltransferase (TPMT) methylates and inactivates thiopurines and is therefore a major determinant of toxicity. Approximately 11% of Caucasians have reduced TPMT activity and 1 in 300 are completely deficient, making pre-treatment TPMT assessment essential. Phenotyping is often preferred over genotyping due to lower cost and faster turnaround, yet conventional assays require labour-intensive red blood cell lysate preparation. We aimed to simplify TPMT phenotyping using volumetric absorptive microsampling (VAMS) combined with automated sample preparation.

Materials and methods

A sensitive LC-MS/MS assay for 6-methylmercaptopurine (6-MMP) was developed (linear range 1.56-200 ng/mL). Incubation and extraction were automated on an Andrew+ liquid handler in a 96-well format. A 10 µL air-dried VAMS tip was rehydrated in 250 µL 0.1 M phosphate buffer (pH 7.4), generating a lysate-like specimen. Equal volumes of DTT, internal standard, S-adenosyl methionine

(cofactor) and 6-mercaptopurine (substrate) were added sequentially, followed by incubation for 60 min at 37°C. The reaction was quenched with 40% perchloric acid, centrifuged and diluted in mobile phase whereafter 2 µL was injected into the LC-MS/MS. For comparison, 10 µL whole blood samples underwent a -80°C freeze-thaw cycle prior to same procedure.

Results

Proof-of-concept in healthy volunteers demonstrated preserved TPMT activity in rehydrated VAMS samples, with mean 6-MMP concentrations of 33.5±2.0 ng/mL. Calculated activities ranged from 38.4-47.5 nmol 6-MMP·g $Hb^{-1}·hr^{-1}$, consistent with expected reference values. Rehydration of VAMS eliminated red blood cell washing steps. Automated 96-well processing minimized manual handling and enabled high-throughput preparation. TPMT activities from whole blood lysates agreed within 15% of VAMS results.

Discussion / Conclusion

Automated VAMS-based processing enables reliable TPMT phenotyping while eliminating labour-intensive lysate preparation, offering a faster and more practical alternative for clinical implementation.

Keywords

TPMT, thiopurines, VAMS, LC-MS/MS, automation

00404
Effects of genetic polymorphisms on olanzapine plasma concentrations in psychiatric patients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Olanzapine is an antipsychotic drug with high pharmacokinetic variability. The influence of clinical factors (sex, age, body weight, smoking and co-medications) on olanzapine plasma concentrations was studied previously [1]. In the present study, we aimed to investigate the association between genetic variants and olanzapine concentrations.

Materials and methods

Therapeutic drug monitoring (TDM) data from a psychiatric cohort (PsyMetab) were analyzed, including 307 steady-state dose-normalized olanzapine concentrations (C/D ratios) from 146 European-ancestry patients (53% male). Olanzapine concentrations were quantified by ultra-high performance liquid chromatography coupled to tandem mass spectrometry. Candidate single nucleotide polymorphisms (SNPs) in genes potentially involved in olanzapine pharmacokinetics were identified through literature review. Genetic variants were determined by standard genotyping or imputation methods on a Global Screening Array chip. A linear mixed-effects regression model with stepwise selection based on Akaike information criterion was used, to assess the association between SNPs and natural-log-transformed (ln-transformed) olanzapine C/D ratios, adjusted for the clinical covariates listed above.

Results

Among the 54 SNPs included in the analyses, 24 were retained in the stepwise model, and 16 showed significant association with ln-transformed olanzapine C/D ratios. The significant SNPs were located in genes encoding enzymes involved in olanzapine metabolism (CYP1A2, CYP3A43, UGT1A4, UGT2B10 and FMO1), as well as transcription factors (AhR), nuclear receptors (CAR), electron transfer proteins (POR), and other enzymes (CYP2A6). The genetic factors explained 22.4% of the variation in ln-transformed olanzapine C/D ratios. The combination of clinical and genetic factors (fixed effects of the model) explained 56.4%, and the overall variation explained by both the fixed and random effects was 75.6%.

Discussion / Conclusion

Several SNPs were associated with olanzapine C/D ratios, suggesting a genetic influence on pharmacokinetics. Future studies should determine whether these SNPs could be incorporated into predictive models, alongside clinical variables, to individualize dosing, in addition to TDM and clinical assessment.

Reference(s)

[1] Ansermot N, et al. Therapeutic drug monitoring of olanzapine: effects of clinical factors on plasma concentrations in psychiatric patients. Therapeutic Drug Monitoring 2024;46(6):828-836.

Keywords

Olanzapine; Plasma concentrations; Therapeutic Drug Monitoring; Pharmacogenetics.

00407
ACKR1 (Atypical Chemokine Receptor 1) genotype: a new player in chemotherapy-induced neutropenia

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

High prevalence of asymptomatic absolute neutrophil counts (ANC) among individuals of African ancestry, formerly called Benign Ethnic Neutropenia, has been linked to a mutation in the promoter of the *ACKR1* gene (T>C-rs2814778). The mutant CC genotype confers the Duffy-null variant in which carriers lose expression of the ACKR1 receptor (the Duffy antigen) on erythrocytes[1]. Studies have reported the association between the Duffy-null variant and inappropriate dose modification or treatment discontinuation due to lower ANC among Duffy null patients[2,3.] The 3 following cases highlight the need for specific therapeutic management for these patients upon chemotherapy administration

Materials and methods

We describe three patients with digestive cancers who received Folfiri-(Foliinic acid, Fluorouracil, and Irinotecan) and/or Folfox-(Folinic acid, Fluorouracil, and Oxaliplatin)-based chemotherapies and developed severe neutropenia in a context of

low pre-therapeutic neutrophil counts. The patients of African ancestry were genotyped for ACKR1 rs2814778 by allelic discrimination.

Results

Patient 1 with metastatic stomach cancer received first-line treatment with Folfox. Pre-therapeutic neutrophil count was 1.3 G/L (normal range 1.5-7). After 4 cycles, treatment was discontinued due to neutropenia at 0.72 G/L. Second-line treatment with Folfox was associated with severe neutropenia requiring GCSF administration.

Patient 2 with metastatic colorectal cancer received treatment with Folfiri combined with bevacizumab. Pre-therapeutic neutrophil count was 2.25 G/L. The patient developed spontaneously resolved neutropenia at 0.89 G/L.

Patient 3, with colon adenocarcinoma received Folfox and atezolizumab and developed severe neutropenia at 0.51 G/L requiring GCSF administration and oxaliplatine dose reduction (-30%). Pret-therapeutic neutrophil count was 1.16 G/L.

All the 3 patients are *ACKR1* CC genotype. None of them experienced any infectious episodes.

Discussion / Conclusion

Among Duffy-null patients receiving anticancer drugs associated with neutropenia risk, neutropenia definitions and grade toxicity have to be re-assessed. These patients are more likely to be subject to unnecessary dose reductions or discontinuations of their standard therapies, which may affect cancer outcomes[4,5].

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Keywords

Duffy null variant, ACKR1 genotype, anticancer drugs, neutropenia

00436
Pharmacokinetics of Belatacept in kidney transplant recipients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Belatacept, a CTLA-4-Ig fusion protein that prevents T-cell co-stimulation by disrupting CD80/86–CD28 signaling between antigen-presenting cells and T lymphocytes, has received formal approval for maintenance immunosuppression in kidney transplantation. However, few data on its pharmacokinetics are available. The study aimed to describe belatacept trough concentration (Cmin) and to identify the determinants of belatacept exposure in a cohort of kidney transplants recipients.

Materials and methods

Kidney transplant patients treated with belatacept were retrospectively included. Belatacept Cmin measured between 26 and 30 days after the last administration, were determined using a validated liquid chromatography-tandem mass spectrometry method. Demographic (age, gender), clinical (hospitalization for infection, weight, body mass index), and biological (time after first administration, glomerular filtration rate (GFR), urinary albumin to creatinine ratio (ACU), transaminases, C reactive protein level) data were recorded. Univariate and multivariate analysis were conducted to identify determinants of belatacept Cmin using a linear mixed effect model with the patient as random factors.

Results

157 patients with 273 belatacept Cmin determinations were included. The median (10th-90th percentiles) of belatacept Cmin was 5.5 mg/L (1.8-12.9). The inter- and intra-individual coefficients of variation were 65.5% and 31.9%, respectively. In multivariate analysis, the patient age (estimate = 0.055, sd = 0.023), GFR (estimate = -0.040, sd = 0.015) and ACU (estimate = -0.012, sd = 0.006) were independently associated with the belatacept Cmin. We found no association between belatacept Cmin and sex, age, inflammation or liver function parameters. Cmin were not statistically different between patients hospitalized for infection (n=18) and those not hospitalized for infection (n=139).

Discussion / Conclusion

This study illustrates the high interindividual variability of belatacept Cmin and suggests that exposure to belatacept may be weakly associated with patient age, GFR and ACU. Further studies are needed to better understand belatacept pharmacokinetics and to investigate a potential pharmacokinetic-pharmacodynamic relationship.

Keywords

Belatacept, kidney transplantation, immunosuppression, pharmacokinetics

00438
Does early CYP2C19 and CYP2D6 genotyping reduce the risk of venlafaxine treatment failure?

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Venlafaxine exposure is influenced by metabolic activities of the polymorphic enzymes CYP2C19 and CYP2D6. Genotype-guided dosing of venlafaxine may therefore reduce the risk of off-target serum concentration and prevent treatment failure. The aim of this study was to investigate whether early genotyping of *CYP2C19* and *CYP2D6* is associated with reduced risk of treatment failure, measured as drug switch.

Materials and methods

This retrospective study used data from the routine therapeutic drug monitoring (TDM) and pharmacogenetics service at Diakonhjemmet Hospital in Oslo, Norway. Participants were included if they had quantifiable serum concentrations of venlafaxine and its active metabolite desvenlafaxine collected between 2011 and 2025, and had available *CYP2C19* and *CYP2D6* genotypes.

Treatment failure was defined as switch to another antidepressant within one year after last TDM of venlafaxine. Participants were stratified into three groups based on

timing of genotyping: 1) early genotyping before, or during venlafaxine treatment; 2) genotyping at the same time as last venlafaxine TDM sampling; and 3) reactive genotyping at a later time point. Rates of treatment failure were compared using chi-square test.

Results

The study included 5,177 venlafaxine-treated participants; 12% (n=599) switched to a new antidepressant other than venlafaxine within one year after the last TDM event. Switch rates differed by timing of genotyping, i.e. 9.1% (n=266/2,930) in the early genotyping group, 11 % (n=127/1,144) when genotyping coincided with last venlafaxine TDM sampling, and 19% (206/1,103) with reactive/delayed genotyping ($p<0.001$ across groups).

Discussion / Conclusion

Early *CYP2D6* and *CYP2C19* genotyping, performed before or early during venlafaxine treatment, was associated with lower rates of treatment failure compared to genotyping interpreted as ‘reactive’. This finding may suggest that genotype information early in the treatment course facilitate personalized dosing and prevent failure in terms of reduced efficacy or side effects.

00449
Development and Analytical Validation of a Simultaneous LC–MS/MS Assay for Four β-Lactams in Dried Plasma Spots: A Feasibility Study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic drug monitoring (TDM) of antibacterial agents is increasingly important for individualized patient care, particularly in the context of rising antimicrobial resistance. Interindividual pharmacokinetic variability can result in inadequate drug exposure, potentially reducing efficacy or increasing toxicity[1]. This study aimed to develop and validate a rapid liquid chromatography–tandem mass spectrometry (LC–MS/MS) method for the simultaneous quantification of amoxicillin, cefotaxime, piperacillin, and tazobactam in dried plasma spots (DPS). This microsampling approach may facilitate pharmacokinetic/pharmacodynamic (PK/PD) studies and routine dose optimization.

Materials and methods

DPS were prepared from 80 µL of whole blood. Analytes were extracted using methanol with sonication, followed by centrifugation. The supernatant was analyzed by LC–MS/MS. Chromatographic separation was achieved on a C18 column with a total runtime of 4.5 minutes per injection. Method validation followed FDA recommendations, assessing selectivity, carryover, linearity, accuracy, precision, matrix effects, stability, and lower limits of quantification.

Results

The assay met all FDA acceptance criteria. Calibration curves were linear over the range of 1–100 µg/mL ($r^2 \geq 0.99$). Within- and between-run accuracy and precision were within ±15% and <15%, respectively. No significant matrix effects were observed, and neither hemolysis nor lipemia affected quantification. Short-term stability at 5 °C was confirmed for three days for all compounds. At 22 °C, cefotaxime, piperacillin, and tazobactam were stable for two days, whereas amoxicillin remained stable for one day. All analytes degraded at 50 °C.

Application to clinical samples from 24 treated patients showed good agreement between DPS and plasma concentrations.

Discussion / Conclusion

This multiplex LC–MS/MS method provides reliable β-lactam quantification using a minimally invasive sampling strategy, suitable for vulnerable populations and settings with limited resources. Larger studies are needed to confirm matrix equivalence.

Reference(s)

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Keywords

β-lactams, dried plasma spots, LC–MS/MS, therapeutic drug monitoring

00471
Mycophenolic acid in children with idiopathic nephrotic syndrome. Is treating without therapeutic drug monitoring like walking blindfolded?

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Idiopathic nephrotic syndrome (INS) is the leading cause of glomerular proteinuria in children. Mycophenolate mofetil (MMF) is widely used as a steroid-sparing treatment in frequently relapsing or steroid-dependent cases. The efficacy of MMF correlates with the area under the concentration–time curve over 12 hours (AUC_{0-12}) of its active metabolite, mycophenolic acid (MPA), with target values > 45 mg·h/L. Despite this, current pediatrics guidelines only recommend AUC monitoring in cases of treatment failure. This study aimed to identify clinical or biological predictors of subtherapeutic MPA exposure (AUC_{0-12} < 45 mg·h/L).

Materials and methods

A retrospective multicentric cohort study at Brest and Nantes university hospitals over a 10-year period (2015–2025). Children under 18 years with INS treated with MMF, with at least one MPA AUC_{0-12} measurement were included. Demographic data, laboratory results, MMF dose, and clinical outcomes were systematically collected. Mixed-effects logistic regression analyses were used to identify predictors of subtherapeutic AUC_{0-12}.

Results

Over the period children with INS contributed 238 AUC_{0-12} values. Twenty-five were excluded for ongoing relapse and 8 because of missing data. A total of 206 AUC_{0-12} from 93 children were included. Of these, 44.7 % were below the 45 mg·h/L threshold. Three independent predictors were significantly associated with subtherapeutic exposure in multivariate analysis: MMF dose per m²/day (OR = 0.008, p = 0.01), serum albumin concentration (OR = 0.844, p = 0.013) and adverse events including recent infectious episodes (OR = 2.105, p = 0.037). The predictive model demonstrated good performance, with a ROC AUC of 0.904.

Discussion / Conclusion

In pediatric INS, lower MMF dosing, hypoalbuminemia and adverse events were independently associated with inadequate MPA exposure , but did not fully predict subtherapeutic AUC_{0-12} values. These findings underscore the importance pharmacokinetic variability and suggest that a broader implementation of preemptive AUC-based monitoring could improve disease control and treatment efficacy in this population.

00472
Daptomycin Area Under the Curve Over Minimum Inhibitory Concentration: One Efficacy Index to Rule Them All? An In Silico Study.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Daptomycin is approved for the treatment of skin infections, bacteremia, and endocarditis. Several pharmacokinetic-pharmacodynamic (PK-PD) indices have been proposed for efficacy: area under the curve over minimum inhibitory concentration (AUC0-24/MIC) >666, maximum concentration over minimum inhibitory concentration (Cmax/MIC) >60, and Cmax/MIC>100. We aimed to assess whether achieving the AUC target correlated with achieving the Cmax targets for different levels of creatinine clearance (ClCr) and weight.

Materials and methods

Using a population pharmacokinetics model (Dvorchik 2004[1]), we simulated patients with different ClCr and weights. For each patient, we determined the optimal dose to achieve an AUC0-24>333 mg.h/L with a MIC of 0.5 mg/L, then calculated the simulated Cmax and compared the proportions of target attainment for each PK-PD index. Analyses were performed using posologyr v1.2.7, rxode2 v3.0.3 and R v4.3.3 software.

Results

260,000 patients were simulated from 260 different sets of covariates (CrCl from 30 to 150 ml/min, weight from 50 to 100 kg) with 1,000 sets of individual pharmacokinetic parameters each. The correlation between efficacy PK-PD indices was poor, the Cmax/MIC ratio was over 60 for 64.4% of all patients, and over 100 for only 22.8% of all patients. The patients with ClCr=30 mL/min and WT=100 kg had the lowest correlations (39.4% for Cmax/MIC>60, 7.8% for Cmax/MIC>100). The patients with ClCr=150 mL/min and WT=50 kg had the highest correlations (84.6% for Cmax/MIC>60, 45.6% for Cmax/MIC>100). The median doses needed to reach the AUC target were 4.41, 2.92 and 7.70 mg/kg respectively.

Discussion / Conclusion

This in silico study showed that achieving the AUC/MIC targets for daptomycin does not guarantee that the Cmax/MIC targets will be attained. The median doses required to achieve the AUC target were low (median = 4.41 mg/kg). These discrepancies highlight that the various PK-PD indices of daptomycin efficacy are not interchangeable. Further studies are warranted to determine the most appropriate index.

Reference(s)

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00499
Rethinking the potential of tacrolimus monitoring : insights from pediatric kidney transplant patients.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic drug monitoring (TDM) is recommended for calcineurins inhibitors. Previous studies have demonstrated that cyclosporin TDM provides better predictive performance with a single sampling at two hours post-dose. However, for tacrolimus the correlation between C_0 and $AUC_{0\text{-}12h}$ remains debate. Furthermore, there is unclear relationship between tacrolimus concentration and clinical outcomes. In this study, we investigate the correlation between different tacrolimus time-concentration and efficacy-toxicity parameters in pediatric kidney transplant patients.

The aim of this study is to evaluate the relevance of each measured concentration used in the calculation of the $AUC_{0\text{-}12h}$, as well as the C_0/dose ratio, in relation to clinical and biological parameters.

Materials and methods

Pediatric kidney transplant patients treated with tacrolimus bid were retrospectively included from January 2020 to June 2025 at Timone Hospital. We calculated the $AUC_{0\text{-}12h}$ using eight blood samples (C_0, C_1, C_2, C_3, C_4, C_6, C_8 and C_{12h}) for each patient by the trapezoidal method.

Tacrolimus concentrations were determined by LC-MS/MS.

Biological and clinical events were reported by clinicians when the $AUC_{0\text{-}12h}$ was performed.

Statistical analyses were realized using Pearson's correlation analysis and Welch's t-test ($p < 0.05$).

Results

Twenty-five patients were included.

C_{2h} and C_{3h} were significantly higher (18.0 and 13.1 ng/mL vs. 14.3 and 10.9 ng/mL, respectively) in patients with hypertension.

The C_0/dose ratio was lower in patients with hyperkalemia (1.7 vs. 2.7).

C_0 and C_{1h} were lower in patients with ACAL (5.4 and 16.2 ng/mL vs. 6.4 and 22.8 ng/mL, respectively). In patients with DSA, C_{1h} was lower (14.0 vs. 20.7 ng/mL), while the C_0/dose ratio was higher (2.1 vs. 2.4).

Discussion / Conclusion

These results suggest that C_{1h} appears to be an interesting candidate as it correlates with $AUC_{0\text{-}12h}$, clinical and biological markers.

These findings require confirmation through further studies with a larger cohort.

Keywords

Tacrolimus, Paediatric, Kidney transplant, Therapeutic drug monitoring, $AUC_{0\text{-}12h}$, clinical-concentration relationship, C_{1h}

00515
Comprehensive DPYD sequencing uncovers rare variants linked to severe toxicities in fluoropyrimidine-treated patients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Fluoropyrimidines (capecitabine, 5-fluorouracil) are widely used in the treatment of solid tumors, offering significant survival benefits.[1] However, severe toxicities occurs in up to 25% of patients that can be fatal for 1%.[2] They are mainly attributed to dihydropyrimidine dehydrogenase deficiency, the key enzyme in their metabolism, encoded by *DPYD* gene.[3,4] Current pre-therapeutic genetic screening rely on genotyping the four most frequent deleterious *DPYD* variants, but may overlook rare variants that collectively contribute to population variability and discordant clinical outcomes.[5]

Materials and methods

We conducted *DPYD* coding-region sequencing in patients with severe fluoropyrimidine-induced toxicities, despite negative targeted genotyping for the four

commonly screened *DPYD* variants. Concurrently, exome data from nearly 5,000 individuals were analyzed to estimate the prevalence of rare *DPYD* variants in the French population. Identified variants were classified and functionally characterized using optimized *in silico* prediction algorithms and validated through *in vitro* activity assays of site-directed mutagenesis-engineered proteins.[6,7]

Results

We identified rare *DPYD* variants in two patients who experienced life-threatening or fatal toxicities within two weeks of capecitabine initiation for gastrointestinal cancers. Both introduced a premature stop codon in exon 13 and 23, resulting in a truncated protein, with complete loss of enzymatic activity, as confirmed by our assays. In the population dataset, we identified two nonsense mutations, five frameshift, one in-frame insertion, one start-retained variant, and 95 missenses variants. Recombinant proteins were generated for 32 prioritized variants, previously uncharacterized, to assess their functional impact *(ongoing, results to be presented at the congress)*.

Discussion / Conclusion

As the two illustrative cases underscore the clinical relevance of comprehensive *DPYD* analysis to identify patients at risk of severe fluoropyrimidine-induced toxicity, the prevalence of rare, potentially deleterious variants in our population further supports the value of full-gene sequencing. Although decreasing sequencing costs facilitate this approach,[8,9] challenges in variant interpretation remain for pharmacogenetics-guided therapeutic drug monitoring in clinical practice.

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Keywords

Pharmacogenetics, Dihydropyrimidine dehydrogenase deficiency, Fluoropyrimidines, Adverse drug reactions

00527
Phenoconversion of CYP3A4, CYP2C19 and CYP2D6 in paediatrics, adolescents and young adults with lymphoma: the PEGASUS study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Phenoconversion is a change in drug metabolism phenotype from the gene-predicted phenotype due to non-genetic factors like polypharmacy, inflammation, or lifestyle. Although documented, it remains underexplored in paediatric, adolescent, and young adult (AYA) oncology. Identifying phenoconversion in this population may improve precision medicine and treatment outcomes. The PEGASUS study evaluates the feasibility and acceptability of measuring phenoconversion of three major metabolising enzymes (CYP3A4, CYP2C19CYP2D6) in clinical care. This early report summarises preliminary findings from the first nine patients, focusing on implementation experience and feasibility.

Materials and methods

PEGASUS is a prospective, single-arm, single-blind, non-randomized feasibility study enrolling 20 patients aged 6–25 years with newly diagnosed Hodgkin or non-Hodgkin lymphoma at one paediatric and one adult quaternary referral hospital in Melbourne, Australia (NCT06383338). Participants undergo CYP3A4, CYP2C19, and CYP2D6 genotyping at enrolment. Longitudinal phenotyping is performed at up to six chemotherapy timepoints using sub-therapeutic oral omeprazole and dextromethorphan. Enzymatic activity is assessed using blood-based metabolic

ratios. Acceptability is assessed via surveys informed by the Theoretical Framework of Acceptability (TFA).

Results

Of the first nine eligible patients, three AYA (22-24 years) and two paediatric patients (14 and 15 years) enrolled and completed scheduled timepoints; treatments initiated include N-AVD, R-CHOP21, R-EPOCH, ANHL1131. No probe drug-related adverse events were observed. Three paediatric patients (7, 16, and 17 years; all Hodgkin lymphoma) declined participation and completed the survey. TFA-based acceptability findings indicated that non-participation was driven predominantly by feasibility constraints (logistical burden, competing responsibilities, or limited readiness) rather than ethical concerns, highlighting paediatric recruitment as the main feasibility challenge.

Discussion / Conclusion

Early PEGASUS findings support the safety and operational feasibility of longitudinal CYP3A4/2C19/2D6 phenoconversion assessment in AYA and paediatric oncology patients. However, paediatric recruitment remains a key barrier, driven by logistical and priority concerns, underscoring the need for streamlined procedures and better family-centred implementation support.

Keywords

pharmacogenomics, phenoconversion, cytochrome P450 enzymes, lympoma

00544
Direct comparison of DPYD genotyping versus DPD phenotyping for predicting life-threatening toxicities to fluoropyrimidines.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Dihydropyrimidine dehydrogenase (DPD) deficiency is the main known cause of life-threatening fluoropyrimidine (FP)-induced toxicities. FDA and EMA recommend pre-treatment DPYD genotyping while EMA additionally advises plasma uracil (U) measurement. Objective of this meta-analysis on individual patient data was to compare both approaches and their combination for predicting grade 4-5 (G4-5) toxicities.

Materials and methods

We analyzed 906 breast and colorectal cancer patients (4 prospective studies) receiving 5FU or capecitabine, with available DPYD genotype and phenotype (U, UH2/U). Primary end-point was haematological/digestive G4-5 toxicities over first 12 weeks. For U and UH2/U, cubic spline functions adjusted on study, age, sex, body mass index, FP-administration schedule and concomitant anticancer drugs were explored. Multivariable logistic regressions models including above-cited covariates, DPYD variants *2A/*13/p.D949V (at least one mutated allele) and/or U or UH2/U (continuous variables) were built and compared using Akaike criteria (AIC).

Results

Incidence of 12-week G4-5 was 6.0%. DPYD variants prevalence was 2.2%. Mean U was 9.5 ng/. Mean UH2/U was 12.4. Mutated patients expressed higher U and lower UH2/U ($p<0.0001$). Splines showed that U and UH2/U could be considered as continuous in the multivariable model, and suggest a discriminant U threshold from 13 ng/mL (no significant threshold for UH2/U). For both 12-week and 4-week (secondary end-point, incidence 3.8%) G4-5, AIC-based comparisons showed that (i) U was a better predictor than variants; (ii) adding variants did not improve the model. In the combined model, OR was 3.03 [95%CI 0.76-12.10] for variants and 1.76 [95%CI 1.08-2.85] for an increase of 10 ng/ml in U. For 4-week G4-5, variants (OR 5.07 [95%CI 1.12-22.94]) and U (OR 1.95 [95%CI 1.14-3.35] for a 10 ng/mL increase) were significant in the combined model.

Discussion / Conclusion

U improves the predictive model of life-threatening toxicities relative to variants. The French U threshold at 16 ng/mL is relevant.

Reference(s)

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EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine | European Medicines Agency (EMA)

Safety labeling update for capecitabine and fluorouracil (5-FU) on risks associated with dihydropyrimidine dehydrogenase (DPD) deficiency | FDA

Keywords

DPYD variants, DPD phenotype, uracilemia, toxicity, flyoropyrimidine

00549
MONITOR (Medcine persONnallsée en TOxciologie et PhaRmacologie) : Establishing France's first multidisciplinary platform for integrated personalized medicine in pharmacology and toxicology

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Personalized medicine requires coordinated integration of clinical evaluation, pharmacovigilance, therapeutic drug monitoring (TDM) and pharmacogenetics to manage serious adverse events, therapeutic failures, intoxications, and complex polypharmacy. However, fragmentation between clinical, biological, and research domains often limits optimal therapeutic decision-making. MONITOR (Carnot@AP-HP, ANR 20 CARN 0031-01) was established as a structured translational platform in Clinical Pharmacology and Toxicology to bridge these gaps and enhance both patient care and innovation.

Materials and methods

MONITOR is built upon a multidisciplinary network comprising two clinical research centers (CRC/CIC), three regional pharmacovigilance centers (CRPV), three pharmacology–toxicology laboratories, one pharmacogenetics laboratory, two biobanks (CRB), and two hospital pharmacies (PUI) within Paris area. The platform integrates a structured clinical pathway including patient identification (adverse events, intoxications, treatment resistance), biological sampling (blood, urine, hair, dried blood spots), centralized biobanking, combined pharmacological, toxicological and pharmacogenetic analyses, multidisciplinary interpretation, and expert clinical feedback. In parallel, MONITOR supports translational research through development of advanced analytical methods (LC-MS/MS, high-resolution mass spectrometry HRMS, DBS-based applications), PK/PD studies, pharmacogenetic projects, prospective cohorts (depression, immuno-nephrology, new psychoactive substances, and omics investigations), strengthened by academic and industrial partnerships.

Results

Since its implementation in 2025, MONITOR has established structured multidisciplinary coordination across the Paris region, implemented integrated patient pathways from clinical assessment to therapeutic recommendation, deployed innovative technologies including HRMS and DBS-based TDM strategies, initiated clinical cohorts, secured competitive funding through national and European grants (Neurodon, DMU15 Paris Saclay, EUDA, NPS ALERT…), and lunched new industrial partnership (e.g., DBS system). The presentation at the congress will provide a comprehensive overview of these achievements and their impact on clinical care, research development, and innovation.

Discussion / Conclusion

MONITOR provides an operational and scalable model of integrated personalized medicine linking clinical care, advanced bioanalysis, TDM, pharmacogenetics, and translational research to optimize therapeutic management in complex patients.

Keywords

personalized medicine, precision medicine, advserse events, therapeutic drug monitoring, Dried blood spot, high rsolution mass spectrometry, toxicology

00551
Phenotyping-genotyping discrepancies in treatment-resistant Depression: CYP2D6 phenoconversion due to cannabidiol-venlafaxine Drug-Drug Interaction

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

A 29-year-old female patient with inadequate response to venlafaxine (225 mg/day) underwent integrated pharmacogenetic and therapeutic drug monitoring (TDM) assessment through MONITOR (Carnot@AP-HP), a personalized medicine platform in Clinical Pharmacology and Toxicology. Concomitant medications included

cannabidiol (Epidyolex®) and clobazam, along with other treatments not considered clinically significant for drug–drug interactions.

Materials and methods

CYP2D6 and CYP2C19 genotyping was performed. Venlafaxine and O-desmethylvenlafaxine (ODV) plasma levels were measured by LC-MS/MS. metabolite-to-parent (MPR) and concentration-to-dose (C/D) ratios were calculated, and a TDM–pharmacogenetic decision algorithm was applied according to international guidelines.

Results

CYP2D6 genotyping showed a *1/*1 genotype (normal metabolizer), while CYP2C19 was 2*/*17 (intermediate metabolizer). Plasma concentrations were 300 ng/mL for venlafaxine and 343 ng/mL for ODV, yielding an MPR of 1.14 (target 2.7–7.7) and a C/D ratio of 2.85 (target 0.45–0.93), consistent with reduced CYP2D6 activity despite normal hepatic and renal function. This genotype–phenotype discordance supports functional phenoconversion, reported in up to 65% of polymedicated patients. Cannabidiol, a potent reversible and time-dependent CYP inhibitor (CYP2D6 IC50,u = 0.95 µM), and to a lesser extent clobazam, likely contributed to CYP2D6 inhibition. Population pharmacokinetic data indicate that CYP2D6 poor metabolizers have a 3.6-fold higher venlafaxine AUC compared with normal metabolizers, thereby exposing them to a higher risk of toxicity such as hypertension, tachycardia, gastrointestinal symptoms, and central nervous system toxicity.

Discussion / Conclusion

This case demonstrates the critical value of integrating TDM-based phenotyping with pharmacogenetic testing for treatment personalization. While genotyping alone predicted normal CYP2D6 activity, TDM revealed functional enzyme inhibition that genotyping could not detect. The combined TDM-pharmacogenetics approach represents best practice for precision medicine in complex psychiatric patients, enabling detection of genotype-phenotype discordance and optimization of therapy based on actual rather than predicted metabolic capacity. Based on these findings, a switch to a non–CYP2D6 substrate was recommended.

Reference(s)

Hiemke et al., Pharmacopsychiatry, 2018

Keywords

personalized treatment, precision medicine, therapeutic drug monitoring, pharmacogenetic, major depressive episode, CYP2D6, venlafaxine, CBD, drug-drug-interaction (DDI), phenoconversion.

00564
Pharmacogenetic approach to Thiopurine toxicity in Tunisian patients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Despite decades of clinical use, thiopurines remain a cornerstone of maintenance therapy in inflammatory bowel disease (IBD), yet their clinical use is frequently compromised by unpredictable toxicity driven by genetic variability. Most pharmacogenetic data informing clinical practice have been derived from Western populations with a clinical gap in evidence for North African population. This study investigates the relationship between pharmacogenetic determinants and adverse events (AE) in Tunisian patients.

Materials and methods

We conducted a retrospective cross sectional study including patients treated with azathioprine or mercaptopurine who developed AE and were referred to the clinical pharmacology department- Monastir University Hospital- Tunisia(2014-2025). Detection of TPMT*2, TPMT*3B, TPMT*3C, NUD15*3, NUD15*4 and NUD15*5 polymorphisms was carried out using RT-PCR.

Results

A total of 93 patients were included in our study, accounting for 104 AE; notably, 11.8% of patients experienced more than one AE. The mean age was 41±17 years

and mean weight 69 ± 16 kg, with a balanced sex distribution (gender ratio 0.97). IBD was the predominant indication (81.7%), and the median initial thiopurine dose was 150 mg/day IQ [100 - 150].

Hematological and hepatic toxicities were the most frequent AE, occurring in 38.5% and 37.5% of cases, respectively. Five patients (5.4%) experienced concomitant hepatic and hematological toxicity, and pancreatitis was recorded in 5.8% of events.

Among the 93 patients, 37 patients (40%) underwent pharmacogenetic testing for both TPMT and NUDT15 polymorphisms. For TPMT, the most frequent variant allele was TPMT*3B and TPMT*3C (2.7% each). For the NUDT15 testing, no mutations were noted.

Discussion / Conclusion

Our findings reinforce that hematological and hepatic toxicities are the predominant thiopurine-related AE, aligning with previously reported data. Nonetheless, determining the precise contribution of pharmacogenetic testing to these events in the Tunisian population will require larger scale-studies.

Keywords

Pharmacogenetic, TPMT, NUDT15, thiopurine, azathioprine, inflammatory bowel disease, adverse events

00580
Study of tacrolimus exposure in kidney transplant patients: Contribution of AUC and C0/dose ratio

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic drug monitoring of tacrolimus in kidney transplantation is based on measuring its trough concentration (C0). In addition, the area under the curve (AUC) provides a better assessment of exposure. Numerous recent studies have focused on the C0/dose ratio, which could enable the prediction of graft survival.Our objective was to analyse tacrolimus exposure profiles (C0, AUC) and evaluate the C0/dose ratio in kidney transplant patients at the NEDIR Mohamed Tizi-Ouzou University Hospital (Algeria) in order to identify possible associations with various clinical events (transplant rejection, opportunistic infections, nephrotoxicity).

Materials and methods

We conducted a retrospective observational study of 147 tacrolimus pharmacokinetic profiles from kidney transplant patients at different post-transplant time points, followed at the Tizi Ouzou University Hospital between 28 March 2022 and 18 December 2024.

Results

A statistically significant linear correlation was found between AUC 0-12h and C0 ($r = 0.836$, $p<0.05$) for all post-transplant periods combined. However, there was no significant correlation between AUC 0-12h and C0 for patients between 6 weeks and 3 months post-transplant ($p>0.05$). The occurrence of opportunistic infections was significantly associated with higher C0 values ($p=0.001$) and higher AUC0-12h values ($p=0.019$).

The majority of the profiles studied (44.2%) corresponded to a C0/Dose ratio ≥1.55, indicating slow tacrolimus metabolism. Meanwhile, 29.9% of the profiles studied corresponded to rapid tacrolimus metabolism (C0/Dose ≤1.05).

Maximum tacrolimus concentrations (Cmax) were significantly higher in patients with a C0/Dose ratio ≤1.05 ($p=0.002$).

Discussion / Conclusion

No statistically significant link was found between the C0/dose ratio and the occurrence of the clinical events studied; however, certain trends confirmed by other studies appear to be interesting, in particular the link between a low C0/dose ratio and an increased risk of opportunistic infections or nephrotoxicity.

The C0/dose ratio appears to be an interesting marker of the metabolic phenotype of tacrolimus in kidney transplant patients.

00604
Integration of therapeutic drug monitoring (TDM) and pharmacogenetic testing within a structured personalized pharmacology platform (MONITOR): Application to treatment-resistant depression in an older patient

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

In France, 15.6% of adults experienced a major depressive episode (MDE) during 2024, with age being a major risk factor for resistance. Within MONITOR, a structured personalized medicine in Pharmacology and Toxicology, we implement a comprehensive approach integrating TDM and pharmacogenetic testing to optimize antidepressant therapy by individualizing dosing, enhancing efficacy and minimizing adverse effects. We report the case of an older patientwith treatment-resistant depression managed within this integrated framework.

Materials and methods

An 85-year-old man with recurrent MDE since 1999, was managed at the Psychiatry Department of Kremlin Bicêtre Hospital and received multiple treatment lines. Antidepressant plasma concentrations and metabolites were measured at Raymond Poincaré Hospital, pharmacogenetic testing was performed at Bicêtre University Hospital. Metabolite-to-parent (MPR) and concentration-to-dose (C/D) ratios were calculated. An algorithm integrating TDM and cytochrome P450 genotyping was applied according to international TDM guidelines (Hiemke et al., 2018).

Results

Between December 2022 and February 2025, the patient received extended-release venlafaxine (150–375 mg/day), mirtazapine, esketamine, and lorazepam. Venlafaxine, primarily metabolized by polymorphic CYP2D6 and CYP2C19 enzymes, was monitored through five measurements of venlafaxine plus O-desmethylvenlafaxine (V+ODV). Supratherapeutic concentrations were observed: 405 ng/mL at 150 mg, 488–628 ng/mL at 300 mg, and 677 ng/mL at 375 mg (reference 100–400 ng/mL). MPR (7.4–10.1; expected 2.7–7.7) and C/D ratios (1.63-2.70; expected 0.45-0.93) were elevated. Genotyping showed normal CYP2D6 and CYP2C19 activity. No drug interactions, hepatic or renal impairment, or adverse effects were identified. The altered pharmacokinetics are likely age-related, as older adults show C/D ratios 42–61% higher than younger adults, independent of classical factors. Dose reduction was therefore recommended.

Discussion / Conclusion

This case illustrates how combining TDM and pharmacogenetics helps distinguish age-related pharmacokinetic changes from genetic or interaction-based causes, supporting dose individualization in elderly patients with treatment-resistant depression.

Reference(s)

Hiemke et al., Pharmacopsychiatry, 2018

Sigurdsson et al., J Neural Transm (Vienna), 2015

Keywords

personalized treatment, precision medicine, therapeutic drug monitoring, major depressive episode, CYP2D6

00611
Operational Feasibility and Molecular Yield of Broad Genomic Sequencing in Early-Phase Oncology Trials: Addressing the "Precision Gap"

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Early-phase oncology trials are shifting from traditional dose-finding based on toxicity to precision-driven designs. While molecular reclassification has redefined therapeutic strategies, logistical delays often hinder clinical implementation. We evaluated the integration of broad genomic sequencing (SEQOIA) in a specialized French center to identify operational barriers to treatment matching.

Materials and methods

This retrospective study included 85 patients treated at the Centre d'Essais Précoces en Cancérologie (CEPEC) between 2022 and 2025. We compared the molecular yield of broad-panel sequencing (SEQOIA) versus targeted panels and assessed progression-free survival (PFS) using Kaplan-Meier analysis.

Results

Among 85 patients (mean age 64; 58% stage IV at inclusion), primary malignancies were urological (54%) and digestive (27%). Actionable targets were identified in 34% of cases (n=29). Broad-panel sequencing demonstrated a superior molecular yield of 47% (9/19) compared to 29% (5/17) for targeted panels. However, only 28% of patients had genomic results available prior to inclusion. No significant PFS

difference was observed between genomic and phenotypic-only groups (p = 0.235). Disease progression was the primary cause of study discontinuation (44%).

Discussion / Conclusion

Broad genomic profiling (SEQOIA) significantly increases actionable target identification compared to limited panels. However, the 3-to-4-week turnaround time remains a critical barrier, as nearly half of the cohort progresses before clinical benefit can be realized. To close the "Precision Gap," SEQOIA must be integrated "upfront" in the patient journey, well before referral to early-phase centers, to ensure clinical stability at the time of inclusion.

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Keywords

Precision Oncology

Next-Generation Sequencing (NGS)

Early-Phase Clinical Trials

Molecular Reclassification

Actionable Alterations

Therapeutic Attrition

Matched Targeted Therapy (MTT)

Progression-Free Survival (PFS)

Upfront Genomic Profiling

00617
Association between HLA gene polymorphism and cutaneous adverse reactions caused by lamotrigine: a bref review

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Recent advances in pharmacogenetic studies have uncovered an increasing number of genes that predispose individuals to adverse drug reactions. Antiepileptic drugs (AEDs) are a frequent cause of cutaneousADRs (cADRs). However, most pharmacogenomic research has focused on carbamazepine and phenytoin. Currently, there is no comprehensive source of information focusing exclusively on the pharmacogenomic properties of lamotrigine. The purpose of this review is to summarize the literature pertaining to HLA genetic polymorphisms that may increase susceptibility to cADRs by lamotrigine.

Materials and methods

A literature search of Embase,PubMed, Medline was conducted using the following search terms: lamotrigine, pharmacogenetics, pharmacogenomics, AEDs, cADRs and HLA.

We included in our review case control or cohort studies and excluded isolated case reports, basic genetic research, and animal experimental studies, and cases which the imputability of lamotrigine alone was uncertain.

Results

A total of 13 publications were included. Among them, 11 were case control studies and 2 were cohort studies. The sample size in each study ranged from 20 to 86 patients.

The most frequently studied populations were Asian groups (nine studies), including Han Chinese, Korean, and Thai populations, followed by European populations (three studies) and one Mexican Mestizo population.

We identified several significant associations between specific HLA alleles and lamotrigine-induced cADRs. Maculopapular eruption (MPE) was associated with HLA-A24:02 in Koreans, drug reaction with eosinophilia and systemic symptoms (DRESS) was associated with HLA-A24:02 in Spanish populations, and Stevens Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) was associated with HLA-B*24:02 in Han Chinese.

Discussion / Conclusion

Through our review, we identified heterogeneous data regarding genetic susceptibility to lamotrigine-induced cutaneous adverse drug reactions (cADRs). Further studies, particularly robust meta-analyses including a much larger number of patients, are needed to confirm these findings. These studies would help establish ethnicity-specific recommendations for high-risk populations, similar to those developed for carbamazepine in patients of Asian ethnicity.

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Keywords

Cutaneous adverse drug reactions, lamotrigine, pharmacogenomics, human leukocyte antigen, antiepileptic drugs, single nucleotide polymorphisms.

00619
Metabolic determinants of rivaroxaban pharmacokinetics: unveiling the inflammatory axis

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Understanding inter-individual variability in rivaroxaban exposure is crucial to prevent bleeding risks inherent to this drug. A previous pharmacokinetic study, ABSORB

(NCTNCT04180436), revealed large inter-individual variability. Moreover, prior proteomic analyses identified systemic inflammation as a determinant of overexposure, notably associated with increased C-reactive protein and interferon-γ levels [1]. The present study aimed to complement these findings using an untargeted metabolomic approach to characterize metabolic signatures associated with rivaroxaban PK profiles.

Materials and methods

Pre-treatment plasma samples from 64 patients with various gastrointestinal and metabolic profiles (ABSORB study) were used for metabolomic analysis. Patients were stratified into high, medium, and low exposure groups based on their rivaroxaban Cmax at Day 1. Comparative metabolomic profiling was performed between high and low exposure groups. Untargeted LC-HRMS analysis was carried out. Data were processed using Compound Discoverer®, and multivariate analyses (sPLS-DA, Elastic Net) were conducted in R. Functional pathway enrichment analysis was performed using Mummichog and MetaboAnalyst®.

Results

Patients were classified according to rivaroxaban Cmax at Day 1 (high exposure: 318 ng/mL vs. low exposure: 178 ng/mL, $p<0.001$). Supervised sPLS-DA models discriminated between exposure groups and identified a metabolic signature including arachidonic acid and decanoylcarnitine, both significantly overexpressed in the high-exposure group. Functional enrichment analysis revealed significant involvement of tyrosine metabolism ($p=0.003$), the carnitine shuttle ($p=0.003$), and arachidonic acid metabolism ($p=0.038$).

Discussion / Conclusion

This pharmacometabolomic signature aligns with previous proteomic findings, identifying a metabolic–inflammatory axis associated with drug exposure. By characterizing shifts in lipid and redox signaling, the present study provides a biological basis for overexposure. It serves as a proof of concept for using omics approaches to explain drug response variability. Future perspectives include performing integrated multi-omics analysis to better understand the mechanisms of variability.

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Keywords

Pharmacokinetic, Metabolomics, Rivaroxaban, Inflammation, Arachidonic acid.

00625
Clinical Relevance of CYP2C19 Genotyping for Therapeutic Strategy Optimization in Clopidogrel-Treated Patients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Clopidogrel is a key antiplatelet agent used in combination with aspirin as part of early, short-term dual antiplatelet therapy (DAPT) for the secondary prevention of non-cardioembolic minor ischemic stroke or high-risk transient ischemic attack. As a prodrug, its bioactivation mainly depends on cytochrome P450 2C19 (CYP2C19). *CYP2C19* genetic polymorphisms define metabolizer phenotypes ranging from poor to ultrarapid, which significantly influence antiplatelet efficacy and the risk of recurrent ischemic events. This study aimed to assess the clinical relevance of *CYP2C19* genotyping in optimizing antiplatelet therapy and securing the management of patients with ischemic stroke.

Materials and methods

CYP2C19 genotyping was performed using a loop-mediated isothermal amplification technique, targeting the three main *CYP2C19* polymorphisms. In parallel, a

retrospective analysis of hospital medical records was conducted to collect demographic data, vascular risk factors, comorbidities, antiplatelet regimens, and clinical outcomes. In CYP2C19 intermediate and poor metabolizers (IM/PM), Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC;2022) recommended to avoid clopidogrel and use an alternative antiplatelet agent (ticagrelor) in DAPT.

Results

The cohort included 74 patients, admitted to the neurovascular intensive care unit. Allelic frequencies of *CYP2C19*2* (16%) and *CYP2C19*17* (20%) were comparable to those reported in Caucasian populations. *CYP2C19* genotyping identified 33.8% of patients (n=25) with an IM and no PM. In this cohort, guideline recommendations were effectively applied in only 10 patients (prescription limited to 1 month) and ticagrelor was selected as the alternative antiplatelet therapy in combination with aspirin. In 5 patients still treated by clopidogrel, a platelet function testing was performed and showed insufficient antiplatelet activity. In these 10 patients who benefited guideline-based therapeutic adaptation with no ischemic stroke recurrence at one month follow-up.

Discussion / Conclusion

Early *CYP2C19* genotyping enables the identification of patients at increased risk of clopidogrel inefficacy and stroke recurrence. Its systematic integration into acute ischemic stroke management may improve therapeutic strategies, clinical outcomes, and secondary prevention.

Reference(s)

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- Clopidogrel with aspirin in High-risk patients with Acute Non-disabling Cerebrovascular Events II (CHANCE-2): rationale and design of a multicentre randomised trial. Wang Y, Johnston C, Bath PM, Meng X, Jing J, Xie X, Wang A, Pan Y, Xu A, Dong Q, Wang Y, Zhao X, Li Z, Li H; CHANCE-2 Investigators. Stroke Vasc Neurol. 2021 Jun;6(2):280-285. PMID: 33952670

Keywords

Clopidogrel, CYP2C19 genotyping, ischemic stroke, personalized treatment

00631
Late Tachycardia in a Preterm Infant after caffeine withdrawal: Importance of Therapeutic Drug Monitoring

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Commonly used in neonatology to treat and prevent apnea of prematurity, caffeine is well-tolerated and has a wide therapeutic range. However, delayed elimination due to immature liver and kidney function can lead to prolonged accumulation of the drug after treatment cessation.

Materials and methods

The determination of caffeine concentration was performed by an in-house validated high-performance liquid chromatography method at the Clinical Pharmacology in the National Center Chalbi Belkahia of Pharmacovigilance. Caffeine therapeutic range was 8–20 mg/L

Results

A male preterm infant was born at 33 weeks + 4 days of gestational age via cesarean. He received a loading dose of 22.5 mg of caffeine citrate shortly after birth, followed by maintenance dosing of 5 mg/day for the prevention of apnea of prematurity. Caffeine therapy was discontinued at 34 weeks + 1 day, after

approximately four days of treatment. The infant was exclusively formula-fed, with no breastfeeding and no maternal medication exposure, including caffeine. No other medications were administered to the newborn. A faint jaundice was noted. On day two after caffeine discontinuation, the infant developed isolated tachycardia, with heart rates ranging from 197 to 214 bpm, compared to a baseline of 150–158 bpm. These episodes were initially frequent and later became more spaced out and less intense. There were no signs of infection, dehydration, irritability, vomiting, or diarrhea during the episodes. A plasma caffeine concentration, measured seven days after the last dose at 35+1 weeks, revealed a residual level of 7.65 mg/L.

Discussion / Conclusion

Using a mono-exponential elimination model and assuming a 101- hour half-life, the calculated peak (C0) at discontinuation would be 24.23 mg/L, which exceeds the upper limit of the commonly recognized therapeutic range of 8–20 mg/L. This case highlights the potential utility of therapeutic drug monitoring as a diagnostic aid in neonates presenting with unexplained symptoms following caffeine therapy.

00634
Reevaluation of the DPYD*6 Variant: Significant Association with Elevated Uracil as a Marker of Impaired DPD Function In Vivo

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Screening for dihydropyrimidine dehydrogenase (DPD) deficiency is recommended by health authorities to prevent potentially life-threatening fluoropyrimidine toxicity. National and international guidelines advocate either phenotyping (primarily uracil-based) or targeted genotyping of DPYD variants, yet the optimal strategy to identify DPD-deficient patients remains elusive. Phenotyping approaches are prone to confounding factors (hepatic and renal function, circadian variations, diet), whereas genotyping, despite relying on a core list of deleterious variants, exhibits low sensitivity.The functional impact of the DPYD*6 variant remains debated, although several reports have linked it to fluoropyrimidine toxicity.

. In our previous analysis, patients with discordant phenotyping and genotyping results displayed a markedly higher prevalence of DPYD*6 carriers—an observation corroborated by independent studies. Motivated by these findings, we conducted a systematic evaluation of DPYD*6 prevalence in our complete patient cohort and

examined its influence on in vivo DPD activity, using plasma uracil concentration as a surrogate marker.

Materials and methods

The patient cohort is described elsewhere. Genotyping was performed using a validated TaqMan allelic discrimination assay. Uracil levels across genotype groups were compared using non-parametric Mann-Whitney U tests, with significance set at $p < 0.05$ after correction for multiple testing.

Results

DPYD*6 was detected in heterozygous state in 9.8% (n=71) of patients, homozygous in 0.7% (n=5), and in heterozygous combination with c.2846A>T in 0.3% (n=2). Heterozygous carriers exhibited significantly higher uracil levels (12.2 ± 5.1 µg/L) compared to non-carriers (10.5 ± 6.1 µg/L), with the difference remaining significant post-correction.

Discussion / Conclusion

These results reinforce the evidence that the DPYD*6 variant modulates in vivo DPD enzyme activity, despite inconsistent findings from in vitro functional studies. Further mechanistic investigations are needed to define its contribution to fluoropyrimidine toxicity and to optimize personalized dosing algorithms and pre-treatment screening protocols.

00635
Combined Pharmacogenetics and Therapeutic Drug Monitoring (TDM) Approach to Manage Drug–Drug Interactions and Optimize Care in Pediatric Neuropsychiatry: A Case Report

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

In pediatric psychiatry, treatment response varies widely between patients, depending on clinical, developmental, pharmacological and genetic factors. Pharmacogenetics and Therapeutic Drug Monitoring (TDM) help to explain atypical responses and guided therapeutic adjustments.

Objective We present a combined pharmacogenetics and TDM approach to manage drug-drug interactions and optimize care in a psychiatric pediatric patient.

Materials and methods

We reported the case of a 10-year-old child followed in a day hospital specializing for severe child neuropsychiatric disorders. The patient had Langerhans cell neurohistiocytosis, leading to ADHD (Attention-Deficit/Hyperactivity Disorder) and neuropathic pain, treated with encorafenib, trametinib, clonidine and gabapentin, respectively. Due to insufficient efficacy, TDM and pharmacogenetic testing were performed to explain the response and to anticipate a potential association to codeine or tramadol.

Genes involved in psychotropic drug metabolism were analyzed by next-generation sequencing (*CYP2D6/2C19/3A4/3A5/1A2*). TDM for clonidine and gabapentin was conducted using high-performance liquid chromatography–mass spectrometry. A drug–drug interaction analysis was also performed on current and planned medications.

Results

The patient was extensive metabolizer for CYP2D6, CYP2C19 and CYP3A4, and poor metabolizer for CYP3A5. This profile did not explain the current partial treatment response. Moreover, as codeine and tramadol are metabolized by CYP2D6 (morphine) and CYP3A4 (inactive metabolites), no potential dose adjustment was required.

Gabapentin concentration (2.6µg/mL) was within the therapeutic range, whereas clonidine concentration (0.6ng/mL) was low. An interaction was identified between tramadol and trametinib, which might increase trametinib exposure (not observed with codeine). Based on these results, clonidine dose was increase and low-dose codeine was introduced with close monitoring due to the risk of central nervous system depression. Gabapentin dose may be increase if neuropathic pain persist.

Discussion / Conclusion

This case illustrated that combining pharmacogenetics and TDM optimized patient care. This approach could be expanded to improve personalized treatment strategies in pediatric psychiatry, enhancing both safety and efficacy in clinical practice.

Keywords

Pharmacogenetics, Therapeutic Drug Monitoring, Drug-Drug Interaction, pediatric neuropsychiatry, psychotropic drugs

00636
Prevalence of CYP1A2 Allelic Variants in Tunisian Patients: Implications for Olanzapine Prescription

Poster only

S. Souissi[1], K. Ferchichi[1], M. Daldoul[1], M. Ben Sassi[1], S. Ben Hammamia[1], H. El Jebari[1], M. Zouari[1], R. Charfi[1], I. Salouage[1], R. Daghfous[1], E. Gaies[1], S. Trabelsi[1]

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

CYP1A2 is the primary enzyme involved in the metabolism of olanzapine, an atypical antipsychotic widely prescribed for schizophrenia and bipolar disorders. Genetic polymorphisms in the CYP1A2 gene may significantly affect enzyme activity, leading to interindividual variability in drug exposure and response [1].

This study aimed to assess the prevalence of CYP1A2 variants in Tunisian patients.

Materials and methods

Next-generation sequencing (NGS) data were analyzed from 42 patients using a predesigned AmpliSeq for Illumina gene panel. Although none of the patients were receiving olanzapine at the time of sampling, DNA were sequenced for the most common CYP1A2 variants, including CYP1A2*1B (rs2470890) [1], *1C (rs2069514), *1F (rs762551), *1E (rs2069526), *1D (rs35694136) [2].

Results

A high prevalence of CYP1A2 variants (78.6%, n=33) was observed. The majority of patients carried at least one of the tested polymorphisms, with 30 individuals carrying more than one variant.

Notably, the CYP1A2*1F allele, associated with increased enzyme activity, was particularly frequent (71.4%, n=30). The CYP1A2*1B variant was also frequent, identified in 69% of patients (n=29), with 25 patients carrying both SNPs. Data on CYP1A2*1B are inconsistent, but it is likely not associated with olanzapine exposure [1].

The CYP1A2*1D variant, associated with decreased enzyme activity, was detected in nine patients. The CYP1A2*1E and CYP1A2*1C variants, both associated with decreased enzyme activity, were observed in five patients and four patients, respectively.

Haplotype analysis revealed that CYP1A2 *1W (rs35694136; rs2069526; rs762551) was present in five patients, CYP1A2*1L (rs2069514; rs35694136; rs762551) in four patients, and CYP1A2*1V (rs35694136; rs762551) in one patient.

Discussion / Conclusion

The high prevalence of CYP1A2 polymorphisms highlights the need for cautious prescription of olanzapine in Tunisian patients. Particular attention should be given to the CYP1A2*1F and CYP1A2*1B variants, given their high frequency. However, given the inconsistent functional data for CYP1A2*1B, phenotype–genotype studies in our population are warranted to assess its clinical impact on olanzapine exposure.

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00639
Therapeutic Drug Monitoring of Ruxolitinib in a Tunisian Series

Poster only

S. Souissi[1], M. Ben Sassi[1], K. Ferchichi[1], S. Ben Hammamia[1], S. Jelassi[1], H. El Jebari[1], M. Zouari[1], M. Daldoul[1], R. Charfi[1], I. Salouage[1], E. Gaies[1], S. Trabelsi[1]

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Ruxolitinib, a Janus kinase (JAK1-JAK2) inhibitor, is mainly used in glucocorticoid-refractory or -dependent chronic graft-versus-host disease [1]. However, data on ruxolitinib therapeutic monitoring remain scarce. This study aimed to evaluate ruxolitinib trough plasma concentrations in a series of samples from both pediatric and adult patients.

Materials and methods

A total of 32 plasma samples from 9 patients (5 adults and 4 children) receiving ruxolitinib were analyzed using a validated High-Performance Liquid Chromatography (HPLC) method. Based on published recommendations [2], therapeutic ranges were defined according to the administered dose: 10–30 ng/mL for patients receiving ≤5 mg twice daily, and 40 ng/mL as the target for those receiving >5 mg up to 10 mg twice daily.

Results

Among the 32 samples analyzed, only 37.5% (n=12) were within the therapeutic range. The majority (43.7%, n=14) were subtherapeutic, and 18.8% (n=6) were supratherapeutic.

When stratified by dose, 24 samples corresponded to patients receiving ≤5 mg twice daily. In this group, 45.8% (n=11) achieved therapeutic concentrations, while 37.5% (n=9) were subtherapeutic. Among the eight samples from the other group, only one sample was within the therapeutic range, and 62.5% (n=5) were subtherapeutic.

Subtherapeutic concentrations were more frequent in pediatric patients (43.7%) than in adults (33.3%).

Discussion / Conclusion

This series demonstrates that subtherapeutic ruxolitinib levels are common in both pediatric and adult patients. As a CYP3A4 substrate, its metabolism may be affected by genetic polymorphisms and drug-drug interactions. In children, the lack of age-appropriate formulations remains a major barrier; tablet splitting or crushing leads to inconsistent absorption and unpredictable plasma levels [3]. In adults, subtherapeutic levels may result from poor adherence or gastrointestinal intolerance. These findings further support routine ruxolitinib monitoring and highlight the urgent need for pediatric-adapted drug formulations.

00663
Do Phenotypic Tacrolimus Dose Requirements Align with Genotypic Metabolizer Classification in Renal Transplant Recipients?

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Tacrolimus demonstrates marked inter-individual pharmacokinetic variability, largely attributed to CYP3A5-polymorphisms,which account for up to 50% of variability. Although CYP3A5-genotype-based metabolizer classification (expressers vs non-expressers) guides dose individualization,substantial residual variability persists.Additional pharmacogenes such as PXR (NR1I2) and POR may contribute. We evaluated whether phenotypic dose requirements align with genotypic metabolizer classification in stable renal transplant recipients.

Materials and methods

Renal transplant recipients >1-year post-transplant were enrolled(n=100). Tacrolimus C0 was measured using LC–MS/MS, and dose-normalized exposure (C0/dose) was calculated. Patients were categorized into low(≤0.035),intermediate(0.036-0.99),high(≥0.1)dose groups based on their dose requirement. Genotyping for CYP3A5 (*1/*1,*1/*3,*3/*3), PXR-NR112 (CC,CT,TT), and POR (*1/*1,*1/*28,*28/*28) was performed using TaqMan® assays.

Results

Male:female ratio was 81:19. The mean C0/dose was 6.5±3.9,1.9±1.0 and0.9±0.3 in the low(n=28),intermediate(n=35),and high-dose(n=37)groups, respectively.A strong concordance was observed in the high-dose group, all participants carried at least one *1 for CYP3A5. However, 11/28(39.3%) in the low dose group harboured a heterozygous genotype(*1/*3) for CYP3A5.Similarly,the intermediate dose group had two extreme findings; 8/35(22.9%)harboured a homozygous nonexpressor(*3/*3) and 9/35(25.7%) had homozygous expressors (*1/*1). The POR*1 status explained the majority of the discordance in the low dose group (*1 POR was found in 10/11) and the CYP3A5*1/*1 in the intermediate group (*1 POR was found in 9/9). The POR*28 status and PXRNR112 explained the dose requirement for *3/*3 individuals in the intermediate dose group. Despite multi-gene interactions explaining most of the PK variability, isolated outliers remained unexplained by the evaluated polymorphisms.

Discussion / Conclusion

While CYP3A5 genotype shows primary alignment with tacrolimus dose requirement, significant residual variability is explained by POR and PXR. Multi-gene interactions involving these three pharmacogenes contribute to the dose requirement phenotype. Our study supports a polygenic model of tacrolimus pharmacokinetics and also underscores the potential role of next-generation sequencing in uncovering obscure genetic determinants contributing to the residual variability.

Keywords

Tacrolimus; CYP3A5; POR; PXR (NR1I2); Pharmacogenetics; Renal transplantation; Dose requirement; Genotype–phenotype correlation; Residual variability; Polygenic model; Next-generation sequencing.

00669
Precision Phenotyping of UH2:U Using a Hierarchical Bayesian Flux Model

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Dihydropyrimidine dehydrogenase (DPD) converts endogenous uracil (U) to dihydrouracil (UH_2) and is a major determinant of severe fluoropyrimidine (FP) toxicity[1]. Clinical implementation for pre-treatment screening relies on genotyping four established risk variants in the DPD gene *DPYD* or DPD phenotyping (e.g. measurement of plasma UH_2:U ratios)[2]. However, these *DPYD* risk variants explain only a minority of severe FP toxicities[3] and baseline UH_2:U measurements show substantial inter-individual variability[4].

Materials and methods

We developed a hierarchical Bayesian flux model to estimate DPD activity integrating genotype and phenotype information. Genotype data (canonical *DPYD* risk varaints, c.85T>C, c.496A>G, and c.1601G>A), sex, age, and UH_2:U measurements from a cohort of 831 individuals of self-declared European ancestry were analyzed using Markov Chain Monte Carlo (MCMC) sampling with Nimble[5]. DPD flux was modeled as a latent variable informed by relative U clearance and inferred from observed U and UH_2 concentrations. Independent covariate effects on relative U clearance were modeled as a linear combination. The model is extensible to incorporate downstream pyrimidine metabolites.

Results

The canonical *DPYD* risk variants were associated with reduced relative U clearance, consistent with prior evidence. The variant c.1601G>A showed a negative effect with substantial uncertainty (95% CrI: -0.246 to 0.019). Although c.85T>C, c.496A>G, and c.1129-5923C>G are in linkage disequilibrium, the model resolved their distinct contributions, demonstrating a reduced effect for c.496A>G (95% CrI: -0.237 to -0.105) and an increased effect for c.85T>C (95% CrI: 0.023 to 0.121). This flux model fit improved markedly versus an approach using UH_2:U alone (U: R_2 = 0.53; UH_2: R^2 = 0.92 vs R^2 = 0.17).

Discussion / Conclusion

This Bayesian flux model provides a clinically interpretable, uncertainty-aware estimate of DPD activity that integrates genotype and metabolite data. Additionally, this supports refined variant risk stratification and individualized FP dosing research.

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Keywords

Fluoropyrimidine, Bayesian, DPYD, DPD, Pharmacogenetics, Pharmacogenomics, Phenotype, Pyrimidine, Metabolite

00691
Pharmacogenetic Determinants of Methadone Response: The impact of OPRM1, CYP2B6, CYP2D6, and KCNH2 Polymorphisms on Therapeutic Outcomes in Opioid-Dependent Patients Undergoing Methadone Maintenance Treatment.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Background:
Methadone Maintenance Therapy (MMT) represents a fundamental approach in the management of opioid dependence. However, significant interindividual variability in methadone efficacy and safety remains a major clinical challenge. Pharmacogenetic factors, including polymorphisms in genes related to methadone metabolism, receptor binding, and cardiac repolarization, may explain these differences. To date, no pharmacogenetic data have been reported for the Algerian population receiving MMT.

Objectives:
This study aimed to investigate the influence of genetic variants in OPRM1 (rs562859), CYP2B6 (rs45482602), CYP2D6 (rs3892097), and KCNH2 (rs1805123) on methadone response among Algerian patients undergoing MMT, and to characterize interindividual variability in metabolic phenotype in this population.

Materials and methods

A total of 102 opioid-dependent patients receiving methadone were recruited from the Intermediate Care Center for Addiction Treatment in CHERAGUA Algiers. Plasma methadone and its metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidin (EDDP) were quantified by gas chromatography–mass spectrometry (GC-MS), and the methadone/EDDP ratio was used to determine metabolic phenotype. Genotyping was performed using TaqMan® SNP assays on a 7500 Real-Time PCR System. Genotypic and allelic frequencies were analyzed, and deviation from Hardy–Weinberg equilibrium was assessed.

Results

The cohort was predominantly composed of slow metabolizers (43.1%), followed by extensive (26.5%) and ultra-rapid metabolizers (17.6%). Genotype distributions revealed a predominance of wild-type CYP2D6 (CC: 74.5%) and CYP2B6 (CC: 98%), intermediate diversity in OPRM1 (CC: 42.2%; CT: 40.2%; TT: 17.6%), and a high frequency of the KCNH2 TT genotype (47.1%). The KCNH2 variant, associated with increased risk of QT prolongation, underscores the importance of baseline ECG monitoring prior to MMT initiation.

Discussion / Conclusion

This study provides the first pharmacogenetic characterization of methadone-treated patients in Algeria, revealing unique allele distributions that may affect therapeutic response and safety. Integration of pharmacogenetic testing into clinical practice could support precision dosing, improve treatment retention, and minimize adverse cardiac outcomes in MMT programs.

00731
Drug–drug–gene interactions as risk factors for statin- and ezetimibe-associated hepatotoxicity: a pharmacogenomic case series

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Hydroxymethylglutaryl-CoA reductase inhibitors (statins) are the first-line therapy for hypercholesterolemia. In some individuals, statins alone fail to achieve target LDL-C levels, necessitating the addition of ezetimibe. Although both drugs are generally well tolerated, their concomitant use may increase the risk of adverse drug reactions (ADRs), including hepatotoxicity. The pharmacogenetic background of statin-induced hepatotoxicity has not yet been fully elucidated. Given that ezetimibe and statins share pathways involving ABCB1, ABCG2 and OATP1B1/SLCO1B1, which are particularly relevant for statin exposure and the enterohepatic recirculation of ezetimibe, the likelihood of drug–drug–gene interaction is high.

Materials and methods

We present seven cases of patients (4 females, 3 males; aged 27–68 years) who developed moderate hepatotoxicity during concomitant treatment with statins (atorvastatin and/or rosuvastatin) and ezetimibe, with ALT/AST ≥3× upper limit of normal. Patients were genotyped for pharmacogenes of interest: CYP2C9 (*2,*3), CYP2C19 (*2,*17), CYP3A4 (*1B,*22), CYP3A5 (*3), UGT1A1 (*28), UGT2B7 (c.-161C>T), ABCB1 (c.1236C>T, c.2677G>T/A, c.3435C>T), ABCC2 (c.-24C>T,

c.1249G>A), ABCG2 (c.421C>A, c.34G>A) and SLCO1B1 (c.388A>G, c.463C>A, c.1929A>C, c.521T>C).

Results

A consistent finding across all cases was the presence of the ABCG2 c.421A allele, observed in all patients (four heterozygous and three homozygous carriers). Six patients carried at least one ABCB1 variants (four with predicted poor and two with decreased transporter function). Five carried ABCC2 c.-24C>T and/or c.1249G>A. Additional pharmacogenetic variants were detected in SLCO1B1 c.521T>C (n=2) and c.388A>G (n=5), UGT1A1*28 (n=5), CYP2C19*2 (n=3), CYP2C9*2 (n=2) and CYP3A4*22 (n=1).

Discussion / Conclusion

Based on clinical data and pharmacogenetic analysis, we hypothesized that concomitant therapy with statins and ezetimibe, together with multigene pharmacogenetic predisposition, may contributed to impaired liver function. The ABCG2 and ABCB1 polymorphisms appear particularly relevant, potentially affecting drug transport and hepatic exposure. Our findings suggest that multigene pharmacogenomic predisposition may contribute to ADRs during combination lipid-lowering therapy.

Keywords

statins, ezetimibe, hepatotoxicity, pharmacogenomics, ABCG2, ABCB1, drug-drug–gene interactions

00738
Pharmacogenetic determinants of interindividual variability in sertraline exposure and tolerability in patients with depression

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Sertraline is a selective serotonin reuptake inhibitor widely metabolized in the liver by cytochrome P450 (CYP) enzymes (CYP2C19, CYP2B6, CYP2D6, CYP3A4, CYP2C9), primary into N-desmethylsertraline. Besides, it is substrate of ABCB1 and ABCG2 drug transporters. This pilot study examined the impact of selected pharmacogenetic variants on sertraline pharmacokinetics, pharmacodynamics and tolerability in patients with depression receiving sertraline with a benzodiazepine.

Materials and methods

This pilot study included psychiatric patients with depression treated with sertraline and a benzodiazepine. All participants had pharmacogenetic profiles (ABCB1, ABCG2, COMT, CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5, 5-HTTLPR). Patient-reported outcomes (PROs) were determined by using a

questionnaire about current symptoms and possible antidepressant side effects. Sertraline and N-desmethylsertraline serum concentrations were quantified by LC-MS/MS to calculate area under the drug concentration-time curve (AUC) values.

Results

The study included 37 psychiatric patients (24 female, 13 men), age median 41 (18-68), with depression receiving sertraline (20–100 mg/day) in combination with a benzodiazepine. For sertraline patients carrying defective alleles showed the AUC0-6, ng x hr/mL: for CYP2B6 intermediate (IM) compared to normal metabolizers (NM) (7.3 vs. 11.1); for CYP2C19 (IM+PM) compared to rapid and ultrarapid (RM+UM) (11.6 vs. 8.3), for ABCB1 3435C>T, T vs. C allele (11.2 vs 7.2). For N-desmethylsertraline (AUC0-6): for CYP2B6 IM vs. NM (12.2 vs. 19.5), for CYP2C19 RM+UM vs. IM+PM (14.9 vs.21.1), for ABCB1 3435C>T, T vs. C allele (19.1 vs. 13.2). In multivariate analysis, ABCB1 low-function phenotype was independently associated with increased sertraline exposure ($\beta = 3.13$, $p = 0.036$). Patients with normal SERT function showed a better therapeutic response in motivation improvement.

Discussion / Conclusion

Our findings indicate that CYP2C19, CYP2B6 and ABCB1 polymorphisms modulate sertraline and N-desmethylsertraline exposure. Incorporation of pharmacogenetic testing into sertraline therapy may support more individualized dosing and improved benefit–risk balance in patients with depression treated with concomitant benzodiazepines.

Keywords

Sertraline, pharmacogenetics, CYP2C19, CYP2B6, ABCB1, ABCG2, depression

00747
Does CYP3A5 genotype may explain sub optimal area under the curve of tacrolimus in a real-life cohort of transplanted patients ?

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Tacrolimus is the most commonly used immunosuppressive drug for the prevention of graft rejection. A large interpatient variability is observed due to several demographic, genetic, biological and clinical factors. The main objective of this study was to investigate the impact of *CYP3A5* pharmacogenetics on tacrolimus exposure (area under the curve of the concentrations, AUC) in transplanted patients.

Materials and methods

An observational, retrospective study was conducted. Patients who received a solid organ transplant, had a tacrolimus AUC determination (using microsampling) and a genotyping of *CYP3A5* between May 2022 and February 2026 were included. Patients were categorized as non expressors (poor metabolizer (PM), *CYP3A5* *3/*3) and expressors (intermediate metabolizer (IM), *CYP3A5* *1/*3) and extensive metabolizer (EM), *CYP3A5* *1/*1) of CYP3A5. Demographic (age, sex, date of birth), clinical (type of transplanted organ), therapeutic (dose, co-treatments), biological (AUC, trough concentration (C0), C-reactive protein) data were collected. Tacrolimus

apparent clearance (CL/F) was calculated using AUC0-t and dosing. Clearances of tacrolimus were compared between genotype groups using Mann-Whitney tests.

Results

Nineteen patients were included in the study. Two patients were EM, 7 were IM and 10 patients were PM. Median [min-max] CL/F were 69.26L/h [27.57-113.10] in expressors patients and 47.96L/h [14.33-118.3] in non-expressors patients. No significant difference in CL/F was observed between expressor and non expressor patients (p=0.11). Two expressors (both *1/*3) and 3 non-expressors patients had *CYP3A4/5* strong inductor or inhibitor co-treatments. Excluding those patients, median CL/F were 70.28L/h [34.21-113.1] and 30.89L/h [14.33-116.6] for expressors and non-expressors, respectively. No significant difference was observed (p=0.053). It should be noted that no patient had CRP>5mg/L.

Discussion / Conclusion

No significant difference between CL/F was found based on the *CYP3A5* genotype. However, the number of patients was low. Larger studies are needed to better characterize the impact of *CYP3A5* genotype and other confounding factors on tacrolimus pharmacokinetics variability and exposure prediction.

00754
Impact of UGT1A1*28 Polymorphism on Irinotecan Toxicity and Dose Optimization in Algerian Patients with Metastatic Colorectal Cancer

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Interindividual variability in irinotecan toxicity in patients with metastatic colorectal cancer is partly explained by genetic polymorphisms affecting drug metabolism. The UGT1A1 enzyme plays a key role in the glucuronidation of irinotecan's active metabolite, SN-38. The UGT1A128 polymorphism has been associated with reduced enzymatic activity and an increased risk of treatment-related toxicities, particularly diarrhea and neutropenia. However, data on the prevalence and clinical impact of this polymorphism in Algerian patients are limited. This study aimed to assess the distribution of UGT1A128 and its association with irinotecan-related toxicities.

Materials and methods

A prospective study was conducted in 83 patients receiving irinotecan-based chemotherapy at the Cancer Center of Sétif. Blood samples were collected prior to chemotherapy administration, and genomic DNA was extracted and quantified at the Central Laboratory of the Cancer Center. DNA quantification was performed using a Qubit Fluorometer (versions 3/4) with the Qubit DNA assay kit, following the manufacturer's instructions. UGT1A128 genotyping was performed using the EasyPGX® qPCR system, with data analyzed through the dedicated EasyPGX®

Analysis Software. The associations between UGT1A128 genotype and major irinotecan-related toxicities diarrhea, neutropenia, nausea and vomiting were evaluated.

Results

Genotype frequencies were 38.6% for *1/*1, 49.4% for *1/*28, and 12% for *28/*28, consistent with frequencies reported in Mediterranean and North African populations. Patients with the *28/*28 genotype had a higher risk of severe diarrhea, while associations with neutropenia and nausea/vomiting were less pronounced.

Discussion / Conclusion

The UGT1A128 polymorphism is relatively frequent among Algerian patients with metastatic colorectal cancer and significantly increases the risk of severe irinotecan-related diarrhea. Pre-treatment genotyping can help identify high-risk patients, enabling individualized dose adjustment and closer monitoring. Incorporating UGT1A128 testing into clinical practice may improve patient safety, reduce treatment-related complications, and support precision oncology approaches in the Algerian population.

Keywords

UGT1A1*28, Irinotecan, PharmacogeneticsToxicity, Dose optimization, Colorectal cancer, Personalized therapy, Algerian population

Pharmacometrics

00001
Plasma Does Not Forget: From Stochastic Reconstruction to Distribution-Based Inference in PopPK Adherence Detection

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Accurate detection of medication nonadherence remains a major challenge in chronic therapies.

Conventional threshold-based interpretation of single drug concentrations ignores pharmacokinetic variability and exhibits limited sensitivity and specificity.

We previously introduced a PopPK-based framework capable of reconstructing likely dosing histories using stochastic optimization.While effective, this reconstruction-based approach relies on Empirical Bayes point estimates and discrete regimen exploration.

We now propose a conceptual and methodological shift: reformulating adherence detection as a full distribution-based probabilistic inference problem.

Materials and methods

Using a published PopPK model of spironolactone and its active metabolite as an illustrative case study, virtual patients were simulated under all possible dosing scenarios allowing 0, 1, or 2 tablets per day.

For each scenario, the joint probability density function of concentrations was derived. Instead of identifying a single most likely regimen via MCMC sampling, scenario probabilities were computed directly from the level-sets of the joint distribution, enabling probabilistic ranking of all candidate dosing patterns.

Diagnostic performance was evaluated using ROC analysis.

Supervised machine learning was trained on probabilistic outputs to derive clinically actionable adherence classes.

Results

The distribution-based framework markedly improved recognition of nonadherent patients compared with stochastic reconstruction, with substantial gains in sensitivity for partially adherent and compensatory dosing patterns.

Profiles that were previously difficult to distinguish were robustly identified, particularly in recent or strategically compensated nonadherence.

Direct probabilistic inference reduced sensitivity to shrinkage and stabilized classification across adherence scenarios.

Machine learning further stratified patients into three clinically relevant groups: probably adherent (including “intelligent cheaters”), certainly nonadherent, and probably nonadherent requiring further evaluation.

ROC analyses demonstrated a consistent and significant increase in overall diagnostic accuracy.

Discussion / Conclusion

By shifting from stochastic reconstruction to distribution-based inference, this work establishes a generalizable and extensible probabilistic framework that substantially strengthens pharmacokinetic detection of medication nonadherence and broadens its clinical applicability.

Reference(s)

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Keywords

Medication Adherence, Population Pharmacokinetic modeling, Therapeutic Drug Monitoring, Spironolactone, Metabolite, Distribution-Based Inference

00009
Clustering-based characterization of cancer-related variability in amikacin population pharmacokinetic of pediatric with suspected febrile neutropenia

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Amikacin remains a cornerstone treatment for suspected chemotherapy-induced febrile neutropenia, yet its pharmacokinetic (PK) parameters show substantial variability, particularly in pediatric patients.

Materials and methods

To identify relevant PK studies in this population, we conducted a systematic review in PubMed and PKPDAI. Next, we developed a population PK model of amikacin in pediatric patients with cancer. Finally, we explored structured sources of PK variability using an unsupervised clustering approach.

Results

A total of 556 plasma concentrations from 101 patients were analyzed using nonlinear mixed-effects modeling in Monolix®. The number of occasions (infusions) per patient ranged from 1 to 11, with two concentration measurements per occasion. The final one-compartment model incorporated inter-occasion variability (IOV) on clearance (CL) and volume of distribution (V), correlation between random effects, and covariate effects of body weight on CL and V, and estimated glomerular filtration rate on CL.

An exploratory clustering analysis based on empirical Bayes estimates identified solutions with k=2, 3, 4, 8, 14 or 15 clusters with specific PK patterns. Incorporation of cluster-specific fixed effects both on CL and V improved model fit and reduced unexplained IOV, with identifiable bidirectional effects on CL alone and smaller but consistent effects on V alone. Cluster composition remained diagnostically heterogeneous, indicating that clustering captured specific PK patterns rather than diagnosis-specific subgroups.

Discussion / Conclusion

In conclusion, this study displays that a portion of amikacin PK variability in pediatric cancer patients is structured at the inter-occasion level and can be partially uncovered through parsimonious clustering. This exploratory approach provides new insights into amikacin PK and may support future strategies for individualized dosing.

Keywords

cancer; pediatric; amikacin; population pharmacokinetics; clustering analysis of PK parameters.

00048
Recommendations for evaluating risk of bias for population pharmacokinetic systematic reviews

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The reliability of population pharmacokinetic (popPK) models depends not only on the quality of the data but also the robustness of their external evaluation [1]. Although systematic reviews are useful in assessing predictive performance of popPK models, no dedicated framework exists for assessing risk of bias. The study aimed to evaluate the methods and quality criteria used in published systematic reviews of popPK models and to develop recommendations for a more informative risk of bias tool.

Materials and methods

A systematic search was performed from inception to November 2025 following PRISMA guidelines. Studies that conducted a quantitative model evaluation with bias-related criteria were included. Two reviewers (SR, XL) independently performed data extraction and risk of bias was assessed using the ROBIS tool as a template. Limitations that might introduce bias into the model assessment were also extracted and findings were synthesised to inform recommendations for a popPK-specific risk of bias tool.

Results

Twenty-two systematic reviews met the inclusion criteria. All included reviews performed some form of external evaluation. Population-based prediction error metrics were most frequently reported (n = 21), followed by metrics obtained through Bayesian forecasting and simulation (both n = 14). The most frequent sources of bias were limitations in external evaluation datasets (n = 19), heterogeneity in analytical methodologies (n = 8), and treatment-related factors, including concomitant medications (n = 4). Based on the identified gaps, key recommendations were made relating to suitable study selection and external dataset quality.

Discussion / Conclusion

ROBIS demonstrated partial applicability for popPK systematic reviews but did not adequately capture critical limitations unique to model evaluation. An extension to the existing risk of bias framework, incorporating criteria specific to popPK external evaluation, dataset construction, and analytical comparability, is justified. Adoption of this tool may enhance transparency, reproducibility, and comparability across future popPK systematic reviews.

Reference(s)

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Keywords

systematic review, population pharmacokinetic modelling, external validation

00068
Population Pharmacokinetics Modeling of SCT800 by Pooled Data: Free Individualized Medication Guidance for Hemophilia Patients in China

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

High interindividual variability in FVIII pharmacokinetics (PK) complicates maintaining FVIII coagulating activity above targeted levels. Traditional PK methods, requiring complex calculations and numerous blood samples, make optimizing FVIII use while improving patient safety and economy challenging. The population pharmacokinetic (PopPK) approach can reduce blood samples to support precision medication. SCT800 is widely used in China, yet no model exists for it. We developed a PopPK model for SCT800 to quantify factors contributing to variability. The model enables personalized dosing based on individual covariates and desired targets, with regimens reassessed according to the patient's life context to maintain targeted thresholds.

Materials and methods

PK data and basic demographics were collected from hemophilia patients treated with SCT800 in current clinical practice. All patients had severe or moderate HA without inhibitors during PK analysis. The blood samples were collected at different time points and measured using the one-stage clotting assay. PopPK analysis was conducted using nonlinear mixed-effects model in Phoenix NLME 8.3. Meanwhile,

external validation was also performed by data from 6 patients with intensive PK samples.

Results

A total of 62 patients with 242 concentrations were included in model, which also accounted for endogenous and residual factor activity to characterize medication administration in patients. A two-compartment model with linear elimination was identified as the best fit for describing the PK of FVIII of SCT800. Weight and vWF:Ag were included in the model as the significant covariates of the clearance. The final model was proven reproducible and robust enough for PK parameter evaluation via internal validation. According to patient information and sparse samples, the optimized personalized dosing can be achieved through the model.

Discussion / Conclusion

This is the first predictive model of SCT800 in Hemophilia. It enables PK-guided prophylaxis, improving patient outcomes and costs.

Keywords

Clinical Routine Prophylaxis, Chinese Hemophilia A, Factor VIII, SCT800, PopPK Model

00089
The visual predictive check and real-world data

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Real-world data (RWD) allow for development and evaluation of pharmacokinetic models on larger or more diverse datasets than possible from clinical trial data. However, RWD reflect the decisions made by clinicians as they respond to new information about a patient, often resulting in data biases that require careful handling. The visual predictive check (VPC) and the prediction-corrected VPC (pcVPC) have emerged as one of a handful of core model diagnostics[1], however their performance when challenged with features typical of RWD is not well-understood.

Materials and methods

A model was used to simulate clinical dosing scenarios, and the same model was used to construct VPCs and pcVPCs, ensuring perfect model specification. Case 1: Individualized dose amount to achieve a target trough [2]. Case 2: Individualized dosing interval to achieve a target trough. Case 3: Case 1, but with cessation of sampling once the patient achieved the target. Case 4: No dose individualization, but patients identified as having poor clearance were switched from trough monitoring to peak-trough monitoring.

Results

In Case 1, the VPC showed significant misspecification, which was corrected in the pcVPC, as previously published [2]. For all other cases, both VPC and pcVPC

incorrectly indicated a misspecification for the central tendency as well as the variability.

Discussion / Conclusion

Although all data was simulated, these case studies reflect common characteristics of RWD, and to a lesser extent, clinical trial data. In practice RWD will commonly be characterized by a combination of these features. Based on these results, we recommend that pharmacometricians avoid relying on the VPC and pcVPC when the underlying data reflects changes in dosing interval or sample collection based on pharmacokinetic target attainment, Bayesian parameter estimates or measured drug levels.

Reference(s)

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Keywords

model-informed precision dosing, pharmacokinetics, model diagnostics, visual predictive check, real world data

00105
Model-informed estimation of maribavir exposure and its safety profiles: two lung transplant cases

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Maribavir has been approved for cytomegalovirus disease refractory to conventional therapies. It is mainly metabolized by cytochrome P450 (CYP) 3A4 and concomitant azole antifungals elevate maribavir exposure. Previously reported population pharmacokinetic analyses indicate that maribavir exposure (24 h-area under the curve (AUC) of 69.0–817 (geometric mean, 132) μg·h/mL) does not correlate with its safety profiles, except for nausea and vomiting, but real-world clinical data are still limited. Here, we evaluated maribavir exposure and adverse effects in two lung transplant recipients with azole agents.

Materials and methods

In two lung transplant recipients at Kyoto University Hospital who concomitantly used maribavir and azole agents, trough serum concentrations (Cmin) of maribavir were measured. Individual pharmacokinetic parameters were estimated using a population pharmacokinetic model and were compared with the population mean predicted for

the same covariate profiles including body weights and CYP3A-inhibitors.[1)] Adverse effects were evaluated with Common Terminology Criteria for Adverse Events version 6.0.

Results

Both cases were administered maribavir at 400 mg twice daily. A previous study reported maribavir Cmin was 4.69 μg/mL (coefficient of variation, 91.9%).[1)] One case concomitantly used itraconazole. Observed Cmin values ranged in 13.2–19.7 μg/mL. The estimated clearance and AUC were 1.46 L/h (population mean, 1.78 L/h; -0.423 standard deviation (SD)) and 496 μg·h/mL, respectively. This case revealed no apparent adverse effects. The other case was administered isavuconazole. Observed Cmin values were 26.8–28.7 μg/mL. Clearance and AUC were estimated as 0.974 L/h (population mean, 1.55 L/h; -0.993 SD) and 743 μg·h/mL, respectively. This case exhibited grade 1 fatigue, anorexia, and headache, although no nausea or vomiting occurred.

Discussion / Conclusion

The presented cases exhibited 1.22- and 1.59-fold higher exposure relative to the population mean. Adverse events were mild and inconsistent with previously reported exposure–safety relationships. These findings suggest that careful monitoring may be warranted when maribavir is co-administered with azole antifungals.

Reference(s)

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Keywords

maribavir, azole antifungals, lung transplantation, population pharmacokinetic model

00112
Does Model Selection Matter? Impact of Population Pharmacokinetic Model Selection on Cefepime Target Attainment Simulations in Critically Ill Children

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Adolescents and young adults (AYA) receiving continuous renal replacement therapy (CRRT) have altered pharmacokinetics (PK). Yet, PK studies in CRRT are limited, so Monte Carlo simulations (MCS) are commonly employed. We previously developed a CRRT module that can be embedded within a population PK (popPK) model to perform MCS.[1] We published MCS using a cefepime popPK model developed in young children.[2] Subsequently, we developed a cefepime popPK model in pediatric intensive care unit (PICU) patients, including more AYA.[3] Our objective was to perform MCS in children using the PICU model and compare probability of target attainment (PTA) with our previous simulations.

Materials and methods

We repeated 1000-fold MCS in patients 12-<25 years and >40 kg using the PICU model. We calculated total, patient-intrinsic, and extracorporeal clearance (CL_{EC}) for six cefepime dosing strategies when varying residual kidney function (estimated glomerular filtration rate [eGFR] of 5 vs 30 mL/min/1.73 m^2), CRRT prescriptions, (standard total effluent flow vs high-dose: 2500 vs 8000 mL/min/1.73 m^2), and fluid accumulation (0–30%). PTA was defined by percentage of patients with free concentrations exceeding bacterial minimum inhibitory concentration (MIC) for 100% of the dosing interval (100% fT > 1xMIC) and 4xMIC using an MIC of 8 mg/L for *Pseudomonas*.

Results

The PICU popPK model predicted lower patient-intrinsic clearance than the prior model (mean CL 0.63 vs 2.42 L/h at eGFR 5), while CL_{EC} was similar, leading to markedly increased PTA. Whereas prior MCS suggested most patients required extended or continuous infusions for optimal PTA, in the current study these were required only with moderate residual kidney function (eGFR 30), high-effluent CRRT, and stringent targets (100% fT>4×MIC).

Discussion / Conclusion

PopPK model selection significantly influences cefepime dosing simulations in AYA receiving CRRT. Prospective validation is needed to guide empiric dosing and selection of which models to use for MCS.

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Keywords

adolescents and young adults, beta-lactam pharmacokinetics, continuous renal replacement therapy, Monte Carlo simulations

00116
Predictive performance of a mechanistic meropenem PBPK model: Considerations for acute kidney injury during gram-negative bacteraemia.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Physiologically based pharmacokinetic (PBPK) model offers “virtual twin” potential for predicting tissue concentrations during infection. [1] In practice, meropenem doses are adjusted using chronic renal impairment nomographs and its accuracy in systemic bacterial infections associated with acute kidney injury (AKI) is unclear.[2] We developed a meropenem PBPK model to predict plasma concentrations in patients with gram-negative bacteraemia and varying renal functions in the first 48h of therapy.

Materials and methods

A mechanistic kidney PBPK model of meropenem (SimcypTM version 23), accounting for organic anionic transporter, p-glycoprotein and renal dihydropeptidase clearance was developed. Validation was performed using clinical data comprising infected patients with varying renal functions and critical illness. “Virtual twins” were generated for 18 patients with gram-negative bacteraemia, with or without chronic renal impairment by defining age, sex, weight, height, albumin and haematocrit in the respective population files. The predictive performance was assessed by simulating 1000 trials per patient.

Results

Median age was 63 years and there were 12 males. One patient had prior chronic kidney disease, and 5 were critically ill. For those with creatinine clearance >90 (CrCL, mL/min/1.73m2), the model was acceptable with average fold error (AFE) and absolute average fold error (AAFE) of 0.98 and 1.41 (n=5) within 2-fold, with good correlation (R2 = 0.88) and low bias (0.12, 95% CI -1.63-1.68 mg/mL) between predicted and observed values. However, model performance for renally impaired groups was poor: CrCL>60-90: AFE 0.41, AAFE 2.51 (n=3), CrCL 30-59: 0.51, 3.14 (n=7) and CrCL 15-29: 0.46, 2.19 (n=3). For renal impairment, there was poor correlation (R2 <0.6) and systematic underprediction of >-5.1 mg/L.

Discussion / Conclusion

The PBPK model accurately predicts meropenem levels in patients with normal renal function but significantly underpredicts drug concentrations in renally impaired patients. Further model refinement is needed to characterize AKI-associated physiological changes during infection before its clinical implementation.

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Keywords

Virtual Twin, Meropenem, Mechanistic Kidney model, Physiologically-based Pharmacokinetics, Bacteraemia

00138
Modeling of rifampicin exposure, bacilliary elimination rate and intensive phase MGIT culture conversion of Vietnamese non-MDR pulmonary tuberculosis patients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Rifampicin is a key drug responsible for rapid tuberculosis bacilliary elimination; however, its exposure - outcome relationship remains rather unknown. This research aims to explore this by modeling rifampicin exposure, bacillary clearance in sputum in Vietnamese pulmonary tuberculosis patients and their influence within a time-to-event model.

Materials and methods

134 adult, non-MDR Vietnamese patients was enrolled. First, a non-linear mixed-effect population pharmacokinetic model of rifampicin is built; from which individual AUC and Cmax values are derived. Second, data of MGIT-BACTEC sputum culture from biweekly visit up to the 56th day of treatment from 133 patients is incorporated for bacilliary elimination rate (BER) modelling. Finally, a parametric time-to-event model, with each incident of negative culture considered an “event”, is built, with individual BER, AUC and Cmax tested as covariates.

Results

We fitted a one-compartment model with a sequential zero-order followed by first-order absorption process, with a preceding lag time, and fat-free mass as covariate on both volume of distribution and clearance. A linear non-linear mixed-effect BER model based on time-to-positive and time of treatment was built; no correlation between individual exposure and BER model parameters was found. Finally, a Weibull time-to-event model was fitted, with lung effusion status lowering chance of negative culture conversion; none of the exposure or individual BER held significant influence.

Discussion / Conclusion

Pharmacokinetics model result indicates influence of Janmahasatian fat-free mass[1] towards parameters, suggesting an alternate scale for dosing. The first BER model of Vietnamese patients was built; no relationship with (plasma-based) model-derived PK parameters was found, consistence with previous findings that intrapulmonary-based results yield more solid connection[2]. BER having no correlation with intensive-phase outcome may reflect the non-conversion situation of certain number of patients by the end of the phase – which may be further complicated by other factors such as effusion status.

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Keywords

Tuberculosis, rifampicin, time-to-positivity, bacilliary elimination, time-to-event

00143
Artificial Intelligence-Driven Correction of Individual Dalbavancin Pharmacokinetic Parameters: A Hybrid NLME-AI Approach from a Single Sample

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Dalbavancin's extended dosing interval requires precise estimation of individual exposure to avoid underdosing. In practice, therapeutic drug monitoring is limited to a single trough concentration, making accurate parameter estimation challenging. We propose a hybrid population modelling-machine learning approach[1,2] to improve individual pharmacokinetic parameter estimation from a single sample and better guide redosing decisions.

Materials and methods

Pharmacokinetic profiles after 2 infusions of 1,500mg were simulated (n=2,500) using the three-compartment model of Carrothers *et al.*[3]. Four Extreme Gradient Boosting

models were subsequently trained to correct the discrepancy between 1-sample Bayesian estimation and the 7-sample Bayesian estimation, considered as the gold standard. The training incorporated clinical covariates, individual random effects, and prediction residuals. The dataset was split into training (80%) and independent test sets (20%). Performance was assessed using relative bias and imprecision, prediction of time to reach the 8 mg/L threshold, and daily average Area Under the Curve (AUC24) calculated via the trapezoidal rule.

Results

The hybrid approach substantially outperformed standard Bayesian forecasting across all parameters. On the test dataset, clearance bias was nearly eliminated (0.05% vs. 4.52%), with improved Root-Mean-Square-Error (RMSE) (4.96% vs. 6.93%). The most striking improvement concerned peripheral volume, with a six-fold bias reduction (4.24% vs. 24.7%) and markedly lower RMSE (27.8% vs. 40.9%). These gains translated into a highly accurate prediction of time to threshold crossing, reducing bias to 0.83% (vs. 3.53%). Comparable improvements were observed for AUC24 in both bias and imprecision.

Discussion / Conclusion

By extending bias correction beyond clearance to the entire pharmacokinetic profile, this hybrid model overcomes key limitations of single-sample Bayesian forecasting. The resulting precision in target coverage time is clinically meaningful, as it directly supports safe and individualized redosing decisions for drugs with multi-week intervals. This work establishes a robust methodological framework for optimizing individual exposure from sparse sampling and will be confirmed on external dataset.

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Keywords

Dalbavacin; Machine learning; Therapeutic Drug Monitoring; Population Pharmacokinetics

00146
Can Simple Beat Complex? Linear Limited Sampling Strategy versus Extreme Gradient Boosting (XGBoost) for Mycophenolic Acid AUC Estimation

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic drug monitoring of mycophenolic acid (MPA) aims to individualize immunosuppressive therapy in transplant recipients, with the area under the concentration–time curve (AUC) as the key exposure metric. Bayesian estimation based on population pharmacokinetic models is the reference method but requires multiple samples and dedicated software. Data-driven approaches such as limited sampling strategies (LSS) and machine learning (ML) models may represent clinically applicable alternatives. This study compared an optimized linear LSS and an XGBoost model for predicting MPA AUC, using Bayesian estimates as reference.

Materials and methods

A retrospective dataset of 604 pharmacokinetic profiles was analyzed. Plasma MPA concentrations were measured at 0, 20, 60, 120, and 180 minutes post-dose, and AUC values were estimated using a validated Bayesian approach (ABIS, Limoges). Analyses were performed in R statistical environment. The dataset was randomly split into training and test subsets prior to model development (n = 153 for testing). An optimized three-point LSS was derived in the training set using multivariate linear regression; 20, 60, and 180 minutes provided the best predictive performance. These same time points were used to train an XGBoost regression model, with hyperparameters tuned by cross-validation within the training set. Predictive

performance was evaluated on the test subset using RMSE%, R^2, and the proportion of predictions within ±20% of the Bayesian AUC (F20%).

Results

On the test subset, the LSS achieved an RMSE% of 18.4, R^2 of 0.861, and F20% of 78.4%. The XGBoost model showed slightly lower performance (RMSE%=21.5, R^2=0.854, F20%=73.9%). Predictions using both approaches were highly correlated (R^2 = 0.98). Performance of LSS stabilized with approximately 120 training profiles.

Discussion / Conclusion

Both approaches showed high predictive accuracy using identical optimized sampling times. The linear LSS performed marginally better, supporting simple, interpretable models as practical alternatives to more complex ML methods for AUC-guided dose individualization.

00154
Busulfan Population Pharmacokinetic Model Validation in Thalassemia and Sickle Cell Disease

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Model-informed precision dosing (MIPD) with MAP Bayesian cumulative AUC estimation is crucial for optimizing busulfan therapy in hematopoietic cell transplantation (HCT). Population pharmacokinetic (PopPK) models for busulfan have been developed in many HCT populations, including both broad and disease-specific cohorts. In 2025, we developed a model (UCSF 2025) using a broad dataset of 1062 patients and 9123 busulfan concentrations from children and adults across 11 medical centers.[1] However, hesitancy remains in adopting busulfan MIPD for patients with thalassemia and sickle cell disease (Thal/SCD) using models not specifically developed or validate d in these populations, given concerns about altered busulfan pharmacokinetics (PK) due to potential differences in metabolism, chronic hemolysis, iron overload, hepatic dysfunction.[2-4]

Materials and methods

Busulfan PK data from patients with Thal/SCD were collected from 5 US centers. Model predictive performance was assessed iteratively by dose, matching clinical practice where data is collected and utilized for dose adjustment. Performance was quantified as mean percent error (MPE) and normalized root mean square error (nRMSE) with means and standard deviations calculated via bootstrap.

Results

A total of 83 patients provided 831 busulfan concentrations. *A priori* MPE was -7.3 ± 3.7% for Thal/SCD versus -8.2 ± 1.5% for the general population; *a posteriori* MPE was -4.7 ± 1.9% for Thal/SCD versus -4.8 ± 4.3% for the general population. *A priori* nRMSE was 27.2 ± 1.2% for Thal/SCD versus 30.8 ± 0.3% for the general population; *a posteriori* nRMSE was 20.3 ± 1.2% for Thal/SCD versus 24.7 ± 0.5% for the general population.

Discussion / Conclusion

The evaluated busulfan PopPK model maintains predictive performance in Thal/SCD patients without requiring disease-specific modifications, despite not being developed on data from this population. These findings support using this model for MIPD in Thal/SCD populations undergoing HCT.

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Keywords

Busulfan, Thalassemia, Sickle Cell Disease, Model-Informed Precision Dosing, External Validation, Hematopoietic Cell Transplantation

00160
Biomarker and Dosing Insights from Quantitative Systems Pharmacology for nivolumab–ipilimumab in Advanced Hepatocellular Carcinoma

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Many patients with advanced hepatocellular carcinoma (aHCC) show limited response to the combination of nivolumab and ipilimumab, and treatment is further constrained by the dose-limiting toxicities of ipilimumab. There is an urgent need to (1) identify biomarkers that can select patients who benefit most from this combination therapy and (2) optimize dosing strategies to explore safer and more effective regimens.

Materials and methods

Using the Quantitative Systems Pharmacology (QSP)–immuno-oncology platform developed by Sové et al., we integrated pharmacokinetic/pharmacodynamic parameters of both agents to build a QSP model of nivolumab plus ipilimumab as first-line therapy for aHCC. Model parameters were calibrated using the objective response rate (ORR) and median duration of response (mDOR) from the CheckMate-9DW study. External validation was performed using ORR and mDOR from clinical trials of nivolumab monotherapy. After model finalization, we (1) explored predictive biomarkers through subgroup analysis and machine-learning approaches and (2) evaluated the feasibility of reducing the ipilimumab dose.

Results

We incorporated additional cytokines, including chemokine C-C motif ligand 5 (CCL5) and interleukin-2 (IL-2), to characterize their regulatory effects on the tumor immune microenvironment and to better capture the synergistic antitumor activity of nivolumab plus ipilimumab. The final model reproduced clinical outcomes of nivolumab monotherapy (ORR: 15% vs. 16%; mDOR: 23.3 vs. 23.5 months). Biomarker analysis identified the intratumoral $CD8^+$/Treg ratio as the variable most strongly associated with treatment response. Dose-optimization simulations showed that reducing the ipilimumab dose from 3 mg/kg to 1 mg/kg resulted in no meaningful change in ORR.

Discussion / Conclusion

The QSP model for nivolumab plus ipilimumab showed strong predictive performance. Virtual trials identified the $CD8^+$/Treg ratio as the key response-related biomarker and suggested that lowering ipilimumab from 3 to 1 mg/kg preserves efficacy, informing future development and trial design.

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Keywords

advanced hepatocellular carcinoma; nivolumab; ipilimumab; quantitative systems pharmacology; biomarker; dosing insights

00168
Practical Identifiability as a Pre-Validation Tool for Model Selection in Model-Informed Precision Dosing: A Tacrolimus Case Study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Model-informed precision dosing (MIPD) depends on robust, identifiable pharmacokinetic (PK) models. Although external validation (EV) is the gold standard for model selection, it is resource-intensive and often requires refitting to local data, potentially reducing interpretability and generalizability. Considering the growing number of available tacrolimus PK models, there is a need for an objective and reproducible pre-validation framework to inform model selection prior to EV. Practical identifiability (PI) assesses whether parameters can be estimated precisely with available information. This study assesses the ability of PI analysis, relying exclusively on published model specifications, to differentiate reliable from unreliable tacrolimus PK models.

Materials and methods

A literature review identified 50 tacrolimus PK models (brands Prograf, Advagraf, Envarsus). Models relying exclusively on therapeutic drug monitoring data or representing redundant variants were excluded, yielding 27 models for analysis, along with four independent EV publications. PI was assessed using the PFIM 4.0 R function under standardized simulation conditions, including 500 virtual patients and both sparse (based on published sampling times) and rich 48-hour sampling designs. Parameter estimation precision was quantified using relative standard errors (RSEs).

Models were classified a priori as having good (all RSE <30%), moderate (most RSE <30%, none >80%), or poor (at least one RSE >80%) identifiability. PI results were compared with published EV outcomes.

Results

Seventeen models demonstrated good PI, three moderate PI, and seven poor PI. Both models accepted in EV (n=2) exhibited good PI, whereas all poorly identifiable models (n=4) were rejected during EV. Five models with good PI were nevertheless rejected in EV, and one moderately identifiable model (maximum RSE 38%) showed unsatisfactory EV performance.

Discussion / Conclusion

All externally validated models exhibited good practical identifiability, while all poorly identifiable models failed EV, suggesting that PI is a valuable pre-validation tool to streamline model selection in MIPD and reduce reliance on resource-intensive EV.

00170
Validation of free calculators and licensed-based software for vancomycin AUC in non-critically ill patients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Area under the concentration-time curve (AUC) is recognized as a key pharmacokinetic parameter. Internationally, there is a shift from trough-guided to AUC-guided dosing of vancomycin. There are several available methods for predicting AUC, some of which require an expensive license. The objective of this study was to validate vancomycin AUC predicted by several available free online calculators and license-based software in non-critically ill patients in a medium-sized university hospital.

Materials and methods

We recruited 24 patients aged ≥ 18 years with stable kidney function who were given at least 3 doses of vancomycin while admitted to the University Hospital of North Norway. The study period lasted from April 1st 2024 to December 31st 2025. The patients gave written informed consent to donate five blood samples for analysis of vancomycin serum concentration within a dosing interval at steady state: immediately after end-of-infusion, 1-, 2- and 5-hours post infusion and immediately before the next dose (trough). Vancomycin AUC24 calculated using the lin-log trapezoidal method with five serum concentrations was compared to trough-only AUC24 predicted by different calculators and software. The primary outcome was accuracy of AUC24 compared to lin-log-AUC24, calculated by median absolute error, bias and root-mean-squared-error.

Results

The final analysis included data from 22 patients with a median (range) daily vancomycin dose of 2000 (500-3750) mg. The median (range) AUC24 calculated by lin-log trapezoidal method was 543.5 (366-764) mg/L*t. Most free online calculators and license-based software had similar accuracy at predicting vancomycin AUC24.

Discussion / Conclusion

Although the accuracy was similar between the methods, there were differences related to user interfaces and the possibilities to save data for documentation and multiple predictions during a vancomycin course. In a low-resource setting, AUC-guided vancomycin can be implemented using free calculators.

Keywords

Model informed precision dosing

Vancomycin

Area under curve (AUC)

00193
Morphine Should Be Used Early at Adequate Doses to Achieve Ideal Analgesia in Cancer Patients with Moderate-to-Severe Pain: A Population Pharmacokinetic Approach

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Cancer pain is one of the most prevalent clinical symptoms in advanced cancer patients, significantly compromising their quality of life and psychological well-being. Current evidence suggests that maintaining morphine plasma trough concentrations within the 10-100 ng/mL range provides optimal analgesia for hospitalized cancer patients with moderate-to-severe pain. However, morphine's pharmacokinetic profile is highly variable depending on administration routes and patients' pathophysiological status, making the adequacy of conventional dosing regimens to achieve target drug exposure a critical clinical concern.

Materials and methods

Using a published population pharmacokinetic model of morphine in cancer patients (incorporating oral and subcutaneous administration data), we conducted simulation studies to: (1) evaluate the impact of initial morphine tablet titration doses (5/10/15 mg q4h) on trough concentration attainment in 1000 virtual patients with varying renal function (eGFR); (2) assess plasma concentration profiles in 1000 standardized patients (60 kg, eGFR=100 mL/min/1.73m²) receiving guideline-recommended

dosing (day 1: immediate-release morphine 10 mg po q4h; day 2 onward: sustained-release morphine 30 mg po q12h) through day 7.

Results

(1) No clinically significant pharmacokinetic differences were observed across renal function groups (eGFR 55 vs. 100 mL/min/1.73m²). Initial 5 mg q4h dosing failed to achieve target trough concentrations (≥10 ng/mL) in any patient after six doses. Dose escalation to 10 mg and 15 mg q4h yielded attainment rates of 3.4% and 30.7% respectively. (2) All simulated patients receiving standard regimen maintained subtherapeutic trough concentrations (<10 ng/mL) throughout the 7-day observation period.

Discussion / Conclusion

Our pharmacokinetic simulations suggest that aggressive initial dosing with immediate-release morphine tablets may be necessary to achieve timely analgesia in moderate-to-severe pain patients, with dose adjustments guided by pain scores at 1-hour post-dose. Important limitations include the Caucasian-derived model's uncertain generalizability to Chinese populations, and exclusion of breakthrough pain rescue dosing effects. Future studies should incorporate real-world pain episode patterns for comprehensive simulation analyses.

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Keywords

morphine; Cancer pain; population pharmacokinetic; titration doses;

00202
From Population Pharmacokinetics to Machine Learning: Toward Precision Dosing of Hydroxyurea in Pediatric Sickle Cell Disease

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Hydroxyurea is the cornerstone treatment for sickle cell disease (SCD), and its efficacy in children is closely linked to achieving the maximum tolerated dose (MTD) and adequate exposure. However, stepwise dose-escalation strategies are lengthy and often lead to prolonged underexposure. Population pharmacokinetic (POP-PK) approaches with Bayesian estimation enable individualized dosing but remain underused in routine practice due to their complexity. Machine learning (ML) may provide a more accessible alternative for precision dosing.

Materials and methods

Pharmacokinetic profiles were simulated using the POP-PK model of Wiczling et al. in 4,000 virtual pediatric patients. These data were used to train and compare five ML algorithms (MARS, SVM, GLMNET, Random Forest, XGBoost) to predict hydroxyurea exposure (AUC). The best model was internally validated and tested on

an independent dataset generated from the Dong et al. model. External validation used therapeutic drug monitoring data from 52 children with SCD treated at Clermont-Ferrand University Hospital (France). A systematic post-hoc calibration was applied. Dose adjustments based on predicted AUCs were compared with those derived from observed AUCs.

Results

MARS showed the best predictive performance (RMSE 1.26; R^2 0.999), with excellent agreement between observed and predicted AUCs in internal and external validations. In clinical data, calibration corrected systematic bias and eliminated significant differences between predicted and observed AUCs. ML-based dose adjustments were consistent with those based on observed AUCs and corrected underexposure, promoting convergence toward the therapeutic target.

Discussion / Conclusion

An ML model trained on POP-PK simulations accurately predicted hydroxyurea exposure and supported dose individualization in pediatric SCD. A Shiny web application facilitates clinical implementation. By improving exposure targeting, this strategy may enhance efficacy while reducing hematological toxicity.

Keywords

Hydroxyurea; Pediatric Sickle Cell Disease; Population Pharmacokinetics; Machine Learning; Precision Dosing

00214
Model Ensembling and Machine Learning Approaches to Predict the First Dose of Amoxicillin in Intensive Care

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

A priori model informed precision dosing (MIPD) is a method to recommend an appropriate first dose based solely on the patient's covariates enabling faster target attainment without required concentration measurements. Population pharmacokinetic (PopPK) model ensembling and machine learning (ML) approaches were developed and evaluated to predict a first dose of amoxicillin in intensive care patients.

Materials and methods

Following a bibliographic review, a virtual patient population was simulated based on cohorts from four published adult amoxicillin PopPK models. Model-development cohorts were reproduced, and steady-state trough concentrations were simulated.

As reference methods, weighted model ensembling and classification tree-informed ensembling, were implemented. Two novel ensembling strategies were developed:

regression tree (RT)-informed ensembling, using RT to predict the log individual prediction/observation ratio, and factor analysis of mixed data (FAMD), assigning model weights based on patient similarity to original model cohorts. In parallel, four ML algorithms (support vector machine, k-nearest neighbors, random forest, XGBoost) were trained to predict the dose achieving target concentrations based on covariates and dosing scheme. All approaches were compared with single PopPK models, standard dosing (200 mg/kg), uninformed ensembling (same weight to all models), and externally validated using clinical data.

Results

Most MIPD methods outperformed standard dosing. On simulated data, ensembling (30-42 % target attainment) and ML (36-39 %) exceeded single-model approaches (14-32 %). RT-informed and FAMD ensembling improved performance by 6-10 % compared to uninformed ensembling on clinical data. In clinical patients receiving continuous infusion, ensembling further improved performance, with FAMD achieving target attainment of 49 %.

Discussion / Conclusion

PopPK model ensembling used as a complementary tool to a posteriori MIPD until the first available blood sample, increases target attainment and overcomes the challenge of model selection. These methods are available as an R package (openMIPD: https://github.com/INSERM-U1070-PHAR2/openMIPD), making them ready to be implemented to other molecules and clinical scenarios.

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Keywords

therapeutic drug monitoring, model informed precision dosing, machine learning, amoxicillin, anti-infective, intensive care

00229
Application of arterial blood gas sampling for therapeutic drug monitoring of beta-lactam antibiotics in critically ill children: a validation study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

To optimize beta-lactam therapy, Therapeutic Drug Monitoring (TDM) may be beneficial to enhance target attainment (1, 2). Despite the possible advantages, TDM can pose various challenges in clinical practice (3, 4), especially within the paediatric population (5). One way to minimize these challenges is to use scavenged sampling. This approach is more sustainable and aligns with the green principles of waste reduction (6). The aim of this study is to validate the use of scavenged arterial blood gas samples for TDM of beta-lactams.

Materials and methods

Plasma and scavenged blood gas (heparinized astrup syringes) samples were acquired through the EXPAT Kids study. All included patients were admitted to the Paediatric Intensive Care Unit (PICU) between June 2021 and July 2024 and received intravenous treatment with ceftriaxone, cefotaxime, cefuroxime, or meropenem (7). Beta-lactam concentrations were determined by a multi-analyte UPLC-MS/MS (8). In this study, method agreement was considered acceptable when the Deming regression showed no significant constant or proportional bias, and when at least 67% of all measurements fell within +/- 20% of their mean in the Bland-Altman analysis.

Results

From 117 paired samples, plasma and blood gas concentrations of four beta-lactam antibiotics were compared. Deming regression analysis showed slopes close to 1 for cefuroxime and cefotaxime, indicating good proportional agreement. While meropenem and ceftriaxone demonstrated more variability. Bland-Altman plots revealed mean biases ranging from -16.2 mg/L (ceftriaxone) to +2.4 mg/L (cefuroxime). The percentage of samples within +/- 20% acceptance limits was highest for cefuroxime (91.7%) and meropenem (70.4%), suggesting these beta-lactams have the best interchangeability between plasma and blood gas measurements.

Discussion / Conclusion

Blood gas measurements showed variable agreement with plasma concentrations across antibiotics. Cefuroxime and meropenem demonstrated the best interchangeability. In contrast, cefotaxime, ceftriaxone, and especially the free fraction of ceftriaxone exhibited poor agreement, indicating blood gas cannot universally replace plasma for TDM.

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Keywords

Paediatrics

Therapeutic Drug Monitoring (TDM)

Beta-lactam antibiotics

00230
Population Pharmacokinetic Modelling of Plasma and Intracellular Bictegravir in HIV-Infected Patients

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Bictegravir is a second-generation HIV integrase strand transfer inhibitor used in first-line therapy[1]. In routine care, interindividual variability persists (e.g., virologic non-suppression, weight gain, neuropsychiatric adverse effects)[2,3]. While plasma pharmacokinetics have been described[4], bictegravir exposure in peripheral blood mononuclear cells (PBMCs) and its relationship to plasma remain poorly studied. We aimed to (i) develop a population pharmacokinetic (popPK) model for bictegravir plasma concentrations in clinical practice and (ii) link plasma to PBMC concentrations to derive model-based intracellular exposure and its variability, providing a framework for future exposure–response analyses.

Materials and methods

This single-centre retrospective study used bictegravir plasma and PBMC concentrations from adults with HIV collected at follow-up; all participants were genotyped. PopPK modelling evaluated one- vs two-compartment model structures, residual error models, and parameter correlations. PBMC concentrations were related to plasma using either an intracellular compartment or an effect-compartment model. Demographic covariates (body weight, sex, age) and ABCG2/NR1I2 polymorphisms were tested using stepwise covariate modelling. Model selection used objective function value, goodness-of-fit plots, and visual predictive checks; uncertainty was assessed by nonparametric bootstrap.

Results

Fifty-one patients contributed 138 plasma and 42 PBMC measurements. Plasma concentrations over-time were best described by a one-compartment model with first-order absorption (ka 2.60 h^{-1}), lag time (0.24 h), linear elimination, and proportional error (35%). Typical clearance was 425 mL/h (RSE 6%; IIV 20%), and volume of distribution was 10,600 mL (RSE 18%). PBMC concentrations were modelled by an effect-compartment approach, with a steady-state PBMC-to-plasma concentration ratio of 0.04 (RSE 14%; IIV 89%); the effect-compartment rate constant was fixed at 0.90 h^{-1}. None of the tested covariates were significant.

Discussion / Conclusion

A one-compartment popPK model described bictegravir plasma exposure and linked plasma to PBMC concentrations using an effect-compartment model. The steady-state PBMC-to-plasma ratio was 0.04 with high interindividual variability. The model provides a quantitative basis for future exposure–response analyses.

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Keywords

Bictegravir, HIV, Population pharmacokinetics, Peripheral blood mononuclear cells

00237
One model to dose them all: a population pharmacokinetic model for multiple aminoglycosides across the human lifespan

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Aminoglycosides require therapeutic drug monitoring due to substantial unexplained pharmacokinetic variability. Population pharmacokinetic (popPK) models have been developed for individual [1, 2] and multiple [3] drugs across age groups. However, it is unclear whether pooling data across aminoglycosides over the lifespan improves parameter estimate precision and Bayesian predictive performance in model-informed precision dosing (MIPD), or if pooling enhances model generalizability to drug-age subpopulations not directly represented in model development. We therefore developed and evaluated a unified multi-aminoglycoside popPK model spanning neonates, children, and adults.

Materials and methods

De-identified data from amikacin, gentamicin, and tobramycin patients at 154 U.S.-based institutions were split into training and testing datasets. Using the training set, we developed a unified popPK model. Predictive performance in the test dataset was evaluated using normalized root mean square error (nRMSE), and clinical accuracy (peaks within 20% of observation and trough correctly classified as below or above 1 mg/L), and compared with selected published popPK models. To assess generalizability, the final model was refit using single-drug datasets and leave-one-subpopulation-out datasets.

Results

The final dataset included 5659 patients (age range: 0-100 years; 3235 adults, 510 children, 2228 neonates). The unified model achieved the lowest nRMSE across age groups, with absolute reductions of 0.6-24.8%. Clinical accuracy was highest in the unified model, with a posteriori pediatric accuracy of 56.4% vs. 48% (non-overlapping 90% CIs). Leave-one-out refits yielded similar estimates but reduced precision, while single-drug models demonstrated substantially reduced precision and were not identifiable in the amikacin-only case.

Discussion / Conclusion

This unified model improved predictive performance across drugs and age groups and demonstrated robustness to exclusion of individual drug-age group combinations. These findings support use of a unified aminoglycoside model for Bayesian MIPD and demonstrate the advantages of pooling related drugs and developmental stages particularly for subpopulations where data is sparse.

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Keywords

aminoglycosides, population pharmacokinetics, model-informed precision dosing, lifespan modeling

00241
Teicoplanin Precision Dosing Regimen in Critically Ill Patients Undergoing Continuous Renal Replacement Therapy: A Population Pharmacokinetic Study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

To establish a population pharmacokinetic (PPK) model of teicoplanin in critically ill patients undergoing continuous renal replacement therapy (CRRT) and to identify key covariates influencing its pharmacokinetic parameters, thereby providing a reference for the development of precise dosing regimens in this special population.

Materials and methods

Demographic information, clinical biochemical indicators, and CRRT-related parameters were collected from patients. Teicoplanin plasma concentrations were determined using high-performance liquid chromatography. A nonlinear mixed-effects modeling approach was employed to develop the base PPK model, with covariates screened via forward inclusion and backward elimination. The final model was evaluated using goodness-of-fit plots, nonparametric bootstrap analysis, and visual predictive checks. Monte Carlo simulations were conducted to explore optimal dosing regimens under different covariate conditions.

Results

A total of 169 plasma drug concentration data points from 57 patients were included. A one-compartment model adequately described the pharmacokinetic characteristics of teicoplanin. The final model revealed that creatinine clearance (Ccr) and serum albumin (ALB) levels were significant covariates influencing teicoplanin clearance (CL). The typical population values were CL = 0.603 L·h and V = 95.3 L. The final model equation was: CL (L·h) = 0.603 × (Ccr/71)0.564 × (ALB/30)$^{-}$1.46. Model evaluation results indicated good goodness-of-fit, stability, and predictive performance.

Discussion / Conclusion

This study successfully established a PPK model for teicoplanin in critically ill patients undergoing CRRT, identifying Ccr and ALB as important factors influencing teicoplanin clearance. This model provides an important reference for clinicians to develop individualized dosing regimens for this specific patient population.

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Keywords

teicoplanin; critically ill patients; continuous renal replacement therapy; population pharmacokinetic; model-informed precision dosing

00267
Population pharmacokinetics of intravenous Ceftazidime in critically ill paediatric patients

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Ceftazidime is a widely used antibiotic in the treatment of severe infections and cystic fibrosis (CF) in critically ill paediatric patients. The objective of this study was to characterise the population pharmacokinetics of Ceftazidime in critically ill children, to identify significant covariates, and to optimise dosing regimens through Monte Carlo simulations to ensure adequate pharmacodynamic target attainment.

Materials and methods

A population pharmacokinetics (popPK) study was conducted in 57 critically ill children (0.09–18 years) receiving intravenous Ceftazidime in seven paediatric departments, including intensive care units. A total of 246 plasma concentrations were measured by a validated HPLC–MS/MS method. The Concentration–time data were analysed using nonlinear mixed-effects modelling (Monolix, version 2024R1), and the impact of demographic and clinical covariates was tested. The selection of the model was based on goodness-of-fit, likelihood ratio tests, and predictive checks.

The effects of covariates were evaluated through a stepwise forward inclusion and backward elimination. Monte Carlo simulations were performed to evaluate the probability of target attainment (PTA) for different dosing regimens at the EUCAST MIC breakpoint of 8 mg/L, with a PD target of 100% fT>MIC.

Results

Ceftazidime PK was best described by a one-compartment model with first-order elimination. Body weight (allometrically scaled) significantly improved the model fit. Clearance (CL) was further influenced by estimated glomerular filtration rate (eGFR) and cystic fibrosis status (CF). Simulations showed that standard intermittent infusion regimens frequently failed to achieve 100% fT>MIC, particularly in patients with high eGFR. In contrast, continuous infusion of 6 g/day consistently achieved >90% PTA across all simulated groups.

Discussion / Conclusion

Ceftazidime pharmacokinetics in critically ill children are strongly influenced by body weight, renal function, and cystic fibrosis. Standard intermittent regimens may be insufficient, while continuous infusion provides the best target attainment.

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Keywords

Ceftazidime, Paediatrics, Population pharmacokinetics (popPK), PK modelling, dose optimization

00292
Bridging Deep Learning and Bayesian MIPD: A Multimodal Autoencoder Approach for Multi-Objective Cefepime Dose Optimization

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Optimizing cefepime dosing requires balancing antimicrobial efficacy against concentration-dependent neurotoxicity, while conventional PK/PD target-based strategies can be computationally demanding. We developed a decision-support prototype that combines Bayesian Model-Informed-Precision-Dosing (MIPD) with a Multimodal Variational Autoencoder using a Mixture-of-Experts(2) (MMVAE-MoE) as a surrogate model for rapid multi-objective dose optimization.

Materials and methods

A simulated cohort of 2,500 intensive care patients was generated using a published population PK model(1). Covariates included age, weight, creatinine clearance, and continuous renal replacement therapy status. Efficacy was defined as 100% fT>4×MIC. Neurotoxicity risk was simulated with an Emax model, in which neurological sensitivity (EC50) varied with age and renal function, driven by a

composite exposure metric combining mean concentration (Cmean) and excess trough concentration (Cmin). The MMVAE-MoE was trained to encode heterogeneous inputs—covariates, dosing history, and therapeutic drug monitoring (TDM) data—into a 32-dimensional latent space. For dose recommendation, a grid-search algorithm used the MMVAE-MoE as a fast surrogate to screen candidate regimens in real time (dose 0.25–6 g; interval 6–48 h; infusion 0.5–24 h). A multi-objective fitness score maximized efficacy while enforcing pharmacological guardrails: (i) a quadratic penalty to maintain neurotoxicity frequency ≤20%, (ii) a parsimony term penalizing total daily dose, and (iii) a proportional clinical veto for regimens predicting >20% neurotoxicity, prioritizing safer options in frail patients.

Results

MMVAE-MoE integrated static and sequential modalities and handled missing data natively, enabling seamless transitions from a priori to a posteriori (TDM-informed) scenarios. The refined scoring prevented toxic accumulation in simulated renal impairment by redirecting recommendations toward lower daily doses. An interactive interface linked Python to R (Mapbayr) for individual maximum a posteriori estimation and latent-space projection to deliver personalized dosing.

Discussion / Conclusion

This proof of concept suggests that a pharmacological “digital twin” can support real-time precision dosing, but validation on real-world clinical datasets is needed before clinical translation.

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2) Shi Y et al. NeurIPS 2019.

Keywords

Cefepime; Model-Informed Precision Dosing; Deep Learning; Neurotoxicity; pharmacological digital twins

00293
Population Pharmacokinetic/Pharmacodynamic Analysis and Dosing Simulation of Cefmetazole for Urinary Tract Infections by considering Cefmetazole Concentrations in the Urinary Tract

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The cephamycin, cefmetazole (CMZ) is commonly used in Japan for treating urinary tract infections (UTIs), including those caused by extended-spectrum β-lactamase-producing Enterobacterales (ESBL-E)[1)]; however, cephamycins are not recommended for ESBL-E infections in the EU and US guidelines because of a lack of evidence[2,3)]. Therefore, we conducted a population pharmacokinetic/pharmacodynamic (PPK/PD) analysis of CMZ in patients with mild to moderate UTIs, including ESBL-E-induced UTI, by considering its concentration in the urinary tract.

Materials and methods

Japanese adult patients with mild to moderate UTIs receiving CMZ (1 g every 6–24 h), with dose adjustment based on creatinine clearance (Ccr), were prospectively enrolled. CMZ plasma concentrations were measured by high-performance liquid chromatography[4)], and a PPK model was established. Monte Carlo simulation (MCS) was performed using estimated urinary CMZ concentrations to determine the probability of target attainment (PTA) and PK/PD breakpoints in the urinary tract.

Results

A total of 151 plasma samples from 68 patients were used for the PPK analysis. All ESBL-E-induced UTI patients (n = 13) achieved clinical cure with CMZ. A one-compartment model with first-order elimination best described the data, and Ccr was the only significant covariate that affected systemic clearance of CMZ. MCS revealed that 1 g q6, q8, and q12 h for Ccr at 10–100 mL/min and 1 g q24 h for Ccr at 10–50 mL/min achieved a PTA ≥90% in the urinary tract. The PK/PD breakpoints in the urinary tract for these regimens, except for 1 g q24 h for Ccr at 30–50 mL/min, exceeded the minimum inhibitory concentration $(MIC)_{90}$ of 4 μg/mL.

Discussion / Conclusion

We established a PPK model to estimate CMZ pharmacokinetics in patients with mild to moderate UTIs, which included ESBL-E. PPK/PD analysis, incorporating PTA and PK/PD breakpoints in the urinary tract, supports the appropriateness of renal function-based CMZ dosing in this population.

Reference(s)

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4) Sadaka Y, et al. *J Pharm Health Care Sci*. 2025;12(1):12.

Keywords

Cefmetazole, extended-spectrum β-lactamase-producing Enterobacterales, Population pharmacokinetic/pharmacodynamic analysis, Monte Carlo simulation, PK/PD breakpoint

00302
Development and External Evaluation of a Whole-Blood and Intracelluar Tacrolimus Population Pharmacokinetic Model in Liver and Kidney Transplant Recipients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Tacrolimus exhibits high interindividual and inter-occasion pharmacokinetics (PK) variability. Although TDM relies on whole-blood concentrations, intracellular concentrations in peripheral blood mononuclear cells are increasingly investigated as they may better reflect efficacity. We aimed to develop and assess a population pharmacokinetic model describing whole-blood and intracellular tacrolimus concentrations in transplant recipients, and to explore variability sources.

Materials and methods

Data from 115 recipients were analyzed using nonlinear mixed-effects modeling (Monolix®). Ninety-three liver recipients were included: 27 had whole-blood and intracellular full-PK profiles and several trough concentrations (CYPTACH) and 66 had trough concentrations at multiple occasions (OPTILTH). An external dataset from Bellvitge University Hospital included 22 kidney recipients with one full-PK profile. The model was built using CYPTACH and 70% of OPTILTH patients (n=74).

Predictive performances were assessed on the remaining OPTILTH patients (n=19) and Bellvitge patients using mean prediction error (MPE) and median absolute prediction error (MDAPE) at population and individual levels. Finally, datasets were combined to re-estimate parameters,inter- and intra-patient variability and assess organ effects.

Results

A two-compartment model with lag-time, first-order absorption, and dose-dependent bioavailability best described whole-blood concentrations. Intracellular concentrations were modeled with an effect-compartment; influx transfert constant was fixed to 1 (k1e), while efflux transfert constant (ke0) included inter-individual and inter-occasion variability. Post-operative days and hematocrit significantly influenced ke0. Whole-blood predictions were acceptable at both population (MDAPE 18–27%, MPE −1–15%) and individual levels (MDAPE 4.5–8%, MPE −2.3–4%). Intracellular predictions were less accurate at population level (MDAPE 47–66%, MPE −47–97%) but improved at individual level (MDAPE 16–29%, MPE −18 –15%). The combined analysis supported the same structural model with an additional organ covariate on ke0.

Discussion / Conclusion

A whole-blood/intracellular tacrolimus popPK model was developed. Future work should include kidney transplant recipients from Rennes to determine whether the inter-organ effect reflects organ differences rather than inter-center effects due to post-operative days gaps between centers.

Keywords

pharmacometrics, immunosuppression, transplantation, Tacrolimus, intracellular concentrations, non-linear mixed effect models

00317
Safety and Performance Evaluation of an Imatinib Clinical Decision Support System

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic Drug Monitoring (TDM) optimizes clinical outcomes but is hindered by logistical delays and susceptibility to data errors. Integrating Model-Informed Precision Dosing (MIPD) with rule-based validation forms a Clinical Decision Support System (CDSS) to secure this complex workflow.
This study evaluated a rule-based imatinib CDSS by quantifying its error detection capability and characterizing its clinical performance in recommending dosing adaptations compared with a human TDM expert.

Materials and methods

In this in silico study, we simulated 60 virtual patients using an in-house population pharmacokinetic model of imatinib built on 244 concentrations measurements from 146 patients. Forty-five cases were enriched with data quality errors (e.g., timing inaccuracies) to stress-test system resilience. CDSS and TDM expert were compared for error detection, clinical impact on target attainment (1100–2000 ng/mL), and safety.

Results

The CDSS and the expert demonstrated comparable error detection. CDSS sensitivity was 53% (95% CI: 35–70) versus expert 45% (30–61); CDSS specificity was 83% (63–95) versus expert 100% (81–100). Clinically, the CDSS significantly outperformed the expert in target attainment (55% vs. 37%; p=0.046). However, the CDSS produced four detrimental outcomes, where patients within target were shifted outside, whereas the expert generated none.

Discussion / Conclusion

The CDSS acts as a robust digital gatekeeper with superior efficacy in optimizing imatinib exposure compared to a human expert. While active optimization drives higher efficacy, isolated detrimental cases highlight that safety remains contingent on data integrity. This validates the CDSS architecture for prospective clinical trials.

Keywords

Therapeutic drug monitoring, model-informed precision dosing, imatinib, clinical decision support system

00329
Real-World Implementation of EHR-Integrated Model-Informed Precision Dosing for Vancomycin: The Role of Clinician Adherence in Acute Kidney Injury

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Model-informed precision dosing (MIPD) for vancomycin improves PK target attainment, yet evidence for reducing acute kidney injury (AKI) remains limited. Real-world effectiveness may depend not only on system implementation but also on clinician adherence to dosing recommendations. We evaluated whether an EHR-integrated MIPD system reduces vancomycin-associated AKI and whether clinician adherence modifies toxicity through exposure control.

Materials and methods

We retrospectively analyzed inpatients undergoing vancomycin TDM during one year before and after MIPD implementation (April 2021–March 2023). AKI was defined per KDIGO 2012 and considered vancomycin-associated if occurring during therapy or within 3 days after discontinuation. Multivariable logistic regression assessed the association between implementation and AKI. Post-implementation recommendation acceptance was recorded. Target trough attainment (TTA) and proportions of troughs >20 mg/L were compared by acceptance status. Structural equation modeling evaluated whether troughs >20 mg/L mediated the relationship between

recommendation acceptance and AKI. Predictive performance was summarized using MAPE, F20/F30, and R^2.

Results

Among 1334 patients (632 pre-, 702 post-implementation) with 2354 steady-state troughs, AKI incidence was similar before and after implementation (16.9% vs 16.1%; adjusted OR 0.87, P=0.384). Post-implementation, 52.3% of 625 recommendations were accepted. Acceptance significantly increased TTA (59.3% vs 24.0%, P<0.001) and reduced troughs >20 mg/L. Higher trough concentrations were independently associated with AKI. Mediation analysis showed significant paths from recommendation acceptance to fewer troughs >20 mg/L (β=−0.137, P=0.009) and from troughs >20 mg/L to AKI (β=0.364, P<0.001), with a borderline indirect effect (β=−0.050, P=0.050). Predictive performance was modest (MAPE 28.5%, F30 68.6%, R^2 0.24).

Discussion / Conclusion

Implementation alone did not reduce AKI. Clinical benefit depended on clinician adherence, which mitigated toxicity by limiting excessive vancomycin exposure, underscoring the importance of implementation fidelity in precision dosing.

Keywords

Vancomycin; Model-Informed Precision Dosing; Therapeutic Drug Monitoring; Acute Kidney Injury; Implementation Science

00341
An evaluation of different performance metrics for assessing model accuracy in a priori and Bayesian forecasting in pharmacometrics

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

External evaluation of population pharmacokinetic (PK) models utilizes diverse, often unstandardized performance metrics to quantify bias or imprecision. The utility of less conventional metrics remains underexplored. This study identifies optimal metrics for evaluating bias and imprecision in *a priori* and Bayesian forecasting by systematically quantifying metric sensitivity to model misspecification.

Materials and methods

We evaluated 18 performance metrics using nlmixr2 v5.0 and R v4.5.2. Published population models for linezolid, infliximab, and tacrolimus, representing various structural complexity and target variability, were re-coded from the literature. Additionally, fully synthetic models served as neutral controls to alleviate selection bias from using models pre-selected for adequate precision (MdAPE). Reference datasets were generated via simulation from the re-coded models. Performance was evaluated during a priori and Bayesian forecasting. Metric sensitivity was quantified by systematically scaling structural parameters by factors of 0.25 to 4.0 to introduce model misspecification and comparing individual predicted concentrations against reference data.

Results

Analyses revealed distinct differences in metric sensitivity during intentional parameter misspecification. A reliable metric should cross zero for the model without misspecification for bias or show an extremum for precision. The slope (change in metric value with respect to increased degree of misspecification) should be as steep as possible for both. Across most clinical scenarios and drug models, the symmetric mean percentage error (SMPE) and median absolute percentage error (MdAPE) demonstrated the most robust performance for quantifying bias and imprecision in particular when scaling central clearance.

Discussion / Conclusion

Our findings suggest SMPE and MdAPE are sensitive metrics for assessing predictive performance in pharmacometric forecasting with consistent zero-intersections, extrema and the highest median slopes across all scenarios. Standardizing these metrics may enhance the methodological rigor of external validations, thereby promoting the clinical acceptance of model-informed precision dosing.

Keywords

Pharmacometrics, population pharmacokinetics, forecasting, Bayesian, a priori, External model evaluation

00345
Population pharmacokinetics of lorlatinib in real world patients with non-small cell lung cancer

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Lorlatinib, a third-generation ALK inhibitor, is approved for ALK-positive non-small cell lung cancer (NSCLC) treatment [1]. Pharmacokinetics of lorlatinib have been characterized in a population pharmacokinetic (PK) model of the license holder [2], however, external validation with real-world clinical data is lacking. Previous studies demonstrated that higher lorlatinib trough concentrations are associated with increased toxicity [3], suggesting a potential role for model-informed precision dosing (MIPD).

Materials and methods

We externally validated the published lorlatinib population PK model using real-world data from 149 patients in France and the Netherlands. Model performance was assessed through goodness-of-fit plots, visual predictive checks, mean percentage

error (MPE), and mean absolute percentage error (MAPE). When external validation revealed suboptimal performance, the population PK model was refined. In silico simulations were performed to explore the clinical implications of the refined model and evaluated a MIPD strategy with a target steady-state trough level of 75-125 ng/mL as proof-of-concept.

Results

External validation revealed significant bias (MPE: -5.7%, 95% CI: -10.9 to -0.6%) with the original model systematically underestimating trough concentrations. The developed refined two-compartment model included a lower clearance (13.7 L/h vs. 14.5 L/h) than in the published model. Simulations with using the refined model predicted a median steady-state trough level than the original model for the standard 100 mg once-daily dose of (128.0 vs. 106.0 ng/mL; (IQR: 96.6–163.0). MIPD increased the proportion of patients within target from 38% with standard dosing to 62% after one-cycle of dose adjustment.

Discussion / Conclusion

The published lorlatinib population PK model underestimated real-world trough concentrations, highlighting the importance of external validation for clinical trial-derived models. Our refined population PK model captured the pharmacokinetics of lorlatinib in clinical practice better. Simulation suggested that lower lorlatinib doses may be rational and the MIPD strategy could aid in reducing toxicity while maintaining therapeutic efficacy.

Reference(s)

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Keywords

Lorlatib, Population Pharmacokinetics, Model Informed Precision Dosing. NSCLC

00382
Comparing Cystatin-C with Serum Creatinine for Predicting Vancomycin Clearance in Critically ill pediatric Patients: A Population Pharmacokinetic Study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Vancomycin is an antibiotic commonly used in the pediatric intensive care unit (PICU), where kidney function is highly variable. Accurate estimation of glomerular filtration rate (eGFR) is essential for optimizing dosing and therapeutic outcomes. This study evaluated whether serum creatinine (SCr), cystatin C (CysC), or combined biomarker–based eGFR equations best predict vancomycin clearance (CL) in critically ill pediatric patients.

Materials and methods

A prospective population pharmacokinetic (PopPK) study was conducted in PICU patients aged 1 month to 14 years who were receiving vancomycin. Peak and trough concentrations were collected, and a PopPK model was developed using Monolix. Six eGFR equations were evaluated. Covariates were assessed using stepwise forward inclusion and backward elimination. Monte Carlo simulations were performed

to evaluate different dosing regimens and their ability to achieve an AUC_{0-24} of 400–600 µg·h/mL and a trough concentration <20 µg/mL.

Results

Fifty-three patients contributed 102 vancomycin concentrations. A one-compartment model with linear elimination best described the data. CL was allometrically scaled using a fixed exponent of 0.75. CysC-based equations produced the best improvements in model fit, with the Hoek equation showing the largest reduction in the objective function value and the strongest correlation with CL (R^2 = 0.26). The weight and the eGFR calculated by Hoek were the only significant predictors of CL. The final parameter estimates were 1.66 L/h for CL and 10.63 L for Vd. Simulations indicated that 15–20 mg/kg every 6 hours achieved therapeutic targets in patients with normal renal function. Those with impaired renal function benefited from 8-hour intervals, while patients with augmented renal clearance required 20 mg/kg every 6 hours.

Discussion / Conclusion

CysC-based eGFR equations, especially the Hoek equation, more accurately predict vancomycin Cl compared to SCr-based or combined equations in PICU patients. Incorporating CysC into dosing decisions can enhance therapeutic precision and improve outcomes.

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Keywords

Vancomycin, cystatin-C, serum creatinine, clearance, pharmacokinetics

00421
TacDDI: A precision dosing tool integrating Bayesian estimation to manage complex drug-drug interactions

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Tacrolimus has a narrow therapeutic index, heavily metabolized by CYP3A4/5, making it highly susceptible to clinically significant drug-drug interactions (DDIs). Static tools such as "DDI Predictor" provide a single average interaction estimate, and overlook the often-large interindividual variability in DDI magnitude and cannot reliably anticipate the time-course of the interaction (wash-in/wash-out) or tailor predictions to patient characteristics. We developed TacDDI, an interactive web-application bridging this gap by combining established population PK models for

tacrolimus (victim) with mechanism-based interaction modules (perpetrators) and Maximum A Posteriori Bayesian Estimation (MAPBE).

Materials and methods

The application was developed in R Shiny using mrgsolve. We implemented literature-parameterized structural PK models for tacrolimus and key perpetrators (voriconazole, posaconazole, isavuconazole, ritonavir, letermovir, and rifampicin) to simulate dynamic competitive and non-competitive inhibition. A modular architecture supports easy integration of new models, and a Bayesian integrates patient covariates (e.g., hematocrit) and observed tacrolimus concentrations to infer individual PK priors and forecast exposure under complex DDIs.

Results

TacDDI, available at https://tdmhub.shinyapps.io/TacDDI/ accurately simulates dynamic profiles of tacrolimus exposure and time dependent dose recommendation under DDI. Unlike static calculators, it visualizes the latency of enzyme induction (e.g., rifampicin) and the persistence of inhibition after perpetrator discontinuation (e.g., azoles). Validation comparisons show that predicted AUC ratios align with literature values for standard steady-state scenarios. In addition, MAPBE allows real-time refinement. Preliminary validation performed with data from 14 patients showed a 0.95 median obs/pred ratio and 57% of predictions within 2-fold of observed concentrations.

Discussion / Conclusion

TacDDI represents a shift from static look-up tables to dynamic precision dose adjustment. By integrating TDM data and DDI mechanisms, it offers a practical solution to manage complex interactions (initiation or cessation of perpetrators). Individual outliers, likely reflecting unmodeled factors such as co-interactions or inflammation-induced phenoconversion, justify the necessity of therapeutic drug monitoring.

Keywords

Drug Interaction, Dynamic Modeling, Tacrolimus

00423
Beyond “Skip or Take”: Evidence-Based Missed-Dose Guidance Using PopPK Simulations

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Missed or delayed intakes are frequent in chronic treatments and may favor therapeutic failure or toxicity. Recommendations in patient information leaflets are heterogeneous and often empirical or vague (e.g., "skip if close to next dose"). We aimed to propose a general dosing rule after delayed or missed drug intakes.

Materials and methods

Monte Carlo simulations were run in 11,000 virtual patients using published population PK models for eleven representative oral drugs covering various pharmacokinetic profiles: amoxicillin, amiodarone, three tacrolimus formulations (Advagraf, Prograf, Envarsus), levofloxacin, azithromycin, hydroxychloroquine, mycophenolate mofetil (MMF), abemaciclib, and carvedilol (1,000 simulations per drug). Various delayed intake scenarios were simulated, from short postponements to a full dosing-interval omission. Three strategies were compared: (1) "Skip or Take" (SmPC-based advice); (2) “Dose Omission” (always omit the delayed dose); (3) a

"Half-Life Rule" (dose adjusted on delay relative to drug half-life). Performance was assessed using AUC recovery (ratio 0.80–1.25 vs. steady state) and transient overexposure (Cmax increase >25%) compared to steady state.

Results

"Skip or Take" achieved 84.2% AUC target attainment and induced marked excursions (significant underexposure during skips and overexposure at the next intake). “Dose Omission” failed to recover AUC in 31.1% of scenarios. The Half-Life Rule provided the best balance, with 97.7% AUC recovery overall, and 100% for delays up to 50% of the dosing interval across all drugs, while limiting transient Cmax increases. A web-based calculator is available at https://tdmhub.shinyapps.io/MissedDoseApp/.

Discussion / Conclusion

A half-life-based, PopPK-grounded rule offers a simple and standardized approach to manage delayed or missed intakes when evidence-based guidance is lacking. We propose that missed-dose scenarios and recovery rules be systematically evaluated using population PK during drug development and marketing authorization applications, enabling clearer and harmonized wording in SmPCs and patient information leaflets, and straightforward implementation in clinical decision-support tools.

Keywords

Dynamic Modeling, Missed Dose, Catch-up strategy, Compliance

00466
Do updated equations for estimating renal function better capture variability in vancomycin clearance?

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Professional guidelines for assessing kidney function now recommend 2021 race-free Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate (CKD-EPI eGFR)[1] over Cockcroft-Gault estimated creatinine clearance (C-G eCrCL)[2] for dosing renally-eliminated drugs.[3,4] However, applying this change to model-informed precision dosing (MIPD) is complicated, as population pharmacokinetic (popPK) models often use specific eCrCL or eGFR equations to predict drug clearance. Here we investigated the correlation between these estimation methods and model-estimated vancomycin clearance in a large multi-centre adult sample.

Materials and methods

Data from adult patients (≥18 years) receiving vancomycin during routine clinical care between January 2020 and February 2026 were analyzed retrospectively. Patients were included if they had at least one serum creatinine, height, and weight measurement, and excluded if they had <2 serum vancomycin levels, allowing better estimation of individual vancomycin clearance (CLi_{van}). CLi_{van} was estimated using maximum a posteriori Bayesian estimates from a clinician-selected popPK model. Individual kidney function was estimated using CKD-EPI eGFR with serum creatinine (CKD-EPI eGFRcr) and C-G eCrCL with total body weight or fat-free mass (C-G $eCrCL_{TBW}$, C-G $eCrCL_{FFM}$). Correlations between CLi_{van} and each equation were

then compared overall and by whether the popPK model used the same equation to predict CLi_{van}.

Results

629,583 patients from 320 US centres were included. Correlations of CLi_{van} and CKD-EPI eGFRcr (r = .76), C-G $eCrCL_{TBW}$ (r = .70), and C-G $eCrCL_{FFM}$ (r = .72) were high, although differences were small (all $\Delta r \leq .06$). Differences between correlations when popPK models used a matching or different equation to predict CLi_{van} were negligible for CKD-EPI eGFRcr ($\Delta r = -.02$) and C-G $eCrCL_{TBW}$ ($\Delta r = -.01$), and small for C-G $eCrCL_{FFM}$ ($\Delta r = .07$).

Discussion / Conclusion

The 2021 CKD-EPI equation was not more reflective of CLi_{van} than C-G. Future work is necessary to evaluate the impact of switching to updated equations on model predictions.

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Keywords

estimated glomerular filtration rate, Cockcroft-Gault estimated creatinine clearance, model-informed precision dosing

00479
Receptor Occupancy–Based Analysis Incorporating Developmental Changes in infants preterm During Caffeine Therapy

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Caffeine (CAF), which acts as an adenosine A2A receptor (AR) antagonist, is the first-line medication for apnea of prematurity (AOP) in preterm infants. CAF treatment outcomes appear to vary with the infants' maturation because developmental changes are associated with the frequency of AOP episodes[1)] and the pharmacokinetics of CAF[2)]. Thus, differences in developmental stage need to be considered when evaluating the outcomes of CAF therapy. This study aimed to demonstrate a theoretical interpretation of variation in treatment response across developmental stages in preterm infants based on the established receptor occupancy theory.

Materials and methods

We constructed a ligand-receptor binding model in which infant growth stages influenced CAF pharmacokinetics and the concentration of AR. Developmental status was represented by gestational age (GA) and postnatal age (PNA). AOP risk was represented by an occupancy of the AR by the endogenous neuromodulator adenosine, whose binding is competitively inhibited by CAF.

Results

The adenosine occupancy in full-term infants without CAF treatment was theoretically calculated as 0.503, which was assumed to represent the AR occupancy corresponding to an AOP event-free status. The AR occupancy decreased as AR concentration increased without CAF. The presence of fixed CAF exposure reduced adenosine occupancy. AR occupancy decreased as GA increased, and showed a transient increase followed by a decrease depending on the increase of PNA despite the CAF exposure that was achieved with standard CAF treatment. The patterns of changes in the AR occupancy associated with GA and PNA were significantly influenced by differences in the rates of receptor growth.

Discussion / Conclusion

We developed a mathematical model of CAF treatment for preterm infants by combining dynamics across different scales; growth in infants and receptor occupancy. We propose that pharmacotherapy outcomes may change depending on the infant's developmental stage.

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Keywords

Receptor occupancy theory, Growth, Preterm infants, Postmenstrual age, Caffeine, Apnea of prematurity

00502
From Cardiovascular Therapy to Rare Disease Care: PBPK Modeling of Losartan Enabling Application in Epidermolysis Bullosa

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Patients suffering from rare diseases (RDs) often face substantial delays in diagnosis and have access to only limited therapeutic options.[1] The regulatory approval of new treatments is typically complex, time-consuming, and resource intensive.[2] Here, drug repurposing offers a faster and more cost-effective alternative to traditional drug development.[3] For example, losartan, which is widely used in treatment of hypertension was shown to benefit patients with the RD epidermolysis bullosa (EB) when used as a repurposed drug.[4] In this context, the integration of digital twins with drug repurposing strategies may represent a promising and innovative approach to accelerate drug development.[5] Therefore, a whole-body physiologically based pharmacokinetic (PBPK) model of losartan and its metabolite EXP3174 was developed incorporating both the influence of pharmacogenes and concomitant drug treatment.

Materials and methods

The modelling software PK-Sim® was used for model development.[6] The datasets applied were digitized from published literature and divided into a training dataset for model development and a test dataset for model performance evaluation. Predicted areas under the plasma concentration-time curve between the first and last

concentration measurement (AUC_{last}) and predicted maximum plasma concentration values (C_{max}) were calculated to assess the performance in goodness-of-fit plots.

Results

A total of 58 plasma concentration-time profiles were incorporated into the development of the parent-metabolite PBPK model. Various phenotypes of the key metabolizing enzyme CYP2C9 were predicted for 7/16 predicted AUC_{last} ratios and 8/16 predicted C_{max} ratios within the Guest limits.[7] Interactions with grapefruit juice and drugs, such as phenytoin, rifampicin, cimetidine, erythromycin, fluconazole, and itraconazole were predicted accurately with 13/16 predicted AUC_{last} ratios and 13/16 predicted C_{max} ratios within the Guest limits.[7–13]

Discussion / Conclusion

The developed PBPK model can be adapted to the altered physiology of EB patients, combining it with a pharmacodynamic approach to ensure safe, personalized therapy from the very beginning.

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Keywords

Losartan; rare diseases; digital twins; PBPK

00532
Fluconazole population pharmacokinetics in critically ill patients: implications of liver cirrhosis for PK/PD target attainment.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Fluconazole is widely used for invasive candidiasis in intensive care units (ICUs), but high pharmacokinetic variability poses challenges for optimal dosing. Existing population pharmacokinetic (popPK) models predominantly focus on renal function, while the influence of liver cirrhosis remains poorly described. We therefore developed a popPK model including cirrhotic ICU patients and performed simulations to guide dosing strategies for achieving PK/PD target.

Materials and methods

This single-center retrospective cohort study included ICU patients receiving fluconazole with routine therapeutic drug monitoring (n=40). popPK analysis was conducted using nonlinear mixed-effects modeling with stepwise covariate selection. Model evaluation relied on goodness-of-fit diagnostics, bootstrap resampling, and prediction-corrected visual predictive checks. Monte Carlo simulations (MCS) (n=10,000) were implemented with a RShiny application to identify loading and maintenance dose regimens achieving a probability of target attainment (PTA) ≥90% for an AUC/MIC >100.

Results

A one-compartment model best described the data. Typical clearance was 0.73 L/h, increased with higher CKD-EPI values, and was further reduced in cirrhosis. Typical volume of distribution was 65.8 L and increased with total body weight (BW). Bootstrap and pcVPC supported robustness and predictive performance. MCS identified dose combinations maximizing PTA on day 1 and day 14. Standard loading strategies (12 mg/kg, 800 mg, or 400 mg) rarely achieved early exposure targets.

Discussion / Conclusion

BW and CKD-EPI were covariates impacting Vd and CL, respectively, in line with literature. Cirrhosis also impacted fluconazole CL, consistent with a hepatorenal mechanism, and underscores further characterization of fluconazole pharmacokinetics in this specific subpopulation. The recommended dosing regimens were generally insufficient for PK/PD target attainment. Moreover, weight-based dosing may be misleading in ICU practice as BW adjustment may imply individualization without ensuring adequate drug exposure. These findings support using Bayesian a priori tools to select the most appropriate loading and maintenance dose combination in critically ill patients.

Keywords

Fluconazole, population pharmacokinetics, Antifungal, Therapeutic drug monitoring, Model-informed precision dosing.

00533
Nomogram-Guided Micafungin Dosing Regimen in Critically Ill Patients: A Population Pharmacokinetic Study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Micafungin is an antifungal drug recommended as first-line treatment for invasive candidiasis. In critically ill patients, optimal dosing remains uncertain because of marked interindividual pharmacokinetic variability. The aim of this study was to develop a population pharmacokinetic (popPK) model and a nomogram to support model-informed precision dosing (MIPD) of micafungin in intensive care unit (ICU).

Materials and methods

A retrospective, monocentric pharmacokinetic study was conducted in a digestive ICU. Population pharmacokinetic modelling and covariate analysis were performed using Monolix.2024R1. Model qualification relied on standard internal diagnostics and external predictive evaluation using an independent ICU cohort. Monte Carlo simulations (MCS) were performed to construct the dosing nomogram, targeting a probability of target attainment (PTA) above 90% of simulated patients across body weight ranges, total bilirubin concentrations, and dosing regimens.

Results

A total of 404 micafungin plasma concentrations from 100 patients were analysed, including 40% with hepatic impairment. Observations were adequately described by a linear one-compartment model. The estimated PK parameters (between-subject variability) were: 17.3 L (15%) for volume of distribution (Vd) and 0.85 L/h (25%) for clearance (Cl). Total body weight and total bilirubin concentration were found to influence Vd and/or Cl. External evaluation were acceptable for both population and individual predictions.

Discussion / Conclusion

We developed a population pharmacokinetic model in a digestive ICU population with a high prevalence of hepatic impairment, highlighting the influence of total bilirubin and body weight on micafungin pharmacokinetics. Because micafungin is predominantly eliminated via the biliary route, the emergence of bilirubin as a significant covariate is physiologically plausible. A full validation procedure has demonstrated its use for bayesian adaptation of dosages based on AUC estimation. MCS suggested that the recommended dosing regimen of 100 mg/day is likely insufficient for most Candida species at epidemiological cut-off values. Using nomogram coupled with MIPD would ensure optimal exposure by achieving PK/PD target early.

Keywords

Micafungin, population pharmacokinetics, Antifungal, Therapeutic drug monitoring.

00541
Population pharmacokinetics of daptomycin in paediatric patients: influence of renal function on daptomycin clearance

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Daptomycin is increasingly used to treat severe Gram-positive infections. However, data describing its pharmacokinetics and the attainment of pharmacokinetic/pharmacodynamic targets[1,2] in paediatric patients remain scarce. This study aimed to characterise daptomycin exposure and to develop a population PK (popPK) model in this population.

Materials and methods

A French two-centre retrospective study was conducted, included patients were paediatric treated by daptomycin with ≥1 plasma concentration between 2022-2025. Trough and maximum concentrations were compared to therapeutic targets. Bayesian regression was used to estimate are under the concentration-time curve (AUC). PopPK parametric modelling was performed using nonlinear mixed-effects

approach in the Monolix software. Stepwise approach was used to test influence of covariates. Model selection was based on Akaike information criterion, relative standard errors, goodness-of-fit and visual predictive checks. Monolix was used to evaluate the goodness-of-fit of the FDA-reported manufacturer's paediatric popPK model, which includes body weight and post-menstrual age but excludes renal function.

Results

Data from 39 paediatric patients were included, comprising 149 daptomycin concentrations. The respective median values (interquartile ranges) for age, weight and creatinine clearance were 3.7(0.4–12) years, 13(4.3–50) kg and 47.7(14.7–118.8) mL/min. Target attainment rates were 84% for efficacy and 80% for safety. A two-compartment model with first-order elimination and proportional error best described the data. Covariates retained in the final were weight and creatinine clearance calculated with the new Schwartz formula3 on daptomycin clearance. Central volume of distribution was also allometrically scaled to WT. By contrast, the manufacturer model, even after re-estimation of inter-individual and residual variability showed biased population predictions, especially in the youngest patients with impaired renal function.

Discussion / Conclusion

High PK variability as well as a significant proportion of under- and overexposure to daptomycin in paediatric patients was reported. As described in adults, renal function influences daptomycin clearance in children as well and should be considered in dosing regimens.

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Keywords

Population pharmacokinetic, daptomycin, paediatric

00547
Machine Learning–Based Limited Sampling Strategy to Evaluate In Vivo Activity of OATP1B1, OATP1B3, and BCRP Using Rosuvastatin as a Probe

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Machine learning (ML) algorithms have recently emerged as effective tools for predicting individual drug exposure, often outperforming traditional methods (1, 2). This study aimed to develop a limited sampling strategy (LSS) to estimate rosuvastatin exposure, measured by the area under the plasma concentration–time curve (AUC0-24), using only two plasma concentrations.

Materials and methods

Simulated patient data were generated using a population pharmacokinetic (popPK) model and Monte Carlo methods, and then split into training (75%) and test (25%) sets. Four ML algorithms, GLMNet, Random Forest, XGBoost, and Support Vector Machine, were trained to predict AUC based on samples collected at 1.5 and 4 hours after a single rosuvastatin dose.

Results

The Random Forest model demonstrated the best performance, with the lowest root mean square error (RMSE) in both 10-fold cross-validation and the test set. External

validation was conducted using real-world patient data from two independent studies. The Random Forest model provided accurate AUC0-24 estimates across all datasets: 10-fold cross-validation (relative bias/RMSE = 1.5% / 13.0%), test set (2.2% / 13.5%), pregnant women (-4.5% / 15.9%), and post-treatment chronic hepatitis C patients (4.0% / 18.2%).

Discussion / Conclusion

This ML-based approach offers a practical and minimally invasive method to estimate rosuvastatin exposure and has strong potential to support pharmacokinetic studies aimed at evaluating the activity of drug transporters such as OATP1B1, OATP1B3, and BCRP under various physiological and pathological conditions.

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Keywords

rosuvastatin, pharmacokinetics, machine learning, limited sample strategy, population pharmacokinetics, random forest.

00561
Model-Informed Precision Dosing of isoniazid using a Machine Learning Approach

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

For more than five decades, therapeutic drug monitoring(TDM) of isoniazid(INH) has been based on conventional dosing strategies, notably the Vivian approach(1). However, this method achieved target therapeutic concentrations in only 50% of patients, as demonstrated in our previous Tunisian study(2), thereby exposing patients to subtherapeutic or toxic concentrations. These limitations highlight the need for individualized and evidence-based approaches guiding INH. Our aim is to develop and validate a MIPD(Model-Informed-Precision-Dosing) based on Machine Learning approches for INH TDM in Tunisian tuberculosis patients.

Materials and methods

We conducted a longitudinal study at the Department of Clinical Pharmacology, Monastir-Tunisia(2017-2025). Tuberculosis patients treated with INH were included with at least two documented INH concentrations. Blood samples were collected three hours after INH intake(C_3). Six machine-learning algorithms were evaluated: Linear Regression(LR), k-Nearest-Neighbors, Extra-Trees-Regressor, Random-Forest-Regressor, Decision-Tree-Regressor and Extreme-Gradient-Boosting. The output was the ratio of the weight-adjusted INH dose to C_3 (Dp/C) at visitN. Features included Dp/C at visit(N-1), age, gender, and concomitant antituberculosis therapy. Model performance was assessed with root mean square error(RMSE), mean absolute error(MAE), and Pearson correlation coefficient(r2).

Results

A total of 215 patients(N= 430C3) were included. Population was divided: 80% for model training and 20% for external validation. The linear regression model out-performed all others, achieving RMSE=0.35, MAE=0.28 and r^2=0.89(TableI). The resulting predictive equation was:

$Dp/C3_{(N)} = 0.343 + 0.856 * Dp/C3_{(N-1)} - 0.047 * GENDER$

Where: Dp = weight-adjusted INH dose, C3(N-1) and C3(N)= measured C3h concentration in the visit(N-1) and the visit(N), respectively.

Table I: Performance metrics for Machine learing tested models

Algorithms	RMSE	MAE	r^2
Linear Regression	0.35	0.28	0.89
k-Nearest-Neighbors	0.24	0.32	0.86
Extra-Tree-Regressor	0.44	0.30	0.83
Random-Forest-Regressor	0.40	0.30	0.87
Extreme-Gradient-Boosting	0.43	0.29	0.84
Decision-Tree-Regressor	0.46	0.36	0.81

Discussion / Conclusion

The LR showed better predictive accuracy than other machine learning approaches for INH dosing. Based on Dp/C3 and patient gender, the LR estimates the optimal INH dose to reach therapeutic targets. Implementing TDM-based LR model in clinical practice can significantly enhance outcomes in Tunisian tuberculosis patients.

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Keywords

Model-Informed Precision Dosing (MIPD), isoniazid, Machine learning, therapeutic drug monitoring(TDM), pharmacokinetic

00586
Model-Based Precision Dosing and Non-Adherence Remediation of Isoniazid in Chinese Tuberculosis Patients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Isoniazid (INH), a first-line drug to treat tuberculosis (TB) for more than 50 years. However, large inter-individual variability was found in its pharmacokinetics, and effects of non-adherence to INH treatment and optimal remedial dosing remains unclear. This study aimed to develop a population pharmacokinetics (PPK) model of INH in Chinese patients with TB, to provide model-informed precision dosing and explore appropriate remedial dosing regimens for non-adherent patients.

Materials and methods

1012 INH therapeutic drug monitoring (TDM) results from 736 TB patients were included. A nonlinear mixed-effects modeling was used to analyze the PPK of INH. Using Monte Carlo simulations to determine optimal dosage regimens and design remedial dosing regimens.

Results

A two-compartmental model, including first-order absorption and elimination with allometric scaling, was found to best describe the PK characteristics of INH. A mixture model was used to characterize dual rates of INH elimination. Estimates of

apparent clearance in fast and slow eliminators were 28.0 and 11.2 L/h, respectively. Monte Carlo simulations determined optimal dosage regimens for slow and fast eliminators with different body weight. For remedial dosing regimens, the missed dose should be taken as soon as possible when the delay does not exceed 12 h, and an additional dose is not needed. On delaying a INH dose exceed 12 h, only need to take the next single dose normally.

Discussion / Conclusion

TDM and PPK modeling and simulation provide valid evidence on the precision dosing and remedial dosing regimen of INH.

Keywords

Isoniazid; PPK; model-based precision dosing; remedial dosing; tuberculosis; TDM

00587
Population Pharmacokinetics and Concentration-QTc Analysis of Bedaquiline in Patients with Multidrug-resistant Tuberculosis

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Bedaquiline (BDQ) has shown great value in the treatment of multidrug-resistant tuberculosis (MDR-TB) in recent years. However, large pharmacokinetic variability was observed in patients following standard BDQ dosing. BDQ is also reported to induce cardiac QT interval prolongation. This study aims to perform a population pharmacokinetic-pharmacodynamic (PPK-PD) analysis of BDQ in Chinese MDR-TB patients to enable model-based precision dosing and investigate the concentration-QTc relationships of BDQ.

Materials and methods

Blood samples and therapeutic drug monitoring (TDM) results of BDQ were collected for PK evaluation, and ECGs were recorded for QTc calculation at the designed timepoints. The PPK-PD model was developed using nonlinear mixed effects modeling (NONMEM) software. An effect compartment model was utilized to explain the relationship between BDQ concentrations and ΔQTc.

Results

A total of 211 BDQ concentrations and 190 QTc measurements were obtained from 105 Chinese MDR-TB patients. The PK characteristics of BDQ was adequately described using a two-compartment model with first-order absorption and elimination. The estimated apparent clearance and volume of distribution were 1.77 L/h and 52.4 L, respectively. Body weight and albumin were significant covariates for clearance of BDQ, with body weight also affecting the apparent volume of distribution. ΔQTc exhibited a linear relationship with BDQ concentration. A linear model properly characterized BDQ-induced QTc prolongation.

Discussion / Conclusion

A PPK-PD model based on sparse data was established for prediction of BDQ exposure in patients with MDR-TB. TDM and PPK modeling provide valid evidence on the precision dosing of bedaquiline.

Keywords

Bedaquiline; PPK-PD model; concentration-QTc relationship; multidrug-resistant tuberculosis; TDM

00594
Population Pharmacokinetics of Vancomycin in patients with Methicillin Resistant Staphylococcus aureus (MRSA) Infections

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Methicillin-resistant Staphylococcus aureus (MRSA) infections have led to increased use of vancomycin. Due to its narrow therapeutic window, therapeutic drug monitoring is required to optimize efficacy while minimizing nephrotoxicity. Current guidelines recommend targeting an area under the concentration–time curve over 24 hours to minimum inhibitory concentration ratio (AUC_{0-24}/MIC) ≥400 for optimal outcomes. However, pharmacokinetic data for vancomycin in Indian patients remain limited, and trough concentrations may not reliably reflect total drug exposure.

Materials and methods

This prospective observational pharmacokinetic study was conducted in 28 hospitalized patients with MRSA infections at a tertiary care center. Blood samples (2 mL) were collected at 6–7 time points on day 4 of vancomycin therapy (steady state). Plasma vancomycin concentrations were quantified using LC–MS/MS. Pharmacokinetic parameters were estimated using noncompartmental analysis and used to support population pharmacokinetic characterization. MIC values for MRSA isolates were determined using E-test and automated methods. The relationship between trough concentrations, AUC_{0-24}/MIC, and clinical, microbiological, and safety outcomes was evaluated. Patients were followed until discharge or up to 28 days.

Results

The median vancomycin dose was 16.6 mg/kg/dose (range 11.1–28.6). Patients with renal impairment demonstrated a four-fold longer half-life and nearly two-fold higher AUC compared with those with normal renal function. Trough concentrations correlated with AUC_{0-24} but showed poor association with clinical outcomes or nephrotoxicity. AUC_{0-24}/ MIC was significantly higher in patients with bacteriological eradication than in those with persistent bacteremia (902.7 vs. 341.8; p=0.017). All patients with AUC_{0-24}/MIC <400 mg·h/L experienced clinical failure, whereas all patients with AUC_{0-24}/MIC ≥400 mg·h/L achieved microbiological eradication. Nephrotoxicity occurred in 25% of patients but was not significantly associated with AUC exposure.

Discussion / Conclusion

AUC_{0-24}/MIC ≥400 mg·h/L was strongly associated with microbiological eradication in MRSA infections. Although trough concentrations correlated with AUC, they were not predictive of clinical outcomes, supporting exposure-guided dosing strategies and population pharmacokinetic approaches to optimize vancomycin therapy.

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Antimicrob Agents Chemother. 2017;62:e02042-17.

Keywords

Vancomycin, Methicillin-resistant Staphylococcus aureus. Population pharmacokinetics, AUC-guided dosing

00602
Age-Related Differences in Systemic and Brain Exposure to Elexacaftor-Tezacaftor-Ivacaftor: A PBPK Modeling Study in Pediatric and Adult Cystic Fibrosis

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Elexacaftor-Tezacaftor-Ivacaftor (ELX-TEZ-IVA, ETI) has dramatically improved clinical outcome in Cystic Fibrosis (CF). However, neuropsychiatric adverse events (NAEs) have been increasingly reported, particularly in pediatric patients. It remains unknown whether these NAES could be driven by ETI brain exposure. This study aimed to develop a physiologically based pharmacokinetic (PBPK) model of ETI to explore the variability in systemic and central nervous system (CNS) exposure.

Materials and methods

Were included all pediatric patients treated between 2022 and 2024, and for whom at least one ETI plasma concentration was available. Demographic, pharmacokinetics, biological, genetic, and NAEs data were collected. The PBPK model was developed based on published PK data for both adult and pediatric and validated in our population using standard goodness-of-fit diagnostics. The validated model was used to simulate age-related differences in systemic and CNS exposure and to compare predicted exposure between children with and without reported NAEs in our cohort.

Results

Fifty children were included with a mean age 6.6±4.4 years, contributing 279 plasma concentrations. Dose- and weight-Normalized AUCs were 2 times higher in younger children for all 3 drugs. NAEs were documented in 38% of patients, and more frequent in children under 6 years. The PBPK model adequately described both adult and pediatric populations, with over 95% of predicted AUCs and Cmax being within 1.3-fold of their observed values. Simulations revealed that ETI plasmatic exposure was 2 to 4-fold higher in 2-6 years when compared with adults. Although CNS penetration was substantial for IVA and ELX but minimal for TEZ, predicted CNS exposure did not differ between children with and without reported NAEs.

Discussion / Conclusion

Younger children have higher dose- and weight-normalized exposure. While younger children experience more NAEs, the CNS exposure appears similar between both groups suggesting that exposure may not be the only factor driving the NAEs. Further investigations are necessary.

Keywords

PBPK

Cystic Fibrosis

CFTR modulators

00608
Pharmacometric simulation of drug removal during hemodialysis based on mass-transfer coefficient theory: An example using vancomycin

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Hemodialysis techniques continue to advance, affecting drug removal efficiency. Despite these advancements, translating technological progress into individualized drug dosing remains challenging. The aim of this study was to quantify drug removal using a pharmacometric (PMx) approach incorporating the mass-transfer coefficient (KoA) theory, which enables estimation of hemodialytic clearance based on dialyzer performance across various hemodialysis settings and sessions.

Materials and methods

This simulation study was conducted without ethical concerns using randomly generated virtual individuals. Commercially available dialyzers were evaluated using the PMx–KoA combined approach with vancomycin as the target drug. Drug elimination was simulated by incorporating a drug removal compartment into a two-compartment pharmacokinetic model that includes body weight as a covariate [1].

Results

A total of 386 dialyzers were evaluated in a four-hour hemodialysis session (flow rates for blood, dialysate, and convection: 200, 500, and 0 mL/min, respectively) for a virtual patient (n = 1; body weight, 60 kg). Dialyzer components varied substantially

(e.g., median [range] membrane area: 1.5 [0.5–2.6] m²). The PMx–KoA combined approach revealed that drug removal differed across membrane materials (median values: membrane A, 251.9 mg; membrane B, 345.2 mg; membrane C, 217.5 mg; membrane D, 359.9 mg; membrane E, 291.7 mg; membrane F, 281.9 mg; membrane G, 361.0 mg). Considering internal (non-dialytic) clearance, the maintenance dose required after each hemodialysis session performed every 48 hours showed substantial inter-individual variability in the virtual population (n=10,000; mean [standard deviation] body weight, 55.7 [14.8] kg), with a median (minimum, interquartile range, maximum) of 542.8 (286.5, 477.4–604.8, 787.5) mg.

Discussion / Conclusion

The PMx–KoA combined approach demonstrated substantial variability in the maintenance dose of vancomycin, suggesting the need for quantitative dose adjustment during hemodialysis. This strategy may facilitate individualized dosing across diverse hemodialysis settings and dialyzer characteristics.

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Keywords

Hemodialysis; pharmacometrics; simulation; vancomycin; mass-transfer coefficients

00618
A physiologically-based pharmacokinetic model for intraperitoneal irinotecan to evaluate the impact of UGT1A1 variability on SN-38 exposure

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Intraperitoneal (IP) irinotecan is currently being investigated for treatment of peritoneal metastases, to overcome limited IP drug availability associated with systemic administration. However, quantitative understanding of drug transport across the peritoneal-plasma barrier and resulting IP exposure remains limited. Irinotecan is an anti-cancer drug that is converted to the highly active metabolite SN-38, which is subsequently inactivated by UGT1A1-mediated glucuronidation into SN-38G(1). This study aimed to develop a Physiologically-based pharmacokinetic (PBPK) model for IP irinotecan and evaluate the effect of reduced UGT1A1 activity on systemic SN-38 exposure by use of simulations.

Materials and methods

A PBPK model was developed in PK-Sim v.12 (Open Systems Pharmacology Suite) using clinical pharmacokinetic data from 53 patients with colorectal and gastric peritoneal metastases receiving 75 mg IP irinotecan(NCT05379790)(2). Plasma concentrations of irinotecan, SN-38, SN-38G and IP concentrations of SN-38 and SN-38G were used for model calibration and evaluation. Tissue distribution was predicted using PK-Sim standard partition coefficient and permeability algorithms

under perfusion-limited assumptions. Metabolic pathways were implemented mechanistically: irinotecan conversion into SN-38 via Carboxylesterase (CES) 1 and CES2, and glucuronidation of SN-38 into SN-38G via UGT1A1. UGT1A1 poor metabolizer scenarios were simulated by scaling glucuronidation capacity (Vmax) to 20-50% of wild-type activity.

Results

The PBPK model adequately described systemic and IP pharmacokinetics of irinotecan and its metabolites, with predicted exposures within two-fold of observed data. The model described delayed systemic absorption following IP administration and sustained IP exposure. Reduced UGT1A1 activity increased systemic SN-38 AUC (87.9 ng*h/mL) compared with normal metabolizers (59.1 ng*h/mL). Simultaneously, SN-38G exposure decreased and the SN-38G/SN-38 AUC ratio declined substantially, confirming model sensitivity to altered glucuronidation capacity.

Discussion / Conclusion

We developed the first mechanistic model describing IP administration in humans. Simulations demonstrate that reduced UGT1A1 activity increases systemic SN-38 exposure after IP administration. This framework provides a generalizable strategy for integrating non-standard administration routes into PBPK platforms.

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00624
Pharmacokinetics of rituximab and progression free survival for interstitial lung diseases: a PK-TtE model from EVER-ILD trial.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

EVER-ILD study (NCT: 02990286) compared the efficacy of mycophenolate mofetil (MMF) associated or not with intravenous (IV) rituximab in patients with interstitial lung diseases (ILD) with a longer Progression-Free Survival (PFS) in patients receiving rituximab[1]. The use of MMF is considered an option for refractory disease and rituximab showed benefits in some observational studies[2]. Thus, it was assumed that rituximab could increase PFS. Trial dosing regimens were based on approved practices for MMF with 1-gram tablets twice daily for 6 months. The goal of this work was to investigate the influence of rituximab addition on PFS by establishing a PK-PFS joint model.

Materials and methods

Patients were randomized in MMF+placebo or MMF+rituximab arms following a 1:1 ratio and subjects in experimental arm received 1-gram IV rituximab at D1 and D15. The subjects were all followed up for 1 year. Peak and trough rituximab

concentrations were measured using an in-house ELISA technique[3]. Rituximab PK was computed with a population PK approach. Time-to-event (TtE) data were described using parametric modeling of hazard function. PK-TtE modeling was made using Monolix Suite 2024 R1 (Lixoft®). Models were compared and selected based on objective function (-2LL) and visual inspection.

Results

59 and 63 patients were respectively enrolled in arms 1 and 2. 296 samples were collected. A two-compartment model best described the PK data, with a central volume of distribution of 3.55L and an elimination clearance of 0.38L/d. Time-to-progression data were best described using an exponential model. Hazard to progression was significantly decreased with higher rituximab concentrations (Δ(-2LL)=5.23, with C_{50}=17.77mg/L) compared to an independent relationship.

Discussion / Conclusion

This is the first time that the relationship between rituximab pharmacokinetics and PFS in ILD has been simultaneously described, using joint modeling. The results highlighted an increase of PFS for patients in experimental arm until one year.

Reference(s)

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Keywords

rituximab, interstitial lung disease, pharmacokinetics, progression-free survival, joint modeling

00633
Accounting for FcRn interactions in pharmacokinetics of monoclonal antibodies: a population compartmental framework

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The neonatal Fc receptor (FcRn) plays a central role in all pharmacokinetic processes of monoclonal antibodies (absorption, distribution, and elimination), yet it has not been explicitly incorporated into compartmental models in population pharmacokinetics. This study aimed to develop and evaluate pharmacokinetic models accounting for mAb–FcRn interactions.

Materials and methods

Two-compartment models accounting for mAb-FcRn interactions were tested on five mAb PK datasets, from previous published studies i.e. bevacizumab[1], cetuximab[2], infliximab[3], rituximab[4] and trastuzumab[5] These models were compared to a reference linear 2-compartment model (M.1). Model parameters were estimated using population approach.

Models that were tested accounted for mAb-FcRn interactions in an endosomal compartment (M.2) [6], in central compartment[7] (M.3), between central and peripheral compartments while estimating (M.4) or fixing (M.5) the value of Fc-FcRn binding affinity constant (KD,FcRn) This value was fixed to 750 nM[8], [9] in M.2, M.3 and M.5. In each database, mAb-FcRn models were compared to reference model using Bayesian Information Criterion (BIC).

Results

In all databases, concentration-time data description was improved by at least one mAb-FcRn model; M.2 was the best in infliximab database, (ΔBIC -59.39) while M.5 was the best in bevacizumab (ΔBIC -63.84) and cetuximab (ΔBIC -136.12) databases, and M.4 in trastuzumab (ΔBIC –300.3) and rituximab (ΔBIC -128.86) databases.

Discussion / Conclusion

This study is the first to demonstrate the benefit of incorporating mAb–FcRn interactions into population pharmacokinetic models. Such an approach may be especially relevant under conditions of FcRn blockade or receptor saturation

Reference(s)

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Keywords

Neonatal Fc receptor

Population Pharmacokinetics

Monoclonal antibodies

Rituximab

Trastuzumab

Cetuximab

Infliximab

Bevacizumab

00651
Determinants of Vancomycin Concentrations in Hemodialysis Patients: A Linear Mixed-Effects Model Analysis

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Vancomycin is widely used for the treatment of severe Gram-positive infections in patients undergoing chronic hemodialysis. However, its pharmacokinetics are significantly altered in this population. Achieving therapeutic concentration of vancomycin is therefore crucial, yet it may be influenced by demographic characteristics as well as hemodialysis-related parameters.

The objective of this study was to analyze demographic and dialysis session factors associated with vancomycin concentrations in patients on intermittent hemodialysis.

Materials and methods

Clinical and pharmacokinetic data were retrospectively analysed from patients undergoing chronic hemodialysis and receiving vancomycin between 2022 and 2025.

Vancomycin was administered after hemodialysis session and pre-dialysis trough plasma concentrations (Cpre-HD) was measured just before the next one, in the clinical pharmacology department in Monastir. We applied a linear mixed effects

(LME) model and we analysed the variability of Cpre-HD to assess the independent contribution of patient-related factors and hemodialysis related parameters

Results

Our study included 44 patients for whom 141 Cpre-HD were available, corresponding to an average of three measurements per patient collected over consecutive dialysis sessions. The mean Cpre-HD was 14.1 mg/L±4.5

We assessed the similarity of repeated measurements within the same patient using the Intraclass Correlation Coefficient (ICC). The ICC was 0.357, indicating that approximately 36% of the variability in Cpre-HD was attributable to differences between patients.

After stepwise backward variable selection, three factors were identified as independently associated with Cpre-HD: blood flow rate (**Qb**) ($p = 0.002$), vancomycin dose (**D**) ($p = 0.034$), and the dosing-to-sampling interval (**IT**) ($p = 0.075$).

The predictive equation used: Y_pred (**Cpre-HD**) = $1.7 + 1.305 \times$ **Qb** $+ 1.881 \times$ **D** $- 0.741 \times$ **IT**

Discussion / Conclusion

This study highlights the substantial intra- and inter-individual variability of pre-dialysis vancomycin concentrations in chronic hemodialysis patients. The proposed predictive equation provides a pragmatic tool to anticipate pre-dialysis concentrations and may support more individualized dose adjustment strategies.

00656
Physiologically based pharmacokinetic modeling of elexacaftor–tezacaftor–ivacaftor during pregnancy with integrated ex vivo human placental transfer to predict maternal and fetal exposure

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The widespread use of elexacaftor–tezacaftor–ivacaftor (ETI) has led to a rapid increase in pregnancies among women with cystic fibrosis (wwCF)[1,2]. Pregnancy is associated with major physiological changes which can substantially alter drug pharmacokinetics[3]. Further, increasing evidence of placental transfer of ETI raises clinically important questions regarding fetal exposure[4]. Despite ETI use during pregnancy, quantitative data to guide dosing and assess maternal–fetal exposure remain limited, creating an urgent clinical need to support safe and effective care[5,6,7].The aim was to develop a mechanistic, experimentally informed maternal–

fetal physiologically based pharmacokinetic (PBPK) model of ETI during pregnancy and to predict maternal and fetal exposure across gestation.

Materials and methods

A PBPK modeling framework was implemented using the Simcyp™ Simulator. Experimentally derived transplacental transfer parameters were obtained from *ex vivo* human term placenta perfusion experiments and estimated using Monolix™. These parameters were integrated into a permeability-limited placental model to construct a coupled maternal–fetal PBPK model. Model evaluation leveraged real-world pharmacokinetic data from a nationwide French multicenter observational cohort of adults with CF treated with ETI, including maternal plasma concentrations from pregnant women and umbilical cord blood concentrations at delivery.

Results

The integrated pregnancy PBPK models captured maternal and fetal ETI concentration-time profiles, with majority of observations falling within the 5th–95th percentile prediction intervals. Simulations predicted a progressive decrease in maternal systemic exposure, reaching 58.3%, 60.4% and 66.2% decrease for elexacaftor, tezacaftor, and ivacaftor, respectively, by the end of the third trimester. In late gestation, predicted cord blood-to-maternal plasma AUC ratios were 0.64 for elexacaftor ($AUC_{0\text{-}24h}$), 0.65 for tezacaftor($AUC_{0\text{-}24h}$), and 0.48 for ivacaftor($AUC_{0\text{-}12h}$).

Discussion / Conclusion

This study presents a mechanistic, experimentally informed maternal–fetal PBPK model of ETI during pregnancy, by integrating empirical ex vivo placental data to predict ETI disposition in pregnancy. This model provides a model-informed support for ETI therapy, addressing a critical clinical knowledge gap in the management of wwCF.

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Keywords

PB-PK modelling, cystic fibrosis, pregnancy, elexacaftor-tezacaftor-ivacaftor

00666
Real-World Evaluation of Apixaban Dose-Reduction Criteria: Serum Creatinine Versus Creatinine Clearance

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Apixaban (APX) dose reduction is recommended when patients meet at least two of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, and serum creatinine (Scr) ≥ 1.5 mg/dL. Because Scr is influenced by muscle mass, renal function may be overestimated in elderly patients with low body weight, potentially leading to excessive drug exposure. This study aimed to compare Scr-based and creatinine clearance (CLcr)–based dose-reduction algorithms using real-world APX trough concentrations.

Materials and methods

This retrospective study included patients receiving APX (2.5 or 5.0 mg BID) according to the Scr-based dose-reduction algorithm. APX concentrations were measured from serum samples, and individual pharmacokinetic parameters were estimated using Bayesian analysis. Standard-dose trough concentrations (5.0 mg BID) were simulated, and their association with renal function was evaluated. ROC analysis determined the optimal CLcr cutoff for predicting the previously reported safety threshold (230 ng/mL). A CLcr-based algorithm, replacing Scr while retaining

the age and BW criteria, was then simulated, and the proportion of patients with trough concentrations ≥ 230 ng/mL was compared with that under the Scr & body weight & age-based approach.

Results

Among 555 patients (median age: 69 years, M/F=376/179), only 17 (3%) met the Scr criterion (≥ 1.5 mg/dL), whereas 61 (11%) received a reduced dose under the Scr-based algorithm. Simulated trough concentrations at the standard dose showed poor correlation with Scr but strong correlation with CLcr; ROC analysis (AUC = 0.77) identified 60 mL/min as the optimal cutoff. Application of a CLcr-based algorithm reduced the proportion of patients with trough concentrations ≥ 230 ng/mL from 85 (15.3%) to 59 (10.6%).

Discussion / Conclusion

Incorporating CLcr into the dose-reduction algorithm may enhance individualized APX therapy in routine clinical practice.

Keywords

Apixaban, Real-World data, Bayesian analysis

00684
Physiologically-Based Pharmacokinetic and Pharmacodynamic Modeling to Optimize Rivaroxaban Dosing in CA-VTE Patients Coadministered with Ensartinib

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Rivaroxaban is widely prescribed for the treatment of cancer-associated venous thromboembolism (CA-VTE). Its anticoagulant effect may be influenced by ensartinib, an ALK inhibitor used in NSCLC patients, which is also a dual CYP3A4/P-gp inhibitor and may increase rivaroxaban exposure through pharmacokinetic drug-drug interactions (DDIs). This study aimed to quantitatively assess the impact of ensartinib on rivaroxaban pharmacokinetics and pharmacodynamics in patients with non-small cell lung cancer (NSCLC) using physiologically-based pharmacokinetic (PBPK) and pharmacodynamic (PD) modeling, and to propose optimized rivaroxaban dosing regimens for safe and effective CA-VTE management.

Materials and methods

PBPK models for rivaroxaban and ensartinib were developed in PK-Sim® to simulate DDIs, and subsequently linked to PD markers including prothrombin time fold-change and factor Xa activity inhibition. Model parameters and clinical datasets were derived from published literature and publicly available databases. Sensitivity analyses were performed to evaluate the influence of key pathophysiological factors (e.g., renal

function, albumin levels, ethnicity) on rivaroxaban exposure and response. Exposure-response relationships were leveraged to guide dose optimization in the presence of ensartinib.

Results

A robust PBPK-PD model was successfully established for rivaroxaban and ensartinib co-administration. Renal impairment, hypoalbuminemia, and ethnicity were identified as significant determinants of rivaroxaban exposure. In NSCLC patients with chronic kidney disease stage 1–2, dose adjustment to 17.5 mg once daily or 13.75 mg twice daily yielded systemic exposures comparable to standard rivaroxaban monotherapy (20 mg once daily or 15 mg twice daily), thereby maintaining therapeutic anticoagulation without increased bleeding risk.

Discussion / Conclusion

Cancer-related physiological alterations, particularly renal function and protein binding, substantially modulate rivaroxaban pharmacokinetics. The proposed individualized dose adjustments during ensartinib co-administration support safe and effective anticoagulation in CA-VTE patients, achieving a favorable balance between thromboembolic prevention and hemorrhagic risk. These findings underscore the value of PBPK-PD modeling in guiding precision dosing in oncology populations.

Keywords

rivaroxaban; ensartinib; drug-drug interaction; non-small cell lung cancer; physiologically-based pharmacokinetics

00698
Translational PBPK Model Development for Tacrolimus: Mechanistic Integration of Growth, Postoperative Changes, and Voriconazole Interaction

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Tacrolimus is essential after lung transplantation but difficult to dose due to a narrow therapeutic window, low and variable oral bioavailability, and substantial pharmacokinetic (PK) variability. These issues are greater in pediatric recipients, who undergo rapid developmental and postoperative physiological changes, particularly early after surgery. Current dosing remains largely empirical. We developed a physiologically based pharmacokinetic (PBPK) framework to support individualized tacrolimus dosing in pediatric lung transplant recipients.

Materials and methods

A whole-body tacrolimus PBPK model was developed in PK-Sim®. Model building proceeded stepwise from healthy adults to adult lung transplant recipients and then pediatric lung transplant recipients. Pediatric maturation functions were implemented for CYP3A4 activity and plasma albumin. Postoperative recovery was represented using time-dependent exponential functions for intestinal permeability, CYP3A4/5 activity, P-glycoprotein activity, tissue distribution coefficients, and hematocrit across

postoperative day stages. A tacrolimus–voriconazole drug–drug interaction module was added. Model performance was evaluated against published PK data using visual predictive checks, fold error (FE), and geometric mean fold error (GMFE). To enable clinical translation, a web-based dashboard was created for scenario-based initial dose selection.

Results

The final model adequately described tacrolimus PK across populations and captured pediatric-specific exposure patterns. Incorporation of ontogeny and postoperative trajectories improved prediction of concentration-time profiles and PK metrics. In pediatric lung transplant recipients, more than two-thirds of predictions fell within a 0.5–2.0 FE range, with better performance during the stable postoperative phase than the early postoperative phase. The model also reproduced increased tacrolimus exposure during concomitant voriconazole administration. The web tool operationalized the PBPK framework for practical dosing simulations.

Discussion / Conclusion

This study establishes a mechanistic, translational PBPK platform for tacrolimus in pediatric lung transplantation, integrating developmental biology, postoperative physiology, and drug interactions. The accompanying dashboard provides clinically actionable support for individualized initial dosing and may improve early therapeutic optimization in this high-risk population.

Keywords

Tacrolimus; PBPK modeling; pediatric lung transplantation; precision dosing;

00709
From Population to Individual: An Iterative Bayesian Method Using Adherent-State Therapeutic Drug Monitoring Data to Refine Adherence Assessment for Antiseizure Medications

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Accurate assessment of medication adherence is critical for managing chronic diseases. Our previous work established a Bayesian-based pharmacokinetic (PK) framework combined with therapeutic drug monitoring (TDM) data to evaluate adherence to antiseizure medications (ASMs). However, this approach relied solely on population PK parameters, overlooking valuable individual PK information potentially available from prior TDM measurements obtained during confirmed adherent periods. Therefore, this study aims to investigate whether incorporating such individual adherent-state data can further refine adherence assessment capabilities.

Materials and methods

Typical clinical scenarios were simulated for adult and pediatric patients on ASMs using published population PK models. The population-based approach used standard population PK parameters to simulate concentration-time profiles and compute posterior probabilities for various dosing scenarios (full adherence, missed last dose, consecutive missed doses and so on) via Bayes' theorem. The individual-

based approach first used the maximum a posterior Bayes feedback algorithm integrated with TDM data at adherent-state to estimate individual PK parameters, and subsequent adherence assessments were then based on these individualized parameters. The discriminative ability of both approaches to correctly identify true dosing behaviors was compared.

Results

The individual-based approach demonstrated significantly superior discriminative ability in identifying non-adherence patterns compared to the population-based approach. This improvement was most pronounced when between-subject variability was high, with performance converging as variability approached zero. Sensitivity analyses confirmed the robustness of these findings across different ASMs and population PK models. The individualized method has been integrated into our previously developed web-based dashboard for practical application.

Discussion / Conclusion

Leveraging individual adherent-state TDM data to refine PK parameters substantially improves the accuracy of Bayesian adherence assessments compared to population-based approach alone. This personalized approach offers a more precise tool for quantifying medication-taking behaviors, with the potential to enhance clinical decision-making in chronic disease management.

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Keywords

medication adherence; therapeutic drug monitoring; population pharmacokinetics; Bayes

00716
Mechanistic biomarker model of serum creatinine in critically ill patients and external evaluation.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

An important inter- and intra-individual pharmacokinetics variability of antibiotics is observed in intensive care units (ICU) patients, mainly due to modification of renal function. In order to predict this variability, we aimed to develop a serum creatinine (Crs) biomarker model allowing to describe renal function evolution in ICU population.

Materials and methods

Adult intensive care patients were included in a prospective, observational study. Clinical and biological data collected at inclusion and throughout 7 days were analyzed using nonlinear mixed-effects modelling (Monolix 2024R1). A mechanistic turnover model was established to describe Crs kinetics. Then, renal status evolution (stable/deterioration/recovery) was modelled using a three-state probabilistic model, which were structurally linked to the instantaneous Crs slope. For clinical application, a maximum a posteriori approach was used to estimate individual parameters and iteratively update Crs degradation inhibition (INH) based on renal deterioration probability. Graphical and statistical criteria were used to assess models performance. An external evaluation was performed using an independent dataset.

Results

The study included 76 ICU patients (n=597 Crs). Crs kinetic was described using a turnover model with slow degradation (kdeg_pop = 0.0086 h^{-1}), and transient impairment was captured with INH : kdeg_eff = kdeg·(1 − Ideg·INH). Many patients presented an initial Crs values higher than observed in stable renal status : 68.2 vs 41.9 µmol/L. The instantaneous Crs slope was used as a predictor in the multinomial component : positive slopes increasing deterioration probability and negative slopes indicating recovery. External evaluation showed adequate predictive performances (n= 41 patients and 195 Crs): MDPE ranging from −0.52% to −0.16%, MAPE from 6.47% to 8.71%, and RMSE from 12.0% to 15.3%.

Discussion / Conclusion

We developed and implemented a mechanistic biomarker model describing Crs kinetics and renal functional status in ICU patients. This application could be used in clinical setting and integrated into drug population pharmacokinetic models, to improve dose individualization.

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Keywords

pharmacometrics, intensive care unit; serum creatinine; renal function; therapeutic drug monitoring; bayesian maximum a posteriori approach ; mechanistic model; augmented renal clearance; acute kidney injury, turnover model

00718
Does Nonlinear Absorption of Oral Misoprostol Challenge Guideline-Based Dosing in Late Pregnancy Cervical Ripening? A Population Pharmacokinetic Model to Resolve.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Misoprostol is the first-line agent for cervical ripening in late pregnancy, with oral administration increasingly preferred over vaginal routes per international guidelines[1,2]. Current oral dosing regimens are empirically derived from vaginal protocols, not based on dose-exposure-response relationships. Dosing intervals (typically 2–4 hours) are predicated on an elimination half-life of 20–40 minutes, requiring full elimination before subsequent doses[3,4]. This approach yields suboptimal cervical ripening (failure rates 15–20%) and high uterine hyperstimulation risk (~10%)[4,5] in clinical practice. To bridge this gap, we developed a population pharmacokinetic (PopPK) model using prospective cohort data to optimize oral misoprostol dosing regimens for late pregnancy.

Materials and methods

Prospective cohort of term-pregnant women (37–41 weeks) receiving oral misoprostol for cervical ripening enrolled. Serial plasma samples collected per

standardized protocols, quantified via validated HPLC-MS/MS (LLOQ: 2.5 pg/mL). A PopPK model developed using NONMEM® and R. After model validation, Bayesian estimation was used to simulate guideline dosing to characterize pharmacokinetics and optimize dosing regimens.

Results

This study enrolled 87 term-pregnant women (228 plasma samples) for oral misoprostol pharmacokinetics. Contrary to literature-reported first-order absorption[6], the final PopPK model incorporated lagged absorption (T_{lag}), parallel zero- and first-order kinetics, one-compartment distribution, and first-order elimination. Nonlinear absorption was hypothesized to be attributed to food intake in real-world pregnancy. Model validation confirmed that current regimens (25 μg q2h or 50 μg q4h) cause incomplete elimination and accumulation due to nonlinear kinetics. Simulations identified C_{max} post-50 μg dose as a safety threshold. Optimized regimens (total ≤200 μg/day) reduced cervical ripening duration (9.5 vs. 12 hours) without safety compromise.

Discussion / Conclusion

This study establishes the first PopPK model for oral misoprostol in late pregnancy cervical ripening. Real-world data revealed nonlinear absorption kinetics, which underpin the drug accumulation observed with current guideline-recommended regimens, thereby increasing safety risks. Model-informed optimization yielded regimens that improved safety while significantly reducing cervical ripening duration.

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Keywords

Misoprostol, Nonlinear Absorption, Population Pharmacokinietic Model, Pregnancy, Optimal Dosing RegimenKeywords: Misoprostol, Nonlinear Absorption, Population Pharmacokinietic Model, Pregnancy, Optimal Dosing Regimen

00723
Mechanistic PBPK Modeling of Sirolimus Reveals the Importance of Red Blood Cell Partitioning

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Sirolimus is an immunosuppressant with high pharmacokinetic (PK) variability and a narrow therapeutic window, making therapeutic drug monitoring essential. A major challenge in sirolimus PK is extensive partitioning into red blood cells (RBC), resulting in whole-blood concentrations being significantly higher than plasma concentrations. Because tissue distribution is driven by drug concentrations in plasma, RBC partitioning can complicate the interpretation of sirolimus distribution kinetics. Conventional physiologically based pharmacokinetic (PBPK) models often do not explicitly distinguish plasma and RBC compartments, which may lead to inaccurate predictions of sirolimus concentration–time profiles. This study aimed to develop a mechanistic PBPK model that explicitly incorporates RBC partitioning to improve the characterization of sirolimus PK.

Materials and methods

A PBPK model was developed using mrgsolve. Physiological and physicochemical parameters were obtained from literature. Parameters were optimized using reported PK profiles from eleven studies of oral sirolimus solution in adults. Blood compartment was partitioned into plasma and RBC compartments based on hematocrit, and tissue distribution was assumed to occur from the plasma compartment. Model performance was assessed using predicted-to-observed (P/O) ratios for Cmax and AUC, and Vss/F was compared with reported values.

Results

A model consisting solely of conventional organ compartments failed to adequately reproduce the observed sirolimus concentration–time profile, particularly during the distribution phase. Incorporation of an RBC compartment with optimized blood cell partitioning markedly improved model performance. In the model with RBC compartment, P/O ratios for AUC and Cmax were within two-fold, and Vss/F was consistent with reported values (10–30 L/kg).

Discussion / Conclusion

A mechanistic PBPK model incorporating RBC partitioning successfully described the sirolimus PK profile. These findings suggest the importance of mechanistically accounting for RBC partitioning in PBPK modeling for drugs with high affinity for RBC.

00734
Population pharmacokinetics and PK/PD target attainment of intravenous amoxicillin–clavulanate in adults aged ≥75 years

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Amoxicillin-clavulanate is one of the most prescribed ß-lactam antibiotics for adults aged ≥75 years. Age-related (patho)physiological changes may alter its pharmacokinetics (PK), leading to variability in drug exposure. This study aimed to characterise the PK of intravenous amoxicillin-clavulanate in adults aged ≥75 years, identify predictors of interindividual variability, and evaluate PK/PD target attainment for current and alternative dosing regimens.

Materials and methods

A prospective, observational PK study was conducted in geriatric inpatients (≥75 years) receiving intravenous amoxicillin-clavulanate (1g/0.2g every 6h as a 30-minute infusion, with adjustments based on renal function). Blood samples were collected after the first dose and at presumed steady-state. Total plasma concentrations of amoxicillin and clavulanate were quantified using UPLC-MS/MS. Population PK modelling was performed using Monolix. Monte Carlo simulations were conducted to evaluate the probability of PK/PD target attainment (PTA) for current and alternative dosing regimens. The PK/PD target was 50% *f*T>MIC (8 mg/L).

Results

Sixty patients with a median age of 86 years (IQR 83-90) were included. The data were best described by a two-compartment PK model with allometric weight scaling. In addition, $eGFR_{CKD\text{-}EPI\ cystatin\ C}$ was a significant covariate for amoxicillin clearance; the Cumulative Illness Rating Scale-Geriatric score was a significant covariate for the central volume of distribution of clavulanate. The typical clearance values were 8.04L/h/70kg for amoxicillin and 7.79L/h/70kg for clavulanate. At a MIC of 8mg/L, the study dose achieved PTA rates of 80%, 53%, and 34% in patients with eGFR ranges of 30-60mL/min/1.73m², 60-90mL/min/1.73m², and 90-120mL/min/1.73m², respectively. Simulation with increased dosing frequency to six administrations per day, with a prolonged infusion of 120-minutes, increased PTA rates to 98%, 92%, and 83%, respectively.

Discussion / Conclusion

Standard dosing regimens may result in suboptimal PTA in older adults. Model-based simulations suggest that more frequent dosing combined with prolonged infusion may improve PTA in this population.

Keywords

Population pharmacokinetics; amoxicillin-clavulanate; older adults

00743
Metformin Alters First-Line Anti-TB Drug Pharmacokinetics in Tuberculosis Patients With and Without Diabetes: A Prospective Cohort Study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Pharmacokinetic (PK) variability contributes to poor tuberculosis (TB) treatment outcomes, particularly among patients with type-2 diabetes mellitus (DM). Interactions between metformin and first-line anti-TB drugs (isoniazid, rifampicin, pyrazinamide, ethambutol; HRZE) remain poorly characterized despite rising TB-DM comorbidity. We evaluated metformin's impact on HRZE pharmacokinetics during intensive-phase treatment.

Materials and methods

Prospective cohort study of 95 adults with drug-susceptible pulmonary TB at intensive-phase treatment completion: TB-Only (n=49), TB-DM on metformin (TB-DM_t; n=36), TB-DM off metformin (TB-DM_{nt}; n=10). Serum concentrations of HRZE were analyzed by validated LC-MS/MS methods. Geometric median [interquartile range] area under the concentration time curve (AUC_{0-24}), and therapeutic target attainment (isoniazid ≥8 mg·h/L; pyrazinamide ≥363 mg·h/L; rifampicin ≥25 mg·h/L[1,2] were determined using validated population pharmacokinetic models.[3,4] Acetylator status was determined by isoniazid metabolic ratio at 3h post-dose.

Results

TB-DM_t showed significantly lower isoniazid AUC_{0-24} (10.0 [8.3–11.7] vs 12.7 [10.7–14.6] mg·h/L TB-Only; p=0.025) and TB-DM_{nt} (12.1 [8.4–15.9] mg·h/L; p=0.05 vs TB-DM_t). Pyrazinamide trended lower in TB-DM_t (310 [272–348] vs 356 [328–384] mg·h/L TB-Only; p=0.054). Therapeutic AUC_{0-24} target attainment was: isoniazid TB-Only 61% (30/49), TB-DM_t 33% (12/36), TB-DM_{nt} 60% (6/10); pyrazinamide TB-Only 65% (32/49), TB-DM_t 44% (16/36), TB-DM_{nt} 50% (5/10); rifampicin TB-Only 80% (39/49), TB-DM_t 72% (26/36), TB-DM_{nt} 70% (7/10). Fast/intermediate acetylators predominated (91%) across cohorts, and status did not differ significantly.

Discussion / Conclusion

Possible metformin co-administration reduces isoniazid exposure and potentially pyrazinamide levels in TB-diabetes patients, compromising therapeutic targets and highlighting urgent need for PK-guided dosing adjustments.

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Keywords

Tuberculosis; diabetes mellitus; metformin; pharmacokinetics; drug interactions; anti-tuberculous drugs-HRZE

00745
Beyond Population Pharmacokinetics: Machine Learning Classifiers for Early Detection of Subtherapeutic Cabotegravir Exposure in HIV-Infected Patients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Long-acting cabotegravir (CAB-LA) combined with rilpivirine is used for HIV treatment. Subtherapeutic drug exposure at Month-1 and Month-3 has been associated with virologic failure. Published population pharmacokinetic (PopPK) models have shown variable performances in predicting subtherapeutic exposure.[1–3] This study aimed to develop machine learning (ML) classifiers and compare their performances with a priori PopPK predictions for identifying subtherapeutic CAB-LA exposure at Month-1 and Month-3.

Materials and methods

CAB-LA plasma concentrations measured at Month-1 and Month-3 (n=611; n=453) were included. Exposure was classified into three levels (<664, 664–1120, >1120 ng/mL).[4,5] Data were split into training (80%) and test (20%) sets using equilibrated stratified sampling. Five ML algorithms (LASSO/ElasticNet, random forest, XGBoost, SVM, MLP) were trained independently at each timepoint using routinely available clinical covariates (weight, BMI, sex, smoking status, age) and virological history (nadir CD4, treatment and infection duration).[6] Hyperparameters were optimized using random grid search (10-fold cross-validation). Class imbalance was addressed through resampling strategies combining majority downsampling and synthetic minority oversampling (SMOTE). Performance was assessed using ROC-AUC and class-specific metrics (Sens-1: sensitivity for <664 ng/mL; Spec-3: specificity for >1120 ng/mL).

Results

Both PopPK models failed to identify subtherapeutic exposure at Month-1 and Month-3 (Sens-1=0.00, Spec-3≤0.15 at Month-1 and Spec-3≤0.40 at Month-3), despite an apparently adequate overall accuracy (0.76), reflecting class imbalance rather than true predictive performance. Classifiers outperformed PopPK models at both timepoints, albeit with moderate absolute performance. At Month-1, the best model achieved ROC-AUC=0.62, Sens-1=0.38, Spec-3=0.54. At Month-3, ROC-AUC=0.52, Sens-1=0.29, Spec-3=0.64.

Discussion / Conclusion

Despite the inherent challenge of predicting drug exposure from baseline covariates alone, ML classifiers consistently outperformed PopPK models in detecting subtherapeutic CAB-LA exposure. These findings support their potential as early

triage tools to prioritize monitoring in at-risk patients, complementary to therapeutic drug monitoring rather than a substitute for it.

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Keywords

HIV, Cabotegravir Long-acting therapy, Therapeutic Drug Monitoring, Machine Learning

00750
The use of artificial nonparametric pharmacokinetic quasi-models for managing intravenous piperacillin therapy in critically ill adults with unstable physiology

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Critically ill patients unreliably attain pharmacokinetic–pharmacodynamic (PK–PD) targets for piperacillin/tazobactam. Standard model-informed precision dosing assumes parameter stability and typically fails when patients have rapidly changing physiology. The interacting multiple modeling (IMM) algorithm in the BestDose software addresses these cases by tracking unexpected shifts in PK, different from random interoccasion variability, but its performance depends on the number of support points.

Materials and methods

We compared the performance of a pop-PK model with 11 support points from real subjects to three artificially constructed “quasi-models”, each containing 399 randomly generated support points that densely covered the entire parameter space, each with equal prior probability. The study population comprised 15 critically ill adults with 18-30 samples per patient and a total of 235 piperacillin/tazobactam doses over 3-5 days. Models were two-compartment with creatinine clearance linked to elimination. Bayesian maximum a posteriori estimates obtained without or with

IMM (probabilities of parameter change: 0.1%, 1.0%, or 10%) were compared. We calculated the 100% time unbound drug concentrations (estimated as 70% of the total concentrations measured) exceeded the MIC (100%fT>MIC) using the EUCAST epidemiological cut-off for Pseudomonas (16 mg/L).

Results

IMM reduced the median of the mean squared errors from 997 (no IMM) to 2.62, 2.09, and 10.9 (0.1%, 1.0%, and 10% probabilities of change, respectively). The performance of the Pop-PK model and the artificial quasi-models was comparable under all conditions. By considering concentrations estimated by the best-performing model after each dose, continuous PK–PD target attainment was achieved in 46.7%, whereas it lasted for 1 day or less in 26.7% of patients.

Discussion / Conclusion

Nonparametric quasi-models offer an alternative to Pop-PK models with a limited number of support points when IMM is needed, including the verification of the robustness of parameter estimates and the evaluation of antimicrobial PK-PD target attainment.

Keywords

Nonparametric population pharmacokinetic modeling; beta-lactam; model-informed precision dosing, interacting multiple modeling

TDM in Oncology

00011
Retrospective and Prospective Pilot Study Looking at Clinical Utility of Pharmacogenomics and Therapeutic Drug Monitoring (TDM) of Antineoplastic Agents Dabrafenib and/or Trametinib.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Targeted antineoplastic therapy for melanoma has led to increased response rates/survival, but with large pharmacokinetic variability many patients experience side effects. The purpose of this study was to determine if therapeutic drug monitoring (TDM) of dabrafenib or trametinib along with CYP3A4/CYP3A5 and CYP2C8 genotyping would correlate with effectiveness and/or toxicity in melanoma patients.

Materials and methods

Seven prospective adult patients with metastatic BRAF-mutant melanoma and fifty-five retrospective patients (222 unique EDTA plasma samples) treated with dabrafenib or trametinib were included. Plasma concentrations of dabrafenib, hydroxy dabrafenib, and trametinib were quantified using LC-MS/MS. Genotyping of *CYP3A4, CYP3A5* and *CYP2C8* was performed using a polymerase chain reaction (PCR)-based 5'-nuclease assays or Sanger sequencing. Toxicity (e.g. pyrexia, liver dysfunction) was determined by chart review while effectiveness was assessed using imaging studies and Response Evaluation Criteria in Solid Tumors (RECIST). Generalized linear mixed-effects models were used, with a Gamma distribution for dabrafenib:hydroxy dabrafenib ratio and logistic models for toxicity and effectiveness; random intercepts were included except for response due to limited observations.

Results

With limited variants, genotyping-ratio associations weren't statistically significant. However, the *CYP3A4* genotype *1/*22 was associated with a 2.16-fold higher dabrafenib:hydroxy dabrafenib ratio compared to the reference (normal metabolizer; *1/*1) (95% CI: 0.88, 5.31; p = 0.09). Furthermore, the *CYP2C8* genotype 1/4 was associated with a 1.17-fold higher ratio compared to the reference (95% CI: 0.47, 2.92; p = 0.74). Toxicity was significantly associated with higher concentrations of dabrafenib and hydroxy dabrafenib (OR=5.84, 95% CI: 1.45, 23.5; p=0.01; and OR=9.22, 95% CI: 2.00, 42.5; p = 0.004, respectively). No statistically significant associations were observed between effectiveness using imaging and RECIST calculations with TDM trough levels.

Discussion / Conclusion

Additional studies are warranted to characterize the effectiveness of TDM and pharmacogenomics for dabrafenib and trametinib, but preliminary TDM results of dabrafenib and its metabolite are encouraging.

Keywords

Dabrafenib, hydroxy dabrafenib, trametinib, melanoma, TDM, pharmacogenomics

00018
Establishment of Therapeutic Drug Monitoring Methods for Fruquintinib and Its Clinical Application

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Colorectal cancer (CRC) ranks as the 3rd most common malignancy globally and remains a leading cause of cancer-related mortality. The introduction of tyrosine kinase inhibitors (TKIs) has significantly improved patient outcomes in CRC management. Fruquintinib, a domestically developed highly selective inhibitor of tumor angiogenesis, has demonstrated survival benefits in third-line and beyond treatment of metastatic CRC (mCRC).

Despite its clinical efficacy, substantial inter-individual variability in drug disposition—including absorption, metabolism, and elimination—results in heterogeneous therapeutic responses to standard dosing regimens. Additionally, drug-drug interactions in combination therapy may compromise treatment efficacy and increase adverse event risks. These pharmacokinetic and pharmacodynamic variations underscore the critical need for therapeutic drug monitoring (TDM).

This study establishes a high-performance liquid chromatography (HPLC) method for TDM of fruquintinib in colorectal cancer patients to support individualized dosing.

Materials and methods

An HPLC method was developed using a Welch Ultimate XB-C18 column (4.6×150 mm, 5 μm) at 35°C with UV detection at 240 nm. The mobile phase consisted of

acetonitrile and 10 mmol/L potassium dihydrogen phosphate (pH 3.15) at a ratio of 40:60 (v/v) with a flow rate of 1.0 mL/min. Apatinib was used as the internal standard. Plasma samples (200 μL) were extracted with ethyl acetate, evaporated under nitrogen, and reconstituted with mobile phase before analysis.

Results

The method demonstrated satisfactory linearity over the concentration range of 15.63-500.0 ng/mL (r=0.9999). Intra-day and inter-day precision (RSD) both less than 7%, with recovery rates ranging 95% ~110%. Extraction recovery exceeded 97% at all concentration levels. Stability valid under freeze-thaw cycles, room temperature storage (6 hours), and autosampler storage (24 hours).

Discussion / Conclusion

This validated HPLC method offers high specificity, simplicity, and cost-effectiveness compared to LC-MS/MS approaches. It is suitable for routine TDM of fruquintinib in clinical oncology practice, enabling individualized medication management and optimization of therapeutic outcomes in colorectal cancer patients.

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Keywords

Fruquintinib；Therapeutic drug monitoring(TDM)；HPLC；Individualized medication

00026
Population pharmacokinetics supports pembrolizumab de-escalation while meeting target exposure in advanced non-small cell lung cancer

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Pembrolizumab has transformed outcomes in advanced non-small cell lung cancer (NSCLC)[1], yet exposure–response plateaus suggest a potential for lower/less-frequent dosing[2,3]. We used population pharmacokinetic (popPK) modelling and simulation to assess whether alternative regimens maintain putative minimum effective concentrations (MECs).

Materials and methods

We performed a prospective, observational study in patients with NSCLC receiving standard pembrolizumab therapy. Serum concentrations, dosing and clinical data were used to develop a popPK model (NONMEM 7.5). The final model was used to

simulate 1,000 virtual patients under standard (200 mg Q3W; 400 mg Q6W) and alternative regimens (100 mg Q3W; 200 mg Q6W; 400 mg Q9W). Target attainment was investigated for MECs 1.5 µg/mL and 15 µg/mL after the first dose and at steady state[4,5].

Results

Twenty-eight patients contributed 91 concentrations. Trough concentrations (n=46) had median and range of 35.9 (14.3–80.0) µg/mL, with one concentration <15 µg/mL. Most patients received 200 mg Q3W (n=20).

A one-compartment model with time-dependent clearance (sigmoidal decrease) best described the data. Initial clearance was 0.187 L/day (4% RSE) and decreased ~60% to 0.072 L/day by ~7 months. Interindividual variability was estimated on volume of distribution (V) and IMAX, and allometric scaling was included on CL and V.

In simulations, fifth-percentile minimum concentrations (95% of concentrations above) were 6.5 µg/mL (100 mg Q3W), 2.3 µg/mL (200 mg Q6W) and 1.0 µg/mL (400 mg Q9W) at first dose, and 14.0 µg/mL, 5.9 µg/mL, and 3.1 µg/mL, respectively, at steady state.

Discussion / Conclusion

We identified two dose-de-escalation/extended interval regimens of pembrolizumab (100 mg Q3W, 200 mg Q6W) that meet the 1.5 µg/mL MEC. Although 400 mg Q9W could be sufficient as a maintenance treatment, more frequent infusions are needed during early treatment. Our findings support prospective evaluation and underscore the need for consensus on clinically relevant exposure targets and the role of therapeutic drug monitoring.

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Keywords

Pembrolizumab, non-small cell lung cancer, population pharmacokinetics, pharmacometrics, extended-interval dosing

00037
Simultaneous Determination of Venetoclax and Posaconazole in Human Plasma by UPLC-MS/MS: Application to Therapeutic Drug Monitoring in Acute Myeloid Leukemia Patients

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Acute myeloid leukemia (AML) is the most common acute leukemia in adults and is characterized by pronounced biological heterogeneity and poor clinical outcomes, especially in elderly patients. Venetoclax, a selective inhibitor of B-cell lymphoma 2 (BCL-2), has improved clinical outcomes by inducing apoptosis in leukemia stem cells. BCL-2 overexpression contributes to AML progression by inhibiting mitochondrial-mediated apoptosis and maintaining leukemia stem cells in a quiescent state. However, posaconazole strongly inhibits CYP3A4, markedly increasing venetoclax exposure and the risk of toxicity. Therapeutic drug monitoring (TDM) is therefore important, yet a validated method for simultaneous quantification of both drugs in human plasma is still lacking.

Materials and methods

This study developed and validated a rapid and sensitive ultra-performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS) method for the simultaneous quantification of venetoclax and posaconazole in human plasma.

Plasma samples were pretreated using acetonitrile precipitation. The chromatographic separation was achieved using an Acquity BEH C18 column with gradient elution. The mobile phase consisted of 0.1% formic acid in water and acetonitrile, with a flow rate of 0.4 mL/min.

Results

The method demonstrated good sensitivity and linearity within the concentration ranges of 10–15,000 ng/mL for venetoclax and 10–10,000 ng/mL for posaconazole, respectively. Additionally, the method showed acceptable selectivity, intra-day precision, inter-day precision, accuracy, matrix effects, extraction recovery, and stability under various conditions. The trough concentrations of venetoclax were markedly elevated in patients receiving concomitant posaconazole compared to those treated with venetoclax alone, consistent with the known CYP3A4 inhibitory effect of posaconazole.

Discussion / Conclusion

A rapid and simple method was established and successfully applied to the simultaneous determination of the concentrations of venetoclax and posaconazole in AML patients, providing a basis for TDM and clinical pharmacokinetic analysis of these drugs in AML patients.

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Keywords

invasive fungal disease, acute myeloid leukemia, therapeutic drug monitoring, UPLC-MS/MS

00038
Pharmacokinetics of Alectinib and Active Metabolite M4 Following Simple Suspension in Pediatrics.

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

In pediatric patients, swallowing alectinib capsules can be difficult, necessitating administration using the simple suspension method (SSM) either as an oral suspension or via a nasogastric tube. No published pediatric clinical pharmacokinetic data comparing warm-water–based SSM with conventional administration are available. We therefore compared the pharmacokinetics (PK) of alectinib and its major active metabolite (M4) between conventional administration and warm-water–based SSM.

Materials and methods

This exploratory non-crossover, parallel-cohort comparison used PK data from two studies in patients (≥15 to <25 kg) receiving 300 mg/day twice daily (150 mg per dose). Intensive sampling followed a single 150 mg dose (Cycle 0): predose and 1, 4,

6, 10, 24, 48, and 72 h. SSM was prepared by suspending capsule contents in warm water and administered orally or via a nasogastric tube under protocol-specified conditions. Plasma alectinib and M4 were quantified by LC–MS/MS; non-compartmental AUC_last and Cmax were log-transformed. GMRs (SSM/conventional) were calculated as exp(Δmean) with Welch's t-based 90% CIs.

Results

Eight patients were included (conventional n=5; SSM n=3); In the conventional group, all patients had neuroblastoma (n=5), with a median age of 7 years (range, 4–7) and median body weight of 15.4 kg (15.2–22.8). In the SSM group, diagnoses were soft tissue sarcoma (n=1) and CNS glial tumors (n=2), with a median age of 4 years (3–4) and median body weight of 15.6 kg (15.4–16.6). For alectinib, GMRs were 1.26 (90% CI 0.37–4.25) for AUC_last and 1.45 (0.73–2.87) for Cmax. For M4, GMRs were 0.95 (0.42–2.15) for AUC_last and 0.95 (0.46–1.98) for Cmax.

Discussion / Conclusion

In this small exploratory pediatric analysis, single-dose exposure to alectinib and M4 with SSM was broadly similar to conventional administration, with wide CIs reflecting limited sample size.

Keywords

alectinib, pediatric patients, simple suspension method

00041
Lenvatinib Exposure Governs Therapeutic Response in HCC via Lipid Metabolic Reprogramming and Spatial Remodeling of the Immune Microenvironment

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Lenvatinib (LEN) is a standard first-line therapy for unresectable hepatocellular carcinoma (HCC), yet therapeutic outcomes are compromised by pharmacokinetic variability and resistance. The biological mechanisms linking sub-therapeutic exposure to metabolic and immune adaptations remain elusive.

Materials and methods

We conducted a prospective multi-omics study involving 103 HCC patients. Plasma drug concentrations were correlated with clinical outcomes. Resistance mechanisms were interrogated using untargeted plasma metabolomics, in vitro cell validation, exosomal miRNA sequencing, multiplex immunohistochemistry (mIHC), and single-cell RNA sequencing.

Results

We suggested 26.5 ng/mL as the critical plasma trough concentration threshold; patients maintaining levels above this cutoff achieved significantly superior progression-free survival (11.0 vs. 6.0 months, P=0.004). Metabolomically, sub-

therapeutic exposure was associated with systemic lipid metabolic reprogramming, characterized by acylcarnitine accumulation. This was mechanistically validated in vitro, where LEN treatment in Hep3B cells directly altered unsaturated fatty acid and CoA biosynthesis pathways. In the tumor microenvironment, resistance manifested as a "hot but suppressed" phenotype. Spatial analysis revealed that CD163+ M2-like macrophages were physically closer to CD8+ T cells in tumor tissues (<40 μm), forming an immunosuppressive niche. scRNA-seq further identified the CXCL signaling pathway as a key mediator recruiting exhausted T cells into this trap.

Discussion / Conclusion

Optimal LEN efficacy relies on maintaining plasma concentrations >26.5 ng/mL. Sub-therapeutic exposure drives resistance through specific lipid metabolic reprogramming and macrophage-mediated spatial exclusion of T cells. These findings advocate for therapeutic drug monitoring and combinatorial strategies targeting metabolic-immune axes.

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Keywords

Hepatocellular carcinoma, lenvatinib, therapeutic drug monitoring, tumor microenvironment , metabolic reprogramming

00055
Simultaneous Determination of Osimertinib and Gefitinib in Lung Cancer Patients'Plasma by HPLC

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

To establish an effective and simple HPLC method for the determination of gefitinib and osimertinib in lung cancer patients'plasma.

Materials and methods

The analysis was conducted using a Waters X-bridge C18(150 mm×4．6 mm，5 μm) column with the column temperature at 30℃． The flow rate was 1 ml·min－1 and the detection wavelength was at 251 nm． The mobile phase consisted of acetonitrile and 5 mmol· L－1 potassium dihydrogen phosphate (containing 0．3% triethylamine，pH= 4．0，32∶68 V∶V)． The internal standard substance was icotinib．

Results

The linearity of gefitinib and osimertinib in plasma was good within the range of 0．062 75-2．51 μg·ml －1 and 0．063 25-2．53 μg·ml －1，respectively (r＞0．999)． The recoveries of the method were between 95% and 110% with the ＲSDs less than 11%． The extraction rates of the method were all higher than 85%． The stability tests met the relative requirements． Ten patients were treated with gefitinib and osimertinib in oncology and the plasma concentrations were

measured by this method． The results showed the mean valley concentration of osimertinib was (0．206±0．098) μg·ml －1 and the that of gefitinib was (0．571±0．206) μg·ml －1 ．

Discussion / Conclusion

A high performance liquid chromatography method for the determination of gefitinib and osimertinib in human plasma is established． The method has good speciality，and can be used to detect the blood concentrations of gefitinib and osimertinib in clinical practice to improve the individualized medication．

Keywords

Osimertinib; Gefitinib; HPLC; Therapeutic drug monitoring

00073
Development and validation of a UPLC-MS/MS method for simultaneous determination of furmonertinib and its metabolite AST5902 in human plasma

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

To develop and validate a ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method for simultaneous quantification of furmonertinib and its active metabolite AST5902 in human plasma.

Materials and methods

Plasma samples were pretreated by acetonitrile protein precipitation using osimertinib as internal standard. Chromatographic separation was achieved on an ACQUITY UPLC BEH C18 column (2.1 mm × 50 mm, 1.7 μm) maintained with a mobile phase of methanol and 5% ammonium acetate solution under gradient elution. Detection was performed on a Waters Xevo TQ-S cronos triple quadrupole mass spectrometer equipped with positive electrospray ionization in multiple reaction monitoring mode. The ion transitions were m/z 569.1→71.9 for furmonertinib, m/z 555.1→498.1 for AST5902, and m/z 500.1→71.8 for osimertinib. Quantification was performed using the internal standard method.

Results

The method demonstrated excellent linearity over the concentration range of 0.5–100 ng/mL ($r > 0.999$) for both analytes. Intra- and inter-batch precision (RSD) were within 15%, and accuracy (RE) ranged from -10.8% to 8.2%. The lower limit of quantification was 0.5 ng/mL for both compounds. Extraction recoveries were consistent and matrix effects were within acceptable limits. Furmonertinib and AST5902 showed good stability under various storage and processing conditions, including 24 h at room temperature, 30 days at -80°C, and three freeze-thaw cycles.

Discussion / Conclusion

A simple, sensitive, and reliable UPLC-MS/MS method was successfully developed and validated for simultaneous determination of furmonertinib and its major metabolite in human plasma. This method is suitable for clinical therapeutic drug monitoring and pharmacokinetic studies.

Keywords

Furmonertinib; AST5902; therapeutic drug monitoring; UPLC-MS/MS

00076
Factors Associated With Immune-Related Adverse Events and Development of a Prediction Model in Patients With Malignant Tumors

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Immune-related adverse events (irAEs) significantly impact the safety and prognosis of cancer patients receiving immune checkpoint inhibitors (ICIs). This study aimed to identify risk factors for irAEs and develop a prediction model to enable personalized risk assessment and management.

Materials and methods

We retrospectively enrolled 498 cancer patients who received ICIs at a single center from July 2020 to June 2025. Patients were divided into irAEs and non-irAEs groups. Least absolute shrinkage and selection operator (LASSO) regression was used for variable selection, followed by multivariate logistic regression to identify independent risk factors. A nomogram prediction model was constructed and evaluated using receiver operating characteristic (ROC) curve, calibration curve, decision curve analysis (DCA), and clinical impact curve (CIC). Internal validation was performed using bootstrap resampling.

Results

irAEs occurred in 289 patients (58.03%), with a median onset time of 246 days. Independent risk factors for irAEs included higher body mass index (BMI), higher nutritional risk score, history of targeted therapy, decreased platelet count, elevated AST/ALT ratio, reduced cholinesterase, decreased β2-microglobulin, reduced iron levels, and increased prealbumin. The prediction model showed good discrimination with an area under the ROC curve (AUC) of 0.680, well-fitted calibration (mean absolute error 0.027), and positive net benefit in DCA and CIC. Internal validation confirmed model stability. An interactive web tool was developed for real-time individualized risk stratification.

Discussion / Conclusion

We identified multiple clinical factors associated with irAEs risk and developed a stable predictive model with a user-friendly web tool. This may facilitate early risk identification and personalized management of irAEs in clinical practice.

Keywords

immune checkpoint inhibitors; predictive model; immune-related adverse events; risk stratification; personalized treatment

00084
Higher ibrutinib exposure leads to higher risk of withdrawal due to toxicity

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Patients with chronic lymphocytic leukemia (CLL) routinely receive ibrutinib in a flat dose of 420 mg daily. This is despite phase I trials demonstrated a flat exposure-response > 2.5 mg/kg/day (≈ 175 mg/day for a 70-kg patient), which lead the US Food and Drug Administration (FDA) to recommend post-marketing evaluation of lower doses [1]. Unnecessary high dosing may contribute to off-target effects, potentially explaining why 25% of patients withdraw from ibrutinib due to toxicity [2].

Materials and methods

We performed a post-hoc analysis of phase III ibrutinib registration trial data (PCYC-1112-CA RESONATE) from patients with relapsed/refractory CLL. Data

access was granted through the Yale University Open Data Access Platform (see data attribution statement). Per protocol, adverse events ≥ grade 3 required treatment pause, with dose reductions after the second and third occurrence. Treatment was withdrawn after the fourth occurrence or a pause exceeding 28 days.

The aim was to investigate if patients with higher ibrutinib exposure – measured as area under the curve (AUC), based on pharmacokinetic sampling at 0, 1, 2, 4, and 6 hours after the first 420 mg dose – had a higher risk of treatment withdrawal due to adverse events compared to patients with lower AUCs.

Results

Of 174 patients in total, patients with AUC above the median had a 2.53-fold higher hazard of treatment withdrawal due to adverse events compared patients below the median ($p = 0.006$). When AUC values were stratified on quantiles, this risk was primarily driven by patients in the highest exposure group (> 645 ng*hours/mL).

Discussion / Conclusion

Our findings suggest that a subset of patients receive too unnecessary high ibrutinib doses leading to withdrawals due to toxicity. Next step is to determine if the exposure-response relationship in this group necessitates high exposures to gain effect, or whether some patients could achieve adequate therapeutic effect at lower exposures.

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Mandatory data attribution statement:

“This study, carried out under YODA Project # 2022-5123, used data obtained from the Yale University Open Data Access Project, which has an agreement with JANSSEN RESEARCH & DEVELOPMENT, L.L.C.. The interpretation and reporting of research using this data are solely the responsibility of the authors and does not necessarily represent the official views of the Yale University Open Data Access

Project or JANSSEN RESEARCH & DEVELOPMENT, L.L.C..”

Keywords

therapeutic drug monitoring, toxicity, ibrutinib, chronic lymphocytic leukemia, adverse events, treatment withdrawal

00088
Acid-Induced Artifacts in DPD Phenotyping: A Source of Misleading Biomarkers

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

5-Fluorouracil (5-FU) toxicity is strongly associated with dihydropyrimidine dehydrogenase (DPD) deficiency. Indirect phenotyping using plasma uracil (U) and dihydrouracil (UH_2) concentrations is widely implemented to identify patients at risk. Previous reports have shown markedly increased U and UH_2 concentrations following protein precipitation with perchloric acid (PCA), which was attributed to incomplete disruption of plasma protein binding by organic solvents. The present study aimed to investigate the impact of sample preparation on U and UH_2 quantification and to elucidate the mechanisms underlying PCA-induced concentration increases.

Materials and methods

Multiple extraction procedures were compared, including liquid–liquid extraction, protein precipitation with acetonitrile (ACN), trichloroacetic acid (TCA), and PCA. U, UH_2, uridine, and dihydrouridine were quantified by LC–MS/MS using calibration curves prepared in bovine serum albumin. Conversion experiments were conducted using spiked BSA, water matrices, and pooled patient plasma samples. Recovery of protein-bound analytes was assessed by re-extracting protein pellets after ACN precipitation.

Results

U and UH_2 concentrations were significantly influenced by the precipitation solvent. UH_2 levels were modestly elevated with ACN ($p = 0.0125$) and significantly increased with TCA ($p < 0.001$), whereas PCA caused a marked increase in both U and UH_2 ($p < 0.001$). PCA treatment resulted in near-complete disappearance of dihydrouridine, accompanied by a dose-dependent formation of UH_2, following a linear relationship ($[UH_2] = 415.05 \times [\text{dihydrouridine}] - 9.22$). This conversion was reproducible in BSA, water, and patient plasma samples. Re-extraction of ACN protein pellets yielded negligible residual U and UH_2, indicating effective disruption of protein binding by ACN.

Discussion / Conclusion

The increase in UH_2 observed after PCA precipitation is primarily caused by acid-induced cleavage of dihydrouridine rather than enhanced recovery of protein-bound analytes. Careful selection of extraction procedures is therefore critical to ensure reliable U and UH_2 measurements and accurate clinical decision-making in precision dosing of fluoropyrimidines.

Reference(s)

van den Wildenberg SAH, Genet SAAM, Streng AS, Broeren MAC, Deenen MJ, van Dongen JLJ, Brunsveld L, Scharnhorst V, van de Kerkhof D. Partial protein binding of uracil and thymine affects accurate dihydropyrimidine dehydrogenase (DPD) phenotyping. J Pharm Biomed Anal. 2024 Oct 15;249:116381. doi: 10.1016/j.jpba.2024.116381. Epub 2024 Jul 25. PMID: 39067280.

Keywords

DPD phenotyping ; uracil ; dihydrouracil ; dihydrouridine

00142
Central nervous system exposure to imatinib in pediatric and young adult acute lymphoblastic leukemia: Pharmacokinetics and clinical implications

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Tyrosine kinase inhibitors (TKIs) have improved outcomes in Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) and are increasingly incorporated into treatment protocols of Philadelphia chromosome-like (Ph-like, ABL-class) ALL. However, central nervous system (CNS) relapse remains a significant challenge despite intrathecal chemotherapy backbone. Imatinib, a first-generation TKI, demonstrates limited CNS penetration in adults, yet data in children are sparse.

Materials and methods

This prospective, multicenter study investigated cerebrospinal fluid (CSF) and matched plasma concentrations of imatinib and its primary bioactive metabolite, N-desmethyl-imatinib, in children and young adults with Ph+ or Ph-like (ABL-class) ALL. Plasma and CSF samples were analyzed using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Linear mixed-effects models were applied to assess concentrations across compartments and over time.

Results

Between January 2023 and June 2025, 32 paired plasma and CSF samples were collected from ten patients (range 1–8 samples per patient; median 3). Overall, 78% of plasma imatinib concentrations exceeded 1,000 ng/mL, a therapeutic exposure threshold associated with improved molecular response in adult chronic myeloid leukemia. Plasma imatinib concentrations were on average 189-fold higher than in CSF (geometric mean ratio, 95% CI: 142–249, $p<0.001$), which was even more profound for N-desmethyl-imatinib (geometric mean ratio 273, 95% CI: 218–339, $p<0.001$). The highest measured CSF imatinib concentration was 63 ng/mL. During therapy, both plasma and CSF imatinib concentrations declined by an average of 0.32% per day ($p<0.001$), resulting in stable CSF-to-plasma ratio over a median follow-up of 5.7 months (range: 0–14 months).

Discussion / Conclusion

The very low CSF exposure to imatinib, despite systemic therapeutic plasma concentrations, supports the rationale for alternative TKIs with improved CNS distribution in ALL patients at risk of CNS relapse.

00149
Measuring the Unmeasurable: Tucatinib Exposure in Plasma, CSF and Brain Tumor Tissue

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Tucatinib is a highly selective HER2 tyrosine kinase inhibitor used in combination regimens for HER2-positive metastatic breast cancer, including patients with brain metastases. Although plasma pharmacokinetic data are available, clinical data on cerebrospinal fluid (CSF) exposure remain scarce, and data on brain exposure are derived exclusively from physiologically based pharmacokinetic (PBPK) modeling.

Materials and methods

We report a case with simultaneous determination of tucatinib concentrations in plasma, CSF, and brain tumor tissue in a patient treated with tucatinib 300 mgx2 for brain metastases of HER2 overexpressed breast cancer, and eligible to neurosurgery (frontal metastasectomy). Total drug concentrations were measured, normalized to tissue mass, and converted to estimated free brain concentrations using a published unbound fraction (fu,brain = 0.015), assuming 97.1% plasma protein binding.

Results

Plasma trough concentration was 169 ng/mL, within expected residual levels for standard dosing. CSF concentration was 2 ng/mL, below the reported tucatinib IC50 (3.3 ng/mL). Assuming a 3% free plasma fraction, the CSF-to-unbound plasma ratio was 0.4, consistent with prior patient data but lower than published mean values

(~0.83). In brain tumor tissue, total concentrations were 519 ng/g (deep) and 483 ng/g (superficial). These values are of the same order of magnitude as PBPK-predicted total tumor concentrations (~1040 ng/g), derived from reported free tumor concentrations and brain unbound fractions.

Despite acceptable brain delivery of tucatinib, we observed intracranial disease progression. Subsequent molecular analysis of the brain metastasis identified an HER2 copy number of 12 by NGS, along with a concomitant PIK3CA hotspot mutation, a known mechanism of resistance to anti-HER2 therapies.

Discussion / Conclusion

Despite limited CSF penetration relative to IC50, tucatinib achieved substantial accumulation in brain tumor tissue, consistent with PBPK predictions and differential tumor permeability. These findings support the clinical relevance of integrating tissue-level pharmacokinetics, when available, into precision oncology.

Reference(s)

Li J, Jiang J, Bao X, Kumar V, Alley SC, Peterson S, Lee AJ. Mechanistic Modeling of Central Nervous System Pharmacokinetics and Target Engagement of HER2 Tyrosine Kinase Inhibitors to Inform Treatment of Breast Cancer Brain Metastases. Clin Cancer Res. 2022 Aug 2;28(15):3329-3341. doi: 10.1158/1078-0432.CCR-22-0405. PMID: 35727144; PMCID: PMC9357092.

Keywords

tucatinib ; brain tissue ; TDM ; cerebral metastasis

00175
Model-Informed Precision Dosing of Palbociclib in Oncogeriatric Patients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

More than 60% of cancers occur in patients aged >65years, yet older adults remain markedly underrepresented in anticancer drug trials. Aging-related pharmacokinetic changes often lead to empirical dose adjustments in clinical practice. Therapeutic drug monitoring (TDM) enables objective assessment of drug exposure but is limited by practical sampling constraints. Pharmacokinetic modeling may address these limitations. However, models are rarely validated in geriatric populations. This study evaluated the performance of the Courlet pharmacokinetic model for palbociclib in patients aged >70 years.

Materials and methods

Model-based predictions were generated using the runITKmetrics package (Monolix) implemented in R. Patients aged >70 years who underwent TDM of palbociclib at Institut Curie between 2024 and 2026 were included (SEINIOR-PK cohort, approved by the internal ethics committee). Measurements were excluded when the time of last dose was unknown or when the sampling occurred >48 hours after the last administration. Observed concentrations were compared with individual model-predicted concentrations. Model was considered acceptable if median prediction error (MDPE) was within ±20% and median absolute prediction error (MDAPE) ≤30%.

Results

A total of 54 palbociclib concentrations (32 patients, median age 85years, range 74-99) were analyzed. Model predictive performance was acceptable, with a MDPE of -6.3% and a MDAPE of 8.3%, despite a tendency to underpredict higher observed concentrations. Daily doses were 75, 100, and 125mg in 42.6%, 27.8%, and 29.6% of patients. The median predicted trough concentration (Cmin,pred) was 58.5ng/mL. Five of Cmin,pred (9.26%) exceeded 100ng/mL; all occurred at a daily dose of 125 mg (5/16 patients at this dose); 4/5 were associated with neutropenia. The median estimated elimination half-life was 40h.

Discussion / Conclusion

The model demonstrated suitability for use in an unselected oncogeriatric population. Age-related sources of pharmacokinetic variability were associated with differences in elimination half-life (40h vs 29h), raising questions about optimal dosing in older patients and highlighting the potential value of TDM.

Keywords

palbociclib; MIPD; elderly

00215
MTX Risk Calculator: A Full Bayesian NLME-based Decision Support Tool for Individualized Risk Predictions After High-Dose Methotrexate in CNS Lymphoma

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

High-dose methotrexate (HD-MTX) is a cornerstone of central nervous system lymphoma treatment but carries substantial toxicity risk when elimination is delayed (>72 h to 0.2 µM) [1,2]. Interpreting MTX Therapeutic Drug Monitoring (TDM)

samples and biomarkers to guide rescue interventions is challenging. Pharmacokinetic nonlinear mixed-effects (PK-NLME) models can inform clinical care but rarely reach the bedside. The few existing tools [3,4] rely on maximum-a-posteriori estimation, neglecting uncertainty and risking overconfidence with sparse data. To address this limitation, we developed a full Bayesian NLME-based decision support tool that explicitly quantifies predictive uncertainty.

Materials and methods

A previously developed three-compartment PK-NLME model was translated into a full Bayesian framework using Stan and Torsten [5–7]. The Bayesian engine was embedded into an R Shiny web application via CmdStanR [8]. The app requires patient demographics, dosing history, biomarkers, and MTX TDM samples. Using these inputs, the app simulates the posterior predictive MTX plasma concentration-time profiles (4 chains, 1000 iterations). These simulations derive the expected elimination class (median time-to-0.2µM > 72h), delayed elimination risk (fraction >72h), and probability of glucarpidase indication (fraction exceeding the dose-specific 2-standard-deviation excretion threshold [9]). Computation time was benchmarked by simulating an exemplary patient (first cycle, two TDM samples) ten times.

Results

The freely accessible application (https://mtxriskcalculator.bcp.fu-berlin.de/) allows to generate individualized MTX concentration-time profiles with 95% prediction intervals and corresponding time-to-0.2µM distributions. Summary panels report the predicted elimination class, time-to-0.2µM, delayed elimination risk, and probability of glucarpidase indication. Predictive performance improved with increasing TDM data, and early uncertainty was explicitly reflected by wide, well-calibrated prediction intervals [5]. Median computation time was 26.5 seconds.

Discussion / Conclusion

The MTX Risk Calculator translates advanced pharmacometric modelling into a freely accessible bedside application, showcasing how personalised medicine could be implemented in clinical care. Ultimately, this tool aims to enable clinical pharmacists/clinicians to make better-informed decisions by explicitly quantifying predictive uncertainty.

Reference(s)

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Keywords

Oncology, Therapeutic drug monitoring, High-dose methotrexate, Central nervous system lymphoma, Nonlinear mixed-effects modelling, Population pharmacokinetics, Uncertainty Quantification, Bayesian forecasting, Pharmacometrics, Clinical decision support, Precision medicine, Glucarpidase

00234
Pharmacodynamics of Ruxolitinib in pediatric transplant recipients with graft-versus-host disease

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Graft-versus-host-disease (GvHD) is one of the major complications of stem cell transplantation with a high mortality rate. Ruxolitinib is approved for the treatment of patients aged 6 months and older with steroid-refractory GvHD. The main objective of this study was to assess the relationship between Ruxolitinib exposure and efficacy at day28 and to describe its safety.

Materials and methods

Pediatrics patients, who received Ruxolitinib for treatment-naïve or corticosteroids-refractory GvHD and had a least one area under the curve (AUC_{0-12h}) between November 2017 and November 2025, were included in this multicenter retrospective study. Demographic (age at allograft), clinical (type of graft, conditioning regimens, dosing, GvHD localisation and grade) and biological ($AUC_{0-12h,}$ trough concentrations (C_0)) data were collected. Response was defined as complete (all symptoms resolved) and as partial (improvement of at least one organ with no other progression). Relationship between Ruxolitinib and response was assessed using logistic regressions. The safety of Ruxolitinib was analysed according to the French drug reaction assement method.

Results

Sixty-six patients were enrolled (199 occasions). At day 28, 85% of patients were considered responders and 15% were non-responders. The median AUC_{0-12h} was 664 ng.h/mL IQR [415-929] and 735ng.h/mL IQR [290-1129] in the responders group and in the non-responders group. The median C_0 was 8 ng/mL IQR [<5-14] vs. 10 ng/mL [<5-33] and the median dosing was 5 mg bid [5-10] for both groups. Response rate did not significantly differ based on age at allograft (p=0.12), conditioning regimen (p=0,8) and grade (p=0.063). The AUC_{0-12h} did not significantly affect the response rate (p=0.5). Overall, 51.7% of patients presented hematotoxicity, 38,2% infections, 14,6% hepatic disorders and 4,5% renal disorders.

Discussion / Conclusion

No significant association between exposure and efficacy was shown. However, this analysis has some limitations due to modification of exposure over time. We intent to assess the pharmacodynamics of Ruxolitinib further using longitudinal statistical analysis.

Keywords

pediatrics, therapeutic drug monitoring, janus kinase inhibitors

00347
Ruxolitinib pharmacokinetics and exposure–toxicity relationship in hematologic malignancies and immune-mediated diseases: a prospective observational study

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Ruxolitinib pharmacokinetics (PK) have been described in clinical trials, but data from real-world populations remain poorly documented. We aimed to investigate ruxolitinib PK, identify factors associated with its variability, and explore exposure–response relationships in real-world practice to assess the potential role of therapeutic drug monitoring (TDM) in patients with hematologic malignancies and immune-mediated diseases.

Materials and methods

We conducted a multicenter prospective observational study in Switzerland and analyzed 221 steady-state ruxolitinib plasma concentrations from 77 adult patients. Demographic and clinical data were recorded at the time of sampling. Population pharmacokinetic (popPK) modeling was performed using MonolixSuite®. Based on the final popPK model, simulations were used to predict trough concentrations (C_{min}) and 24-hour area under the curve (AUC_{24}) for recommended dosing regimens, as a function of covariates. We conducted an exploratory pharmacokinetic/pharmacodynamic (PK/PD) analysis to assess the relationship between exposure markers and response outcomes in the overall cohort.

Results

Ruxolitinib PK was characterized by marked between-subject variability in clearance (CV: 45%). Co-administration of strong CYP3A4 inhibitors or dual CYP2C9/CYP3A4 inhibitors reduced clearance by 39%. In patients receiving 10 mg twice daily, simulations predicted that CYP inhibition increased median C_{min} and AUC_{24} by 2.9-fold and 1.7-fold, respectively. No significant exposure–efficacy relationship was identified, whereas higher exposure tended to be associated with an increased probability of toxicity in the overall cohort (C_{min} and AUC_{24}; $p \approx 0.02–0.03$).

Discussion / Conclusion

In routine clinical practice, ruxolitinib exposure shows substantial variability and is strongly influenced by CYP inhibition, which is frequently encountered. Higher exposure tended to be associated with increased toxicity risk. These findings support careful dose adjustment in patients receiving strong CYP inhibitors or with other metabolism-altering factors and suggest a potential role for TDM.

Keywords

Myeloproliferative disorder; Myelofibrosis; Graft-versus-Host disease; Ruxolitinib; JAK inhibitors; Pharmacodynamics; Pharmacokinetics; Therapeutic Drug Monitoring.

00350
Enabling model informed precision dosing of busulfan in HSCT patients: an external model evaluation

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Busulfan is frequently used in conditioning prior to allogeneic hematopoietic stem cell transplantation (allo-HSCT) and requires therapeutic drug monitoring (TDM) due to its narrow therapeutic window and high pharmacokinetic (PK) variability1–3. Model informed precision dosing (MIPD) is considered the gold standard of personalizing busulfan therapy4,5. The aim of the study was to assess the predictive performance of available population pharmacokinetic (popPK) models of busulfan in an external patient cohort and to investigate the extent to which concomitant therapy with deferasirox influences the model predictions.

Materials and methods

A total of 23 popPK models were evaluated in NONMEM® (version 7.5) using retrospectively collected PK data from adult and pediatric patients prior to allo-HSCT6–9,9–28. Adult patients were stratified according to concomitant deferasirox therapy, with a subset receiving deferasirox. Model predictive performance was assessed using *a priori* prediction of the first dosing interval and Bayesian forecasting of the second dose based on prior observations collected during TDM. Evaluation metrics included median absolute prediction error (MAPE) and median prediction error (MPE).

Results

PK data from 419 allo-HSCT patients were included in the model evaluation. The a priori predictions showed the greatest variability. Under concomitant deferasirox therapy, a systematic underprediction was observed (MPE: -95.25 to 12.67%) compared with patients without deferasirox comedication (MPE: -80.47 to 125.5%). Bayesian predictions incorporating measured busulfan concentrations from the previous dose (n= 246) were overall more accurate and precise, regardless of concomitant deferasirox therapy (with deferasirox: MPE -34.65 to 48.46%), MAPE 6.37 to 48.47%; without deferasirox; MPE -28.36 to 48.54%, MAPE 7.63 to 48.75%).

Discussion / Conclusion

Several models demonstrated acceptable model performance. *A priori* predictions were less adequate in the deferasirox co-medication subgroup; however, Bayesian forecasting minimized the impact. Further model evaluations are required for reliable MIPD implementation. In addition, a dedicated popPK model explicitly accounting for deferasirox is planned to be developed.

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Keywords

Busulfan, Deferasirox, MIPD, Population Pharmacokinetics

00353
Asciminib CSF distribution: a case report

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL) management has improved dramatically with the incorporation of tyrosine kinase inhibitors (TKI). However, 20-30% of TKI-treated patients relapse, mainly due to mutations in BCR::ABL1 tyrosine kinase domain. A recent study in patients with R/R Ph+ ALL treated with asciminib showed promising result[1], but there is little data on central nervous system (CNS) distribution of asciminib despite its development in the PH1ALL and LBC CML trials. Here, we present the case of a Ph+ ALL patient with CNS involvement for which a pharmacokinetic exploration was conducted in plasma and cerebrospinal fluid (CSF).

Materials and methods

A 52-years old male patient diagnosed with Ph+ acute myeloid leukemia in 2022, was treated in first-line with imatinib followed by a low intensity chemotherapy combined with dasatinib. He experienced a first relapse in 2023 with exclusive CNS localization and a lineage switch to Ph+ B cell precursor ALL. Intrathecal therapy was started followed by blinatumomab+asciminib. Trough plasma and CSF samples were collected at steady state (6 days after asciminib initiation) and analyzed by LC-MS/MS according to a validated and published quantification method[2].

Results

Plasma trough concentration reached 559.64 ng/mL and CSF trough concentration was 1.56 ng/mL displaying a CSF-to-plasma ratio of 0.28%. on day 6 of asciminib 40 mg BID. After 2 years of maintenance therapy including asciminib 40 mg BID, the patient remains in remission with undetectable BCR::ABL transcript.

Discussion / Conclusion

Plasma trough concentration was slightly higher than expected concentrations (265 ng/mL (CV 64%))[3]. CSF trough concentration was above usually effective concentration in vitro (IC50 BCR-ABL1 wt = 0.27 ± 0.09 ng/mL)[4]. Despite the very low CSF-to-plasma ratio, asciminib may have contribute to clinical response in CNS localization. Blood-brain barrier penetration by allosteric TKIs is of great interest, as suggested by the recent development of TGRX-6785. Further studies would be of high interest.

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00357
New Insights from the Two-Ratio Hypothesis for Therapeutic Drug Monitoring of Temozolomide

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Temozolomide (TMZ) combined with radiotherapy is the standard treatment for high-grade gliomas (HGG). TMZ metabolism yields equimolar amounts of its active species and the metabolite 5-aminoimidazole-4-carboxamide (AIC), forming the theoretical basis of the Two-Ratio Hypothesis for therapeutic drug monitoring. This study aimed to develop and validate a method for the simultaneous quantification of TMZ and AIC, providing its first analytical validation and investigating relevant clinical pharmacokinetics.

Materials and methods

We analyzed 46 plasma samples from 37 HGG patients. A UPLC-MS/MS method was developed and validated to address the polarity differences between TMZ and AIC. Sample preparation involved ethyl acetate liquid-liquid extraction for TMZ and strong cation exchange solid-phase extraction for AIC. The method was validated for linearity, precision, accuracy, recovery, and stability per guidelines.

Results

The method demonstrated wide linear ranges (TMZ: 77.66–19,415 ng/mL; AIC: 5.00–2,000 ng/mL), with precision (intra-batch RSD ≤ 11.85%, inter-batch RSD ≤ 10.23%), accuracy (relative error: TMZ -7.48% to 4.94%; AIC -5.25% to 5.26%), and recovery (97.26–102.5%). Clinical analysis revealed higher dose-normalized TMZ

concentrations during concurrent versus adjuvant therapy (7.78 *vs.* 5.39 μg/mL, $P < 0.05$). Females showed 45.9% greater TMZ exposure than males (7.57 *vs.* 5.19 μg/mL, $P < 0.05$), while AIC showed no significant sex- or treatment-related variations. A moderate positive correlation was observed between TMZ and AIC concentrations ($r_S = 0.530$, $P < 0.01$).

Discussion / Conclusion

This study established a reliable UPLC-MS/MS method for simultaneous quantification of TMZ and AIC, providing the first analytical validation of the Two-Ratio Hypothesis. The results reveal significant sex-dependent differences in TMZ pharmacokinetics, whereas AIC levels remain stable. This finding highlights the importance of considering sex for personalized dosing in TMZ therapy for HGG, offering a new rationale for optimizing neuro-oncology treatment.

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Keywords

Temozolomide; Metabolite; Therapeutic Drug Monitoring; High-grade gliomas; LC-MS/MS

00389
Toward personalized imatinib therapy in GIST: sex differences and the clinical value of Therapeutic Drug Monitoring in a real-world Italian cohort

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Substantial inter-individual variability in imatinib systemic exposure may influence both efficacy and toxicity. Based on IATDMCT recommendations, the IRCCS-CRO of Aviano offers therapeutic drug monitoring (TDM) diagnostic service of imatinib as supportive tool for treatment management. This study aims to evaluate the clinical utility of imatinib TDM in predicting response and toxicity in a mono-centric real-world cohort of 63 Italian patients with GIST treated across different clinical settings.

Materials and methods

Imatinib and its active metabolite norimatinib trough concentrations (Cmin) were quantified using a validated LC–MS/MS method. Associations between drug exposure and clinical–demographic characteristics, treatment-related toxicity, and progression-free survival (PFS) were evaluated.

Results

A total of 437 plasma samples were collected. Marked inter- and intra-patient variability in imatinib exposure was observed (43% and 31%); 67% of patients receiving 400 mg/day had Cmin below the recommended target concentration (1100 ng/mL). Female sex was significantly associated with higher imatinib exposure (median Cmin 1114 vs 786 ng/mL in males; p=0.0018). Combined age–sex analysis showed a significant difference between women and men <60 years (1041 vs 668 ng/mL; p=0.0068, Bonferroni-adjusted). A strong exposure–toxicity relationship emerged, with higher imatinib levels in toxic vs non-toxic samples (1728 vs 927 ng/mL; p<0.0001), without a direct association between sex and toxicity. No overall significant association between Cmin and PFS was observed; however, lower exposure was observed in progressing patients, reaching significance among c-KIT exon 11 mutated females (974 vs 1730 ng/mL). Progression was more frequent in markedly underexposed patients and absent in those with Cmin >1500 ng/mL, supporting a narrow therapeutic window.

Discussion / Conclusion

TDM was demonstrated to be clinically useful in predicting relevant toxicity and may help identify patients at risk of reduced efficacy. Sex significantly influences exposure, supporting personalized dosing strategies.

00399
Bioanalytical method validation of gilteritinib, midostaurin and venetoclax in serum, plasma and dried blood spots

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Gilteritinib, midostaurin and venetoclax are targeted therapies with distinct mechanisms of action in hematologic malignancies, including chronic lymphocytic leukemia, relapsed/refractory acute myeloid leukemia and other myeloproliferative disorders(1). Given their variable pharmacokinetics, potential drug-drug interactions and narrow therapeutic windows , these agents are strong candidates for therapeutic drug monitoring (TDM)(2). Conventional venous sampling may limit frequent monitoring, particularly in outpatient settings. Dried blood spots (DBS) represent a convenient, minimally invasive alternative that facilitates remote sampling, simplified logistics and improved patient compliance(3).

Materials and methods

Liquid chromatography tandem mass spectrometry (LC-MS/MS) assays were developed and analytically validated for the quantification of gilteritinib, midostaurin and venetoclax in both plasma/serum and DBS samples. Separate methods were optimized for each sample type, integrating established tyrosine kinase assay principles with DBS-specific extraction procedures. Sample preparation included purification using stable isotope-labeled internal standards, with protein precipitation applied for plasma/serum samples. Protocols were optimized to ensure an optimal

compromise between peak quality and signal intensity. Validation was conducted in accordance with bioanalytical method validation guidelines.

Results

The assays demonstrated dynamic ranges of 10-1000 µg/L for giltertinib, 30-3000 µg/L for midostaurin and 50-5000 µg/L for venetoclax, covering clinically relevant concentrations. Matrix effects, selectivity, carry-over, calibration curve and range, accuracy, precision, reinjection reproducibility and short- and long term stability all met the predefined acceptance criteria. The serum/plasma assay has already been applied, with all concentrations within the calibration ranges except those above the therapeutic range. Two Hemaxis™DB10 spotting approaches were compared, allowing more sustainable laboratory practices by reducing single-use plastic consumption.

Discussion / Conclusion

These validated assays enable reliable quantification of all three agents in both plasma/serum and DBS samples. The methods support pharmacokinetic studies and TDM strategies while offering a practical and potentially cost-effective sampling alternative. Further investigation, particularly regarding hematocrit effects for direct plasma-DBS correlation, is required before routine implementation.

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Keywords

LC-MS/MS; Dried blood spots; Tyrosine Kinase Inhibitors; Microsampling; Therapeutic Drug Monitoring

00403
The INTEGRATE Study: Integrated Pharmacogenetics, TDM and Active Pharmacovigilance as Innovative Tools for the Optimisation and Appropriateness of Drug Therapy

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

In the context of personalized medicine, a prospective multicenter clinical study (NCT06822959) was conducted at IRCCS-CRO and IRCCS-Burlo Garofolo to implement an integrated model combining pharmacogenetics (PGx), Therapeutic Drug Monitoring (TDM), and Drug–Drug Interaction (DDI) assessment in adult oncology and non-oncological pediatric care, with the aim of supporting personalized and safer treatments.

Materials and methods

Consenting patients underwent PGx analysis (DNA from blood or saliva) and periodic TDM (steady-state trough concentration (Cmin) measured by LC–MS/MS). These data were integrated with DDI assessment to generate a pharmacological consultation report.

Results

A total of 407 patients were enrolled: 245 adult oncology patients treated with 8 different TKis and 162 pediatric patients with chronic immune-mediated diseases treated with infliximab, adalimumab, methotrexate or azathioprine. PGx analyses were performed on clinically relevant genes (CYP3A4/5, ABCB1/G2, TPMT, NUDT15, etc.). Among the 306 patients evaluable for TDM, 45% showed Cmin values outside the therapeutic range. Clinically relevant toxicities (CRT) occurred in 58% of oncology and 35% of pediatric patients. Patients with high Cmin developed CRT in significantly shorter times (adjusted HR, 1.67; 95% CI, 1.01-2.58, p= 0.029 in oncology; HR not evaluable; p= 0.037 in pediatrics). Moreover, patients with in-range or high drug exposure exhibited longer time to treatment failure due to inefficacy compared with underexposed patients (HR not significant, p= 0.098 in oncology; adjusted HR, 1.52; 95% CI, 1.05-2.21, p= 0.025 in pediatrics). A survey of healthcare professionals involved in the study demonstrated high acceptability and a strong perceived clinical utility of the integrated model.

Discussion / Conclusion

This integrated pharmacological consultation model is feasible in oncological and pediatric practice and supports TDM as a predictive tool for toxicity and efficacy across 13 drugs with oncologic and pediatric indications. It represents a sustainable and transferable strategy with potential benefits for both patient outcomes and healthcare efficiency.

00468
A High-Throughput LC-MS/MS Assay for TPMT Phenotyping in Clinical TDM

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

6-Mercaptopurine (6-MP) is a cornerstone in maintenance therapy of childhood acute lymphoblastic leukemia (ALL). Its cytotoxic effect depends on intracellular formation of 6-thioguanine nucleotides (6-TGN), while thiopurine methyltransferase (TPMT) competes for substrate inactivation via S-methylation. Due to genetic polymorphism, TPMT activity exhibits a trimodal distribution, and deficient patients are at high risk of severe myelotoxicity during standard 6-MP dosing. Phenotypic TPMT testing remains clinically relevant for individualized dosing. Herein we present a rapid LC-MS/MS based TPMT phenotyping assay suitable for routine therapeutic drug monitoring.

Materials and methods

TPMT activity was determined by quantifying 6-methylmercaptopurine (6-MMP) formed in erythrocyte lysates after incubation with 6-MP and S-adenosyl-L-methionine (SAM). Detection was performed by LC-MS/MS using multiple reaction monitoring (MRM). Sample preparation was optimized using organic protein precipitation with acetonitrile, eliminating acidification steps.

Results

The final method demonstrated stable retention time and reproducible peak shape with minimal matrix interference. Total run time was 3.4 minutes per sample. During method development, previously undescribed non-enzymatic background methylation of 6-MP was observed in the absence of TPMT, showing temperature- and concentration-dependent reaction rates. Reduction of SAM concentration by

50% effectively suppressed background methylation without compromising analytical sensitivity or linearity. The assay is linear from 100–4000 nmol/l 6-MMP with no observed carry-over. The simplified protein precipitation workflow reduced sample preparation time and improved reproducibility. Stability studies demonstrated robust analyte stability under relevant pre-analytical and analytical conditions.

Discussion / Conclusion

A robust and reliable LC-MS/MS based TPMT phenotyping assay was successfully developed. Non-enzymatic methylation generated a measurable LC-MS/MS signal that could influence clinical interpretation of TPMT activity; this was effectively controlled through assay optimization. The final method provides accurate TPMT activity assessment with minimal hands-on time and high throughput, supporting individualized thiopurine dosing in pediatric ALL patients.

Keywords

TPMT, ALL, 6-Mercaptopurine, LC-MS, TDM, acute lymphoblastic leukemia

00518
Therapeutic drug monitoring of fentanyl transdermal patch in cancer patients: preliminary report of a multi-center, prospective clinical study from cancer specialized hospitals in Chinana

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Fentanyl transdermal patch (FTP) is commonly used in treatment of cancer pain. It is indicated for patients who cannot tolerate the adverse drug reactions (ADRs) of oral strong opioid receptor agonists or are unable to take oral analgesics. In clinical practice, there are significant individual variations in the efficacy and ADRs during FTP treatment. Additionally, there has been little report about plasma concentrations of fentanyl in patients treated with FTP in the real-world setting. Thus, the aim of this study was to monitor plasma concentrations of fentanyl and the relationship among concentration, efficacy and ADRs.

Materials and methods

A multi-center, prospective clinical study has been conducted since May 30th, 2025, in Cancer Hospital Chinese Academy of Medical Sciences and Beijing Chaoyang Sanhuan Cancer Hospital. Adult patients with cancer pain receiving FTP were included in the study. We measured steady-state plasma concentrations of fentanyl (determined by high-performance liquid chromatography coupled to tandem mass spectrometry), collected pain information (nature, site, visual analogue scale (VAS), breakthrough pain) and ADRs during FTP treatment.

Results

Preliminarily, 16 patients with 26 blood samples were included. The median fentanyl concentrations were1.64ng/ml (24h), 0.84 ng/ml (48h) and 0.94 ng/ml (72h). VAS improved 1.78 at 24h and 2.31 at 48h, respectively. The main ADRs during FTP treatment were constipation, pruritus, somnolence, and urinary retention.

Discussion / Conclusion

The efficacy of FTP was not satisfactory and ADRs were common in these patients. It is important to continue monitoring plasma concentrations of fentanyl to facilitate individualized, safe and effective treatment in patients with cancer pain.

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Keywords

Fentanyl transdermal patch, cancer pain, multi-center, therapeutic drug monitoring, individualized treatment

00556
Potential Medical and Economic Value of Integrating Therapeutic Drug Monitoring (TDM) into Chronic High-Cost Therapies

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

High-cost medicines become common in rare diseases, oncology, and immune-mediated disorders. Although prescription volumes remain limited, these agents account for an increase healthcare expenditure. Most are administered at fixed doses despite substantial interindividual pharmacokinetic variability and documented exposure–response relationships. With the exception of Imatinib, Vemurafenib and Infliximab [1–4], routine TDM is not recommended for targeted therapies. Consequently, drug assays are not reimbursed in most settings, limiting their use to research contexts

Materials and methods

Direct annual treatment costs in France were obtained from publicly available national drug price databases. The costs of TDM were assessed using the nomenclature of medical biology procedures (NMBP) codes "Antitumor Drugs" (excepted methotrexate) at B140, i.e., €38.40. A focused literature review identified evidence the clinical utility of concentration-guided dosing.

Results

Targeted therapies and monoclonal antibodies have annual costs ranging from €20,000 to €100,000, particularly immune checkpoint inhibitors. In some settings, treatment optimization already relies on pharmacodynamic or immunogenic markers (e.g., IGF-1 during somatropin therapy; neutralizing antibodies to β-interferon).

The cost of a routine drug assay is €19 per sample, whereas non-listed assays range from €40 to €70 in public hospitals. If TDM becomes recommended, with baseline sample at 1 month, then at 3-4 months and at 1 year, and for absence/loss of response or adverse events, 3-8 measurements per year can be expected. The maximum cost would be €500 per year, i.e., 0.5 to 2.5% of the drug cost. The costs of missed opportunities due to premature switching or of serious adverse effects are currently difficult to assess.

Discussion / Conclusion

The marked discrepancy between drug acquisition costs and monitoring costs supports integration of TDM into high-cost therapies. Exposure-guided dose optimization may improve efficacy, limit toxicity, and enhance cost-effectiveness.

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Keywords

Therapeutic drug monitoring ; targeted therapy ; cancer ; expansive drugs ; health cost ; cost-effectiveness ; adverse effect prevention ; dose optimization ; pharmaco-economy

00584
Pre-Therapeutic DPD Phenotyping in Predicting Fluoropyrimidine-Related Toxicity in Tunisian Cancer Patients

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

To limit the toxicity associated with fluoropyrimidines (5-Fluorouracil, Capecitabine), certain health authorities recommend assessing dihydropyrimidine dehydrogenase (DPD) deficiency prior to initiating fluoropyrimidine-based therapy. In this study, we investigated the impact of screening for DPD deficiency, using the dihydrouracil/uracil (UH2/U) plasma ratio, on the occurrence of treatment-related outcomes in Tunisian patients with various types of cancer.

Materials and methods

All patients with solid tumors treated with 5-fluorouracil between January 2020 and December 2024 were included in the study. They were divided into two groups: those who did not undergo DPD activity screening (non-DPD group) (N=100 patients) and those who were screened for DPD deficiency prior to treatment (DPD group) (N=100patients). All fluoropyrimidine-related toxicities, including gastrointestinal, hematological, and neurological adverse events, hand-foot syndrome, and asthenia, were assessed and classified according to grade and episode.

Results

In the DPD-screened group, all adverse events were less frequent, with significant reductions in gastrointestinal toxicity ($p = 0.005$), asthenia ($p < 0.001$), hand-foot syndrome ($p < 0.001$), and neurotoxicity ($p = 0.001$). The total number of adverse event episodes was significantly lower in the DPD group (165 vs. 375 in the non-DPD group, $p < 0.001$), with significant differences across all toxicity types. Adverse events were also less severe in the DPD group (mean severity score: 1.54 ± 0.69 vs. 1.92 ± 0.73, $p < 0.001$). Although all toxicity grades were less frequent in the DPD group, the difference was statistically significant only for grades 2 and 3 ($p = 0.03$ and $p = 0.04$, respectively).

Discussion / Conclusion

Screening for DPD activity by plasma UH2/U ratio could optimize 5-Fluorouracil-based chemotherapy and reduce the frequency, severity, and episodes of toxicity during chemotherapy cycles.

Keywords

Fluoropyrimidines; solide cancer; dihydropyrimidine dehydrogenase; UH2/U ratio; Toxicity.

00629
Limited sampling strategy of busulfan in pediatrics using machine learning

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

For therapeutic drug monitoring of busulfan in pediatrics, usually 5-6 samples are collected to calculate the AUC. An alternative approach is to use a sparse sampling technique or a limited sampling strategy to estimate the AUC with roughly 2-3 samples. Our objective is to develop a limited sampling strategy to predict busulfan AUC at steady state using ML approaches.

Materials and methods

Simulations were performed using the model by Marsit et al. In short, the model is a 1-compartment model with linear elimination. Significant covariates include age and weight for both Cl and V. The model includes an inter-occasion variability term for Cl. We simulated the time concentration profile for 1,000 virtual patients. For each virtual patient, we estimated the AUC at steady state using noncompartmental analysis, this is considered the reference AUC0-tau. Then we created several reduced data sets with different combinations of only 2-3 samples per patients. These reduced data sets were used to predict the AUC. To develop the ML models, we used the Xgboost model from the tideyverse library in R. The reduced data sets were split into training (80%) and test data sets (20%). To evaluate predictions, we calculated both relative bias and relative precision.

Results

For reduced data sets with three blood samples, lowest bias and precision was observed with samples at 0, 1 and 2 hours post end of the infusion (relative bias = 0.1%, relative precision =4.6%). For reduced data sets with two blood samples, lowest bias and precision was observed with samples at time 0 and 2 hours post end of the infusion (relative bias = 0.1%, relative precision =5.7%)

Discussion / Conclusion

The ML models showed excellent accuracy in predicting busulfan AUC at steady state. Our next step is to validate the developed ML models on clinical data sets.

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Keywords

TDM, busulfan, machine learning

00630
Toward a practical Therapeutic Drug Monitoring of capecitabine: Development of limited sampling strategy model in Tunisia

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Capecitabine (CAP), an oral prodrug of 5-fluorouracil (5-FU), exhibits inter-individual pharmacokinetic variability leading to suboptimal efficacy or severe toxicity. Although initial dosing is guided by dihydropyrimidine dehydrogenase activity, toxicity perssists, highlighting the need for therapeutic drug monitoring (TDM). While area under the curve (AUC)-guided TDM is validated for intravenous 5-FU, to date, no practical monitoring strategy is established for CAP. Our aim is to develop limited sampling strategy (LSS) models for 5-FU systemic exposure prediction in a Tunisian population receiving CAP-based chemotherapy regimens

Materials and methods

We conducted a prospective study enrolling adult cancer patients receiving CAP-based chemotherapy at the University Hospital of Monastir, Tunisia. Pharmacokinetic sampling was performed with eight blood samples collected over 12 hours. 5-FU plasma concentrations were quantified using validated high-performance liquid chromatography. Linear regression analysis was employed to develop LSS models incorporating one, two, and three time points. Model performance was evaluated using correlation coefficients (r^2), mean absolute prediction error (MAE), root mean squared prediction error (RMSE).

Results

Twelve patients were enrolled in our study, receiving CAP as monotherapy or in combination regimens. The mean age was 54.3 ±14.5 years with a gender ratio of 0.7. Colorectal cancer was the predominant diagnosis, and most patients had good performance status. A total of 92 LSS models were evaluated. The single-point C2 model showed good predictive performance (r^2 = 0.89). The two-point C0.5_C2 model demonstrated accuracy with r^2 = 0.96. The three-point C0.5_C2_ C3 model achieved r^2=0.99, with MAE of 6.60% and RMSE of 9.40%.

Discussion / Conclusion

This study establishes the first LSS models for monitoring CAP administration in a North African population. The C0.5_C2 and the C0.5_C2_C3 models offer optimal clinical feasibility with excellent predictive accuracy, enabling practical implementation of TDM in resource-constrained settings. These models provide evidence-based strategies for personalizing fluoropyrimidine dosing and optimizing cancer treatment outcomes.

Keywords

Capecitabine, 5-flurouracil, Pharmacokinetic, Area under the curve (AUC), Limited sampling strategy (LSS), Therapeutic Drug Monitoring (TDM)

00641
DPYD Genotype-Guided Dose Reduction Alone Is Insufficient for Exposure Optimization: Real-World Evidence Supporting Systematic 5-FU TDM

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Pre-treatment DPYD genotyping is widely implemented to reduce severe fluoropyrimidine toxicity. However, genotype-guided dose reductions may compromise therapeutic exposure if not followed by systematic therapeutic drug monitoring (TDM). We evaluated large-scale implementation of DPYD testing and its impact on 5-FU exposure in Region Stockholm.

Materials and methods

Between 2020 and 2024, 5,647 unique patients underwent DPYD genotyping. 5-FU TDM has been available since 2016. Among genotyped patients, 90 carriers of clinically actionable CPIC-recommended DPYD variants received 5-FU with genotype-guided starting dose reduction and had evaluable TDM data. 5-FU exposure (AUC) at treatment initiation and after dose adjustment was analyzed.

Results

Adherence to DPYD genotyping prior to fluoropyrimidine initiation exceeds 90%, whereas adherence to 5-FU TDM is approximately 30% despite recommendation.

The frequency of actionable DPYD variants was 6.6%. Among variant carriers with exposure data, 95% demonstrated subtherapeutic 5-FU exposure at treatment initiation following genotype-guided dose reduction; only ~5% achieved adequate exposure at start.

Following TDM-guided dose escalation, adequate exposure increased to approximately 50%, indicating that TDM corrected initial underexposure in nearly half of variant carriers. Substantial interindividual variability persisted across genotype groups.

Discussion / Conclusion

In this large real-world cohort, pharmacogenetic implementation successfully improved safety, yet genotype-guided dose reduction alone frequently resulted in systematic underexposure. These findings suggest that currently recommended genotype-based starting dose reductions, while appropriate for toxicity prevention, may be overly conservative from an exposure optimization perspective. Genotype-guided dosing should therefore be considered a safety-oriented starting point requiring systematic exposure-guided up-titration. Integrating DPYD genotyping with routine 5-FU TDM advances precision medicine from toxicity prevention toward true therapeutic optimization.

Reference(s)

JCO Precis Oncol 2025 Jun 6;9:e2500062. doi: 10.1200/PO-25-00062

Precision Treatment of Patients With GI Cancer Using Pre-emptive DPYD Genotyping/Phenotyping Plus Pharmacokinetic-Guided Dosing of 5-Fluorouracil

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PMCID: PMC12160085 PMID: 40479625

Keywords

DPYD pharmacogenetics

5-Fluorouracil (5-FU)

Therapeutic Drug Monitoring (TDM)

Dose individualization

Underexposure / Subtherapeutic exposure

00654
Exploration of Pharmaceutical Care Pathway for GIST Patients Based on Imatinib Pharmacokinetics

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Gastrointestinal Stromal Tumor (GIST) is a common digestive mesenchymal tumor with imatinib as first-line therapy. Clinical issues including poor medication compliance, high adverse reaction incidence, obvious pharmacokinetic/pharmacodynamic individual variability and polypharmacy seriously affect therapeutic efficacy and patients' quality of life. Therapeutic Drug Monitoring (TDM) enables personalized medication via accurate plasma drug concentration detection, improving the safety and effectiveness of antineoplastic drugs. This study constructed a TDM-based pharmaceutical care pathway for imatinib-treated GIST patients to explore a standardized and precise oncology pharmaceutical care model.

Materials and methods

163 GIST patients receiving imatinib in Affiliated Cancer Hospital of Chongqing University (Jan 2021–May 2024) were divided into non-pathway group (86 cases, 2021–2022) and pathway group (77 cases, 2023–May 2024). The 2023-constructed pathway included pharmaceutical information collection, TDM indication judgment, concentration adjustment and individualized monitoring, with specific TDM frequency protocols. Plasma concentration compliance rate, medication compliance, adverse reaction incidence and quality of life scores were compared between the two groups.

Results

The pathway group showed significantly improved indicators: concentration compliance rate (87.2%→92.2%), medication compliance (68.6%→72.2%); physical (44.6→48.0) and mental health (44.4→49.1) scores increased. Common adverse reactions (rash, edema, gastrointestinal toxicity, liver function injury, anemia etc.) all decreased in incidence.

Discussion / Conclusion

The pathway achieves precise concentration control via full-process TDM and individualized intervention, reducing abnormal concentration-induced poor efficacy and adverse reactions, and improving patients' compliance and quality of life. Its standardized design ensures operability and promotes the transformation of oncology pharmaceutical services to active monitoring, with the limitation of small sample size requiring multi-center research. In conclusion, the pathway optimizes clinical indicators and patients' quality of life, constructs a standardized oncology pharmaceutical care model with clinical promotion value, providing a reference for homogeneous and precise development of oncology pharmaceutical services and the construction of care pathways for other targeted antineoplastic drugs.

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Keywords

Imatinib; GIST; TDM; Pharmacokinetics; Pharmaceutical Care Pathway

00657
Factors influencing lenvatinib trough concentration: Sex, age, and CEA as independen predictors

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Lenvatinib (LEN) is a first-line targeted therapy for advanced unresectable hepatocellular carcinoma (HCC). However, its pharmacokinetics (PK) exhibits moderate-to-high inter-individual variability. Previous studies exploring LEN PK in HCC populations[1-4] have yielded inconsistent results, warranting further investigation.

Materials and methods

47 patients with HCC receiving LEN therapy were enrolled in this study. Steady-state trough concentrations (Cmin) were measured. Laboratory parameters including liver/kidney function tests and tumor markers, and demographic data were collected. Spearman's correlation, Mann-Whitney test, and multivariable linear regression were performed to identify independent predictors.

Results

Spearman correlation analysis showed that LEN Cmin was significantly correlated with sex (P=0.002), age (P=0.015), and CEA levels (P=0.021). The Mann-Whitney test revealed that female patients had significantly higher median Cmin [28.0 ng/mL (IQR: 23.7-38.0)] than males [18.4 ng/mL (IQR: 10.9-23.9)] (P=0.003). Multivariable linear regression confirmed sex, age, and CEA as independent predictors. The model

was statistically significant (F=12.259, P<0.001) and explained 50.5% of the variability in LEN Cmin.

Discussion / Conclusion

Sex, age, and baseline CEA are independent predictors of LEN trough concentration, collectively accounting for over 50% of its inter-individual variability. Our findings partially align with those reported by Hu et al[4]. in a Chinese HCC cohort. Notably, 23 patients with body weight ≥60 kg exhibited lower LEN concentrations (18.4 ng/mL) than those with weight <60 kg (23.5 ng/mL), possibly because 56.5% of patients in the ≥60 kg subgroup did not receive the recommended 12 mg dose due to adverse events. As a single-center exploratory study with a small sample size, our findings require prospective validation.

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Keywords

Lenvatinib; Therapeutic Drug Monitoring; Trough Concentration; Hepatocellular Carcinoma

00660
Monitoring Plasma Asparaginase Activity, Concentrations of Asparagine and Glutamine in Pediatric Patients with Acute Lymphoblastic Leukemia: Grand Round/A Case Study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Treatment of pediatric acute lymphoblastic leukemia (ALL) with chemotherapy is a prolonged and complex process, during which L-asparaginase preparations are the fundamental component of chemotherapy and used at different stages.

Materials and methods

The plasma asparaginase activities, concentrations of asparagine and glutamine, and minimal residual disease (MRD) levels of the bone marrow and cerebrospinal fluid were monitored.

Results

A three-year-old girl was admitted to our hospital for treatment of ALL. Following the first pegaspargase administration, the asparaginase activities on days 7 and 14 were both below 0.03 IU/mL, the asparagine concentration on day 7 was 33.4 μM, and the

bone marrow MRD level on day 19 of treatment was 8%. Following the second administration of pegaspargase, the asparaginase activity on day 7 was evaluated to 0.157 IU/mL, leading to a complete depletion of asparagine (<2 μM), and the bone marrow MRD value significantly declined to 0.009% on day 46 of treatment. Based on these results, we speculated the patient experienced a rare case of metabolic inactivation after the first full dose of pegaspargase, which might be attributable to the activation of macrophages within the mononuclear phagocyte system in the bone marrow during infectious states. Although the patient experienced silent inactivation of pegaspargase and Erwinia asparaginase during subsequent treatment, she has now successfully entered maintenance chemotherapy and is in stable condition.

Discussion / Conclusion

The findings suggest that metabolic inactivation exists in the clinical use of pegaspargase even following the first dose of pegaspargase. For patients with severe infections, increasing the dose guided by model-informed precision dosing should be considered. Besides, this complex yet successful case fully demonstrates the important role of asparaginase activity monitoring in clinical decisions.

Reference(s)

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Keywords

Acute lymphoblastic leukemia, asparaginase activity, metabolic inactivation, asparagine

00662
Predicting Imatinib Concentration Using Machine Learning: A Novel Approach for Personalized Dosing in Gastrointestinal Stromal Tumors

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Imatinib (IM), the first-line therapy for gastrointestinal stromal tumors (GIST), has efficacy and toxicity closely correlated with plasma trough concentration (Cmin). TDM is an optimal tool for dose modification, however, it usually cannot give an appropriate dose recommondation. This study aims to develop a machine learning (ML) model to predict IM Cmin for personalized dosing.

Materials and methods

A total of 916 IM Cmin measurements from 425 GIST patients were enrolled for analysis. Thirteen clinical variables were screened via univariate analysis and sequential forward selection, and their associations with Cmin were explored using restricted cubic splines. Ten ML models were trained and evaluated by 10-fold cross-validation, with SHAP for interpretability. External validation was conducted in 61 independent patients.

Results

The optimal CatBoost model achieved 90.22% accuracy (predictions within ±30% of measured Cmin) in the training set and 85.25% in external validation. IM dose was

identified as the most influential predictor, followed by red blood cell count, hematocrit, total bilirubin and albumin.

Discussion / Conclusion

The CatBoost model enables accurate IM Cmin prediction using routine clinical data, providing a practical tool for individualized IM dosing in GIST patients, especially in resource-limited settings

Reference(s)

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Keywords

Imatinib, Machine learning, Gastrointestinal Stromal Tumors, Personalized Dosing

00667
Evaluation of regorafenib treatment PERSOnalization based on therapeutic drug monitoring in patients with metastatic colorectal cancer (mCRC): RePERSO study.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Regorafenib (REG) has demonstrated a benefit in overall survival (OS) in mCRC patients, but treatment discontinuation are frequent. Managing inter-patient variability of REG pharmacokinetics may represent an opportunity for treatment optimization. In previous study[1], a sum of plasma concentrations of REG and its active metabolites (M2, M5) (Csum) between 2.5–5.5 mg/L at Day 15 of Cycle 1 was associated with improved OS. The RePERSO study aimed to confirm whether Csum could serve as a biomarker to individualize REG dosing and improve OS in mCRC.

Materials and methods

RePERSO was a French multicenter, open-label, single-arm phase II study (9 centers; NCT04874207). Eligible patients were adults previously treated with fluoropyrimidine-based chemotherapy plus oxaliplatin and/or irinotecan and targeted therapy. REG was initiated at 120 mg/day (3 weeks /4). Dose adjustments at cycles 2 and 3 were based on Csum, toxicity, and radiological response. The primary objective was to assess whether “optimal exposure” (Csum 2.5–5.5 mg/L at cycle 1 and/or 2) was associated with improved OS.

Results

Among 110 enrolled patients, 87 were evaluable for the primary endpoint. Median age was 65 years; 56% were male. Optimal exposure was observed in 62% of patients. Mean Csum was 3.9 ± 1.9 and 4.1 ± 2.1 mg/L at cycles 1 and 2 in the optimal exposure group, versus 6.0 ± 4.9 and 4.9 ± 4.2 mg/L in the non-optimal group. Seventy percent discontinued REG before cycle 3 due to toxicity or progression. OS did not differ between exposure groups (HR 1.06 [0.66–1.72], p=0.806). Restricted mean survival time at 21.2 months was similar between exposure groups (9 vs 9.77 months; p=0.551).

Discussion / Conclusion

REG exposure was not associated with improved survival. Interpatient variability of Csum was high. In this real-life cohort of patient, early treatment discontinuation was frequent which may limit the effect of therapeutic drug monitoring and dosage adjustments.

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Fundings : This project received financial support from Bayer and CHU de Rennes (Rennes University Hospital).

Keywords

regorafenib, therapeutic drug monitoring

00685
Understanding the Implementation Gap in Anti-Tumor TDM: A Nationwide CFIR-Guided Study of Knowledge, Attitudes, and Practice in China

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Anti-tumor agents exhibit high inter-individual pharmacokinetic variability and narrow therapeutic windows, making exposure-guided dosing clinically important. Although therapeutic drug monitoring (TDM) is increasingly advocated in oncology, its real-world implementation remains inconsistent. Evidence on multilevel determinants of anti-tumor TDM uptake in China is limited. Guided by the Consolidated Framework for Implementation Research (CFIR), this study evaluated implementation status and identified structural and behavioral determinants influencing routine adoption.

Materials and methods

A nationwide web-based cross-sectional survey was conducted between August and September 2025 among licensed pharmacists and physicians involved in anti-tumor drug management. The questionnaire included demographic variables and Knowledge–Attitude–Practice (KAP) domains (10 knowledge items, 18 attitude items, and practice items: 22 for pharmacists, 18 for physicians), mapped to CFIR domains (intervention characteristics, inner setting, characteristics of individuals, and process). Internal consistency was assessed using Cronbach's α. Correlation analyses explored KAP relationships. Multivariable logistic regression identified independent predictors of TDM practice, reported as adjusted odds ratios (aORs) with 95% confidence intervals (CIs).

Results

A total of 354 valid responses were analyzed (320 pharmacists; 34 physicians). Over 90% of participants recognized the clinical value of anti-tumor TDM; however, technical knowledge gaps persisted, particularly regarding analytical methodologies (LC–MS/MS identification rate: 17.6%–44.4%). Approximately half reported prior TDM practice (pharmacists 50.6%; physicians 47.1%), most commonly for methotrexate (72.8%). Among pharmacists, knowledge modestly correlated with attitude ($r=0.274$, $P<0.001$), and attitude correlated with practice ($r=0.308$, $P<0.001$). In multivariable analysis, absence of in-house analytical equipment (CFIR: inner setting) was independently associated with lower TDM implementation ($aOR\approx0.11$). Professional training and positive implementation beliefs were significant facilitators. Process-level deficiencies, including lack of standardized interpretation reports and closed-loop management, were frequently reported.

Discussion / Conclusion

Despite strong professional endorsement, anti-tumor TDM implementation in China remains structurally constrained. Addressing laboratory capacity, workflow standardization, and multidisciplinary integration may be essential to bridge the implementation gap and advance precision oncology practice.

Keywords

Anti-tumor therapeutic drug monitoring; Precision oncology; Implementation science; CFIR framework; KAP model

00689
Beyond the 0.1 µM Threshold: Real-World Variability in High-Dose Methotrexate Elimination under Standardized Protocols

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

High-dose methotrexate (HD-MTX) requires therapeutic drug monitoring to prevent severe toxicity related to delayed elimination. Although administered according to standardized protocols—such as PETHEMA 2018 for acute lymphoblastic leukemia/lymphoblastic lymphoma and disease-specific regimens for osteosarcoma, Burkitt lymphoma, medulloblastoma, primary CNS lymphoma and selected retinoblastoma cases—interindividual variability in methotrexate clearance persists. We aimed to characterize real-world HD-MTX elimination kinetics using a unified time scale (hours from end of infusion, HEOI) and explore the role of renal function in delayed elimination.

Materials and methods

Retrospective study including all HD-MTX serum determinations recorded between 2024 and 2025 in an institutional database (966 measurements from 86 patients). Treatment cycles were reconstructed using ≥7-day gaps between determinations. Infusion duration was 24 hours in 186 cycles (77.2%), 4 hours in 46 cycles (19.1%, mainly osteosarcoma protocols), and 3 hours in 9 cycles (3.7%, selected CNS regimens). MTX concentrations were analyzed using HEOI to harmonize sampling times. The primary endpoint was time to first MTX concentration ≤0.1 µM/L, analyzed using Kaplan–Meier methods. Apparent elimination half-life was estimated by log-

linear regression. Baseline creatinine and intra-episode changes were evaluated as markers of renal function. Delayed elimination was assessed at ≥72 and ≥96 HEOI.

Results

A total of 241 treatment cycles were identified. Median time to MTX ≤0.1 µM/L was 96 HEOI. Approximately 14% and 8% of cycles required monitoring beyond 72 and 96 HEOI, respectively. Infusion duration influenced elimination kinetics: 4-hour infusions showed longer times to reach ≤0.1 µM/L compared with 24-hour regimens, while 3-hour infusions showed intermediate patterns (limited sample size). Median apparent elimination half-life was 8.2 hours (IQR 6.4–13.0). Reduced eGFR or increases in creatinine during treatment were associated with slower MTX clearance.

Discussion / Conclusion

HD-MTX elimination shows substantial real-world variability despite standardized protocols. Infusion duration and dynamic renal function significantly influence clearance kinetics, supporting individualized therapeutic drug monitoring strategies within precision medicine frameworks.

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Keywords

High-dose methotrexate, Therapeutic drug monitoring, Pharmacokinetic variability, Delayed methotrexate elimination, Renal function, Leucovorin rescue.

00700
Bioanalytical method development and validation of a multiplex LC-MS/MS assay for simultaneous quantification of cabozantinib, dabrafenib, enzalutamide, N-desmethylenzalutamide and olaparib in serum, plasma and dried blood spots.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

In this study, we report the development and validation of a novel, sensitive and selective bioanalytical LC-MS/MS method for the simultaneous quantification of cabozantinib, dabrafenib, enzalutamide, its active metabolite N-desmethylenzalutamide and olaparib in serum/plasma and dried blood spot (DBS) samples. These targeted agents are widely used in oncology and therapeutic drug monitoring (TDM) is increasingly recognized as a valuable tool to address interindividual pharmacokinetic variability, drug-drug interactions and exposure-response relationships in clinical practice(1,2,3). This method aims to facilitate both routine TDM and pharmacokinetic profiling in clinical and research settings. Validation was performed in accordance with the current ICH M10 validation guidelines.

Materials and methods

Methods development builds upon and further optimizes previously established assays for tyrosine kinase inhibitors in serum/plasma and for compounds quantified in DBS matrices. Sample preparation involved analyte extraction, with additional protein precipitation for serum/plasma samples. Stable isotope-labeled internal standards (cabozantinib-2H4, dabrafenib-2H9, enzalutamide-2H6, N-desmethylenzalutamide-2H6 and olaparib-2H8) were added prior to purification to ensure analytical robustness.

Results

The validated dynamic ranges were: 0.050-5.00 mg/L for cabozantinib, 0.020-2.00 mg/L for dabrafenib, 0.25-25.0 mg/L for enzalutamide, 0.25-25.0 mg/L for N-desmethylenzalutamide and 0.10-10.0 mg/L for Olaparib, with mean correlation coefficients of >0.999 for both serum/plasma and DBS assays. The serum/plasma method has already been applied to the analysis of patient samples and all measured concentrations fell within the validated ranges. Matrix effects, selectivity, carry-over, calibration curve and range, accuracy, precision and stability met predefined acceptance criteria. Two Hemaxis spotting methods were compared, and potential clinical applicability was explored. The serum/plasma method has already been applied to patient samples, and all measured concentrations fell within the validated calibration ranges.

Discussion / Conclusion

These validated LC-MS/MS methods provide a reliable and efficient approach for quantifying these agents in serum/plasma and DBS samples, supporting individualized dosing strategies in patient care and clinical research.

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Keywords

LC-MS/MS; Microsampling; Therapeutic Drug Monitoring; Tyrosine Kinase Inhibitors

00710
Intra-patient Variability of Imatinib Concentration as a New Predictor of Recurrence in Patients with Gastrointestinal Stromal Tumor Receiving Adjuvant Therapy

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Imatinib Cmin has been consistently associated with clinical outcomes in patients with advanced gastrointestinal stromal tumors (GIST). However, due to substantial inter- and intra-patient PK variability, no universally validated Cmin threshold has been established for patients undergoing adjuvant imatinib therapy. In other fields, such as tacrolimus, a high intra-patient variability of immunosuppressive drugs has previously been associated with worse outcomes. Whether this also applies to therapeutic modalities in oncology is unknown. The aim of this study was to explore the relationship between imatinib intra-patient variability and clinical outcomes, providing evidence to optimize personalized therapeutic strategies.

Materials and methods

GIST patients who underwent surgical resection and regularly received adjuvant imatinib between February 2015 and January 2026 were retrospectively enrolled. All patients underwent TDM of the same dose of imatinib at least three times. Non-dose corrected estimated trough concentrations were used to calculate intra-patient variability(IPV).

Results

A total of 169 GIST patients were included, 21 patients (12.4%) experienced recurrence and metastasis of the primary disease during follow-up, and 148 patients (87.6%) did not progress during follow-up. The thresholds of IPV was set at third quartile (IPV = 23.44%). Imatinib IPV and the modified National Institutes of Health (NIH) risk stratification were independent factors for short RFS. The rate of 3-, 5-years RFS for patients with high IPV was 90.4% and 79.8%, respectively; with low IPV was 99.2% and 97.7%, respectively. Kaplan-Meier analysis demonstrated that patients with high IPV of imatinib had a statistically significant worse outcome. Kaplan-Meier analysis demonstrated no statistically significant difference in RFS between High risk and moderate risk in GIST patients .

Discussion / Conclusion

This study demonstrates that imatinib IPV is an independent prognostic factor for RFS, thereby addressing a key limitation on a single-timepoint PK metrics , which fail to capture longitudinal fluctuations in systemic drug exposure.

Keywords

Imatinib, intra-patient variability, gastrointestinal stromal tumors

00719
Phenotyping versus genotyping for the adaptation of 5-Fluorouracil therapy

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

5-Fluorouracil displays a large interpatient variability, mainly due to its metabolism through dihydropyrimidine dehydrogenase (DPD) enzyme. Thus, french regulatories require the phenotyping of DPD before initiating 5-Fluorouracil treatment to identify patient with enzymatic deficiency (uracilemia>16ng/mL) and decrease the risk of serious adverse events. Genotyping of *DPYD* is also commonly performed to predict potential DPD deficiency. However, sometimes genotyping and phenotyping display different conclusions. The objective of this study was to assess the relationship between *DPYD* genotyping and DPD phenotyping and 5-fluorouracil clearance and to determine which one is the most accurate for 5-fluorouracil dosing adaptation.

Materials and methods

We conducted a retrospective observational monocentric study in patients benefiting of at least one occurrence of therapeutic drug monitoring (TDM) of 5-fluorouracil and a DPD phenotyping between january 2020 and july 2025. *DPYD* genotyping results were collected if available. Clearance of 5-Fluorouracil (based on 5-Fluorouracil AUC) were compared between normal and deficient metabolizers following phenotype or genotype using Kruskal-Wallis and Mann-Whitney tests. Relationship between genotype and phenotype, and between 5-fluorouracil clearance and uracilemia were assessed using Fisher exact test and linear regression.

Results

Ninety-seven patients were included in the study and 40 had DPD deficiency. Fifty-four had genotype data available: 11 were heterozygous for one of the 4 variants, with 39% of phenotype/genotype mismatchs. The median 5-Fluorouracil AUC was 18.5µg.h/mL (range: 4.7-161.9), mostly underexposed, with no significant difference depending on phenotype and genotype. No significant relationship between phenotype (p=0.1) or genotype (p=0.68) and 5-fluorouracil clearance was found. No significant correlation was found between 5-fluorouracil clearance and uracilemia (R2=0.0492). No significant relationship was found between genotype and phenotype (p=0.32).

Discussion / Conclusion

Phenotyping and genotyping are both imperfect alone to predict 5-fluorouracil clearance. Mostly, patients are under-exposed due to preventive dose reduction, thus TDM of 5-Fluorouracil is highly recommended. The threshold of uracilemia>16ng/mL to define enzymatic deficiency can be discussed.

Keywords

Therapeutic drug monitoring, *DPYD* genotype, DPD phenotype, 5-Fluorouracil

TDM of Biologics

00047
A New High-Throughput, High Drug Tolerance and WHO-Standard-Traceable Assay Kit for Total Anti-Infliximab Antibodies

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The production of anti-infliximab antibodies is a key factor leading to secondary loss of response in patients with inflammatory bowel disease and rheumatoid arthritis. This Total Anti-Infliximab Antibody Assay Kit traced to the World Health Organization International Standard (NIBSC code: 22/272(The panel:19/234)). Performance evaluation demonstrated high-throughput (80 tests per hour), high sensitivity with a limit of detection (LoD) of 0.3 IU/mL, excellent anti-interference capability (with test deviations ≤ ±10% against both endogenous and exogenous interfering substances), outstanding reagent stability (≤8% deviation after 29 days onboard), and sufficient drug tolerance (up to 20 μg/mL of infliximab). The standardized design of the Total Anti-Infliximab Antibody Assay Kit provides a reliable, rapid, and comparable tool for therapeutic drug monitoring, which is expected to improve clinical decision-making and patient outcomes

Materials and methods

The assay employs a sandwich-based principle and developed by Beijing Danda Biotechnology Co., LTD.

2.2 Performance Evaluation

The LoD was determined in accordance with CLSI guideline EP17-A2.

Linearity was evaluated based on CLSI guideline EP06-ED2.

The effects of endogenous and exogenous interfering substances on the assay results were systematically assessed.

Opened-vial Stability: On-board stability of the reagent: A 29-day in-use stability evaluation was performed for the reagent.

Results

3.1 LoD and Linearity

Table 1. Linearity and Within-lab precision CV (%)

Antibody Number	Antibody characteristics	LoD (IU/mL)	Within-lab precision CV (%)	Linearity	R^2
19/234	A high-affinity, human IgG1 binding activity and neutralizing activity	0.3	≤ 6%	y = 0.9985x + 0.4916	0.9996
19/232	a high-affinity human IgG4 (stabilised mutein) with fast dissociation rate	1	≤ 7%	y = 0.9936x + 0.6621	0.9988

3.2 High Drug Tolerance

Table 2. Detection Interference Rate Based on Drug Tolerance Level

Control group (IU/mL)	ADA conc. with 5 μg/mL infliximab	Interference rate (%)	ADA conc. with 20 μg/mL infliximab	Interference rate (%)
0.00	0.00	/	0.00	/
1.03	0.98	-4.64%	0.95	-7.56%
5.05	4.87	-3.59%	4.78	-5.35%
11.03	10.57	-4.14%	9.97	-9.58%
98.92	95.20	-3.76%	95.10	-3.86%
305.23	300.10	-1.68%	285.10	-6.60%

3.3 Anti-Interference Capability

Table 3 Analytical Specificity

Substance	Test Concentration	Interference
Unconjugated Bilirubin	0.2mg/mL	2.40%
Conjugated Bilirubin	0.2mg/mL	2.27%
Albumin	60g/L	-0.23%
Triglycerides	20mg/mL	2.57%
Hemoglobin	5mg/mL	0.45%
Alkaline Phosphatase	0.1mg/mL	5.00%
Human Immunoglobulin G	10mg/mL	-9.31%
Biotin	1000ng/mL	-8.62%

3.4 Stability Evaluation

Table 4. Stability Assessment of Opened-vial Stability

Deviation	Sample concentration (IU/mL)			
	0	5	20	100
3d VS 0d	0.39%	-0.70%	-5.73%	-4.64%
7d VS 0d	2.73%	-1.64%	-5.83%	-3.23%
14d VS 0d	4.45%	2.67%	-3.55%	-1.21%
21d VS 0d	7.29%	4.99%	1.25%	-1.44%
29d VS 0d	5.64%	7.15%	1.39%	-0.50%

Discussion / Conclusion

This study successfully developed and validated a total Anti-infliximab antibody detection kit characterized by high sensitivity, high throughput, excellent drug tolerance, and traceability to the WHO International Standard.

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Keywords

Infliximab， drug tolerance，biologicals

00058
Development and Validation of a UPLC-MS/MS Detection Method of Baricitinib for Therapeutic Drug Monitoring in COVID-19 Patients

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Baricitinib is widely used as a selective Janus kinase (JAK) inhibitor for the treatment of immune-mediated inflammatory diseases in clinic. It is now successfully applied in reducing inflammation and suppressing COVID-19-associated immune dysregulation. As knowledge of the appropriate plasma level of baricitinib in COVID-19 patients is deficient, the measurement of the level of baricitinib in plasma during treatment is necessary and important. So, the aim of this study was to establish a bioanalytical method to detect the concentration of baricitinib in COVID-19 patients' plasma by ultra performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS).

Materials and methods

This study developed and validated a rapid and sensitive ultra-performance UPLC-MS/MS method for the simultaneous quantification of baricitinib in human plasma. The preparation process of the injected sample was to spike 100 μL of plasma and 10 μL of internal standard (IS, upadacitinib) working solution, then add 1:3 of acetonitrile to obtain the supernatant.

Results

The intra-day and inter-day precision and accuracy, matrix effect, recovery, and stability of the established methodology were all required. The method was established to determine the plasma levels in 22 COVID-19 patients. After taking 2 mg/day or 4 mg/day of baricitinib, the mean plasma concentrations of the patients were 15.36 ng/mL and 12.64 ng/mL, respectively.

Discussion / Conclusion

This novel UPLC-MS/MS method enables rapid and accurate determination of baricitinib concentrations in human plasma, which is suitable for the therapeutic drug monitoring (TDM) of baricitinib.

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Keywords

baricitinib; UPLC-MS/MS; drug monitoring; COVID-19

00169
Model-based Evaluation of Individualized and Cost-Saving Dosing Strategies for Pembrolizumab

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Recently the FDA approved pembrolizumab for subcutaneous (SC) administration at a fixed dose of 395 mg Q3W and 790 mg Q6W. Pembrolizumab pharmacokinetics (PK) are influenced by body weight allowing exploration of alternative body weight-based dosing regimens. Given its high cost, there is a need for optimized dosing strategies which may improve cost-effectiveness while maintaining equivalent exposure. We aimed to optimize pembrolizumab SC dosing schedules for individuals with different body weights and explored alternative dosing strategies to decrease treatment expenses.

Materials and methods

We evaluated multiple alternative SC dosing strategies resulting in equivalent exposure as the registered intravenous (IV) 2mg/kg Q3W dosing regimen (reference). First, we assessed whether extending the dosing interval could provide equivalent exposure for SC pembrolizumab irrespective of body weight. Secondly, we investigated body weight-based dosing intervals for SC pembrolizumab. Furthermore, as proof-of-concept we examined if IV administration of the 790mg SC formulation led to cost-savings and explored SC administration of the IV formulation.

Results

A 790mg Q7W SC regimen achieved equivalent exposure as the reference dosing and reduced per patient annual costs by €14,167 (-14%). The following body weight-adjusted SC regimens fulfilled the FDA criteria: SC 790mg Q8W (<55 kg), Q7W (55-85 kg) and Q6W (>85 kg). This strategy would reduce yearly cost by €14,167 (-14%; 55-85 kg) and €24,792 (-25%; <55 kg). Using the SC formulation of 790mg intravenously: Q9W can potentially save annual costs by €33,056 (-33%) while complying with FDA criteria. Using the IV formulation for 100mg SC Q1W may lead to additional savings once the pembrolizumab patent expires and generics become available.

Discussion / Conclusion

The developed weight based SC alternative dosing regimens are associated with significant cost-savings. Furthermore, as proof-of-concept we demonstrated that administering the SC formulation intravenously could further improve cost-effectiveness. After expiration of the IV patent administering the IV formulation subcutaneously could also reduce cost.

Keywords

pembrolizumab, pharmacokinetics, modeling and simulation, cost-effectiveness

00209
Population Pharmacokinetic–Pharmacodynamic Modelling of Secukinumab in Real-World Psoriasis Patients to Support Model-Informed Precision Dosing

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Secukinumab, an interleukin-17A inhibitor, is highly effective for moderate-to-severe plaque psoriasis but requires long-term administration at considerable cost. Model-informed precision dosing (MIPD) integrates population pharmacokinetic–pharmacodynamic (pop-PK/PD) models with patient-specific data to optimise treatment outcomes while minimising unnecessary drug exposure. However, a well-characterised real-world pop-PK/PD model for secukinumab is currently lacking. This study aimed to develop such a model to support evidence-based dose optimisation.

Materials and methods

Data were pooled from two prospective clinical studies, comprising 244 serum secukinumab concentrations and 262 Psoriasis Area and Severity Index (PASI) scores from 61 adult psoriasis patients. Nonlinear mixed-effects modelling was performed in R using nlmixr2 with FOCEI estimation. One- and two-compartment pharmacokinetic models were evaluated. Pharmacodynamics were described using an indirect response model with an inhibitory E_{max} function representing suppression of lesion production. Allometric scaling based on body weight was applied a priori. Model performance was evaluated using goodness-of-fit diagnostics and prediction-

corrected visual predictive checks (pcVPCs). Simulations of 100,000 virtual patients were conducted to derive target trough concentrations.

Results

A one-compartment model with first-order absorption and elimination best described the pharmacokinetics. Body weight significantly influenced clearance and volume of distribution. The pharmacodynamic model incorporated lesion turnover, with E_{max} fixed to 1 and K_{in} fixed to a literature value (0.62 day^{-1})[1]. The estimated IC_{50} was 2.53 µg/mL. Diagnostics and pcVPCs demonstrated adequate model performance. Simulations identified week-24 trough concentrations of 14.5 µg/mL and 35.5 µg/mL as associated with 90% probabilities of achieving PASI ≤2 and PASI ≤1, respectively, remaining stable through week 52.

Discussion / Conclusion

This real-world pop-PK/PD model provides clinically actionable target concentrations and represents a key step toward implementing MIPD in psoriasis care through evidence-based, individualised dose optimisation for secukinumab.

Reference(s)

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Keywords

Psoriasis, biologics, model-informed precision dosing, secukinumab, PK/PD model

00222
Fully Automated Analysis of 164 analytes in Serum / Plasma Using RECIPE® ClinMass® TDM Kit with CLAM-LC/MS/MS System

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic drug monitoring (TDM) is recommended to monitor pharmacokinetic variability, in order to implement more effective and personalized treatment and avoid toxicity.

To suit for an effective routine work the Shimadzu CLAM-2040 in front of the LC-MS/MS was used to provide an easy handling solution, with a fully automated sample preparation, a fast and high-precision analytical workflow.

Materials and methods

The RECIPE ClinMass® TDM Platform (order no. MS9000) in combination with the ClinMass® Add-on set kit for the quantification of 164 widely used analytes in human serum, 8 antimycotic, 15 antibiotic, 27 antiepileptic, 36 antidepressant, 28 neuroleptic, 35 benzodiazepines, 15 tricyclic antidepressants and mycophenolic acid, have been implemented on a Shimadzu CLAM-2040-Nexera X3 UHPLC-LCMS-8060. It achieves results on a fast and high-precision analytical workflow. Due to overlapped sample preparation, the analysis throughput leads to a complete analysis every 7min in average. To prove that the automated sample preparation leads to

reliable results a method verification procedure was evaluated according to the CLSI Guidelines EP06-A, EP15A3, EP17-A2.

Results

The trueness was determined by 4-fold analysis of QCs and the precision by 8-fold. The acceptance criteria were fixed with the deviation in % Bias of ±20% for the trueness and with CV%< 15 % (<20 % near LLoQ) for both trueness and precision.

Following dilution of the low calibrator, the linearity and the LLOQ was determined according to (%CV): < 15 %, Bias of ±15 % for the linearity and (%CV): < 20 % and Bias of ±20% for the LLOQ.

Discussion / Conclusion

The ClinMass® TDM Kit System were successfully verified on the CLAM-2040 with the analytical system LCMS-8060 from Shimadzu. All 164 analytes passed the acceptance criteria for accuracy (trueness, precision) and linearity.

Keywords

TDM, antimycotic, antibiotic, antiepileptic, antidepressant, neuroleptic, benzodiazepines, tricyclic antidepressants, mycophenolic acid

00254
Determination of Perampanel Concentration in Human Serum by High-Performance Liquid Chromatography with Internal Standard Method

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

To develop a therapeutic drug monitoring approach for perampanel in human serum, utilizing high-performance liquid chromatography with an internal standard, to facilitate safe and effective personalized dosing of perampanel.

Materials and methods

Serum samples underwent protein precipitation with acetonitrile, followed by drying with N2 and reconstitution using the mobile phase.A ChromatographHypersil ODS column (4.6 mm × 250 mm, 5 μm) was used, with promethazine serving as the internal standard. The mobile phase was a mixture of 0.05% phosphoric acid aqueous solution (pH 2.38) and acetonitrile (56:44). Detection occurred at a wavelength of 251 nm, with a flow rate of 1 $mL \cdot min^{-1}$, a column temperature of 30℃, and a 40 μL injection volume. This approach was applied to measure trough concentrations of perampanel in epileptic patients' serum.

Results

The method exhibited strong specificity for serum perampanel concentration measurements. The linear detection range for perampanel mass concentration spanned from 50 to 2500 μg·L^{-1} (r > 0.999), with a quantitation limit of 50 μg·L^{-1}. Both intra-day and inter-day precision RSD and recovery rates complied with the biological sample determination criteria outlined in the 2020 "Pharmacopoeia of the People's Republic of China" (Volume IV). Samples maintained stability under various storage conditions: at room temperature for 24 hours, at 4℃ for 7 days, at -20℃ for 30 days, and through three freeze-thaw cycles (RSD < 2.0%). The serum trough concentration of epilepsy patients treated with perampanel is 260.99±223.13 μg· L^{-1}. There was a significant difference in the serum trough concentration-to-dose ratio (C_0/D) of perampanel (PER) between the group co-administered with oxcarbazepine/carbamazepine and the group co-administered with other antiepileptic drugs (P = 0.01).

Discussion / Conclusion

This method offers ease of operation, accurate detection, high sensitivity, and stability, making it suitable for clinical monitoring of perampanel blood concentrations in epileptic patients. Co-administration with enzym-inducing antiepileptic drugs can significantly reduce plasma concentrations of PER.

Keywords

Epilepsy; Perampanel; Internal standard method; High-performance liquid chromatography

00255
Detecting immunogenicity to infliximab or adalimumab in patients using machine learning techniques

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Infliximab and adalimumab are anti-TNF biopharmaceuticals used to treat rheumatoid arthritis and inflammatory bowel disease. However, the development of anti-drug antibodies (ADAs) can significantly reduce drug efficacy [1,2]. Machine learning techniques can help identify patients at risk of developing ADAs by analyzing clinical and demographic data [3,4].

Materials and methods

This study used the data from the ABIRISK multicenter initiative investigating biopharmaceuticals immunogenicity. It included demographic, clinical and pharmacokinetic variables. Immunogenicity was assessed using an ELISA-based assay (Theradiag) and an electrochemiluminescence plateform (Meso Scale Discovery, MSD). Immunogenicity was defined as a time-varying binary variable (1 = ADA detected, 0 = otherwise). A modeling pipeline was implemented to predict patient immunogenicity using an optimized logistic regression, with class imbalance accounted for via class weighting. Feature selection using variance inflation factor mitigated multicollinearity. The best-performing pipeline was selected based on mean area under the ROC curve across validation folds. To identify key immunogenicity predictors, all subsets of up to four features were evaluated, and the subset with highest Youden index was selected. The final model, trained on the full dataset, was deployed in a web application.

Results

For infliximab, Theradiag-based models including time-varying pharmacokinetic parameters (volume of distribution and clearance) achieved strong performance, with time since last infusion further improving identification of immunised patients. For MSD assay, a model excluding pharmacokinetic variables performed comparably to one based on half-life and sex. For adalimumab, the Theradiag-based model which relied solely on clearance performed well despite a moderately high classification threshold. Adalimumab MSD-based models, including one using only adalimumab concentration, showed lower negative predictive value, suggesting some non-immunised patients may still develop anti-drug antibodies.

Discussion / Conclusion

Infliximab and adalimumab models demonstrated high predictive performance, supporting robust identification of patients at risk of developing anti-drug antibodies. The web application allows clinicians to estimate individual immunogenicity risk.

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Keywords

biotherapy, immunogenicity, machine learning, prediction.

00331
Closing the Clinical Blind Spot in Infliximab Therapy: Parallel Quantification of Free and Total Drug

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

The use of therapeutic drug monitoring (TDM) of biologics for a range of autoimmune diseases is well known to improve patient outcomes and treatment cost-effectiveness. However, limitations of commonly used methods lead to inability to measure anti-drug antibodies (ADAs) in the presence of drug, impacting clinical care and research into early ADA development. Using Infliximab (IFX) as a model we developed and validated a targeted mass spectrometry (LC-MS/MS) method to measure both free (active) and total (bound) IFX concentrations. We tested the method on IFX naïve patients post induction and patients with suspected anti-infliximab (ATI) development.

Materials and methods

Using a 96 well, plate-based, rapid, dual LC-MS/MS method, free and ADA-bound IFX were measured as a marker of previously undetected ATI development. The method is optimized for on-plate digestion and automated with robotic sample handling to enable routine adoption of IFX levels in clinical practice.

Results

We report a high-throughput workflow capable of quantifying therapeutic antibodies bound to ADAs in patient serum, applied to IFX for TDM. The free IFX assay results agreed with ELISA and expanded quantitation range (0.5–50 µg/mL). The total IFX assay quantified IFX regardless of ATI presence. IFX naïve patients showed no significant difference between free and total IFX ($p=0.08$) with results < 20% variation between free and total levels. Preliminary results of samples from patients who went on to develop ATIs show that total IFX is increased compared to free IFX at least one dose earlier than the initial detection of ATIs using conventional assays.

Discussion / Conclusion

The dual-assay enables routine quantification of biologic-ADA interactions in a cost effective, high throughput LC-MS/MS workflow. It overcomes key limitations of immunoassays and may improve detection of immunogenicity in patients receiving biologic therapy through early detection and in the presence of drug. The method is generalizable to other therapeutic antibodies affected by ADA interference.

Keywords

Therapeutic drug monitoring, Infliximab, biologics, anti-drug antibodies, anti-infliximab antibodies, LC-MS/MS, Free IFX, Total IFX, Inflammatory bowel disease

00396
Proactive therapeutic drug monitoring versus routine care with the novel biologics in psoriasis: a pragmatic, multicentric, randomised, controlled study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Psoriasis is a chronic immune-mediated inflammatory skin disease for which treatment with biologics is highly effective. In general, these drugs are prescribed according to a ‘one-dose-fits-all’ principle, which might lead to under- and overdosing, causing suboptimal response and unnecessary high drug exposure, respectively. A tool that may support rational use of biologics is therapeutic drug monitoring (TDM). TDM is the measurement of blood drug concentrations in order to individualize dosing regimens to achieve maximal clinical efficacy and minimize adverse events. The primary objective of this trial is to assess if proactive TDM of IL-17 and/or IL-23 inhibitors is non-inferior compared to standard of care (SOC) with respect to sustained disease control in patients with moderate-to-severe psoriasis.

Materials and methods

This is a pragmatic, multicentric, randomised, controlled non-inferiority trial. A total of 210 patients using secukinumab, ixekizumab or guselkumab for at least 6 months according to the standard dosing scheme, will be randomised (1:1) to TDM or SOC. In the TDM group, dosing intervals will be prolonged or shortened in a stepwise

manner. This will happen based on the blood drug concentrations of the biologic, measured every 12 weeks and in accordance with the decision tree pictured in figure 1. Disease activity and quality of life will be monitored every 12 weeks by PASI, IGA, BSA, DLQI-R and SF-36. The primary endpoint is sustained disease control, defined as an absolute PASI ≤ 2 or a delta PASI from baseline ≥ 50% during at least 80% of all 12 weekly study visits over a period of 76 weeks. Secondary outcomes include course of PASI and DLQI, serious adverse events, health related quality of life, cost-effectiveness and treatment satisfaction. Outcomes of TDM will be compared to SOC.

Results

As of December 23, 2024 110 of the planned 210 participants have been enrolled and randomized. No serious intervention-related adverse events were reported. Recruitment and follow-up are ongoing and results are expected in 2028.

Discussion / Conclusion

With this study, we aim to assess whether proactive TDM of IL-17 and IL-23 inhibiting biologics is feasible, safe and cost-effective. Proactive TDM in psoriasis patients may lead to more efficient and rational use of biologics.

Keywords

Psoriasis - Biologics - Proactive TDM - non-inferiority - cost-effectiveness

00475
Therapeutic drug monitoring of Ravulizumab in nephrology

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Ravulizumab is an expensive long-acting complement inhibitor indicated for complement-mediated atypical hemolytic uremic syndrome (aHUS). A trough concentration >175mg/L ensures complete complement blockade[1], while a mean steady-state concentration of 507mg/L was reported in phase III trials[2]. We developed an in-house ELISA and monitored serum concentrations in nephrology inpatients receiving ravulizumab (single-center prospective cohort).

Materials and methods

Plates were coated with C5 (2.6mg/L; 100µL/well) in carbonate buffer for 12h at +4°C and washed with PBS-Tween. Following steps were at room temperature. After adding phosphate buffer saline-bovine serum albumin (PBS-BSA) for 2h, plates were washed. Standards and quality controls were prepared from different batches of ULTOMIRIS (Alexion) in fetal bovine serum (standards: 0.35, 0.5, 1.25, 10, 50, 100, 200mg/L; controls: 1, 12, 45mg/L). Samples, standards, and controls were diluted

1/100 in PBS-BSA1% (samples >upper limit of quantification were further diluted) and incubated 1h. A peroxidase-conjugated anti-Fc antibody was added (1h), followed by OPD development (12min). The reaction was stopped with sulfuric acid, and absorbance read at 490/630nm.

Results

Quantification range was 0.35–60mg/L (validated up to 1/100 additional dilution). Fifty-eight samples were collected from 12 patients: 11 adults with aHUS (3 males) and one 15-year-old girl with C3 glomerulopathy. All were in remission; all previously received eculizumab, including 3 on reduced dosing; 7 had prior kidney transplantation. Mean weight was 65kg (39–80kg). All ravulizumab concentrations exceeded 175mg/L. At D14, concentrations ranged 394–2394mg/L; at D70, 383–1100mg/L. A one-compartment model estimated Vd=2.5L and CL=0.051d^{-1}. No covariate significantly influenced pharmacokinetics, likely due to limited sample size. Unlike phase III data[2], D70 concentrations were <D14, possibly because prior eculizumab exposure led to baseline C5 suppression, reducing early target-mediated drug disposition.

Discussion / Conclusion

All patients exhibited concentrations well above the therapeutic threshold. TDM-guided dose reduction appears feasible and may substantially reduce treatment costs, as previously done with eculizumab[3].

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Keywords

ravulizumab; nephrology; therapeutic drug monitoring; ELISA

00501
Evolution of Infliximab therapy in Inflammatory Bowel Disease: from empirical to precision medicine

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

This study provides a longitudinal analysis of Infliximab (IFX) therapy in Inflammatory Bowel Disease (IBD) over 23 years (2001-2024). The objective was to evaluate the impact of shifting from empirical and reactive strategies to proactive therapeutic drug monitoring (TDM) and model-informed precision dosing (MIPD).

Materials and methods

A retrospective study of 349 patients was conducted. Management was divided into three phases: Empirical (2001-2012, n=61), Reactive (2013-2018, n=141) , and Proactive/MIPD (2019-2024, n=147). Outcomes focused on treatment persistence, immunogenicity (ATI), and loss of response (LOR).

Results

The cohort comprised Crohn’s Disease (58.2%) and Ulcerative Colitis (41.6%). Most patients (80.5%) were bio-naïve. Comparison between the reactive and proactive eras showed:

- Persistence and Retention: 5-year treatment persistence was significantly higher in the proactive cohort (47%) vs. the reactive cohort (34%). Retention rates post-MIPD implementation were 64.6% at 1 year, 61.1% at 2 years, 48% at 5 years, and 32.6% at 10 years.

-Clinical Outcomes: LOR was significantly lower in the proactive period (12.9% vs. 26.2%, p=0.0043). Primary non-response also decreased (11.3% to 8.2%).

-Immunogenicity: ATI incidence declined sharply in the proactive cohort (2.7%) compared to the reactive cohort (10.6%, p=0.0068). By 2024, ATI development reached 0%.

-Intensification: Proactive management led to higher rates of intensified induction (34.5% vs. 11.5%) and maintenance regimens (86.4% vs. 40.2%, p<0.001). The time to first Cmin monitoring decreased from 22.9 to 2 weeks (p<0.001).

-Monotherapy: The immunomodulator was discontinued in 21.6% of the. Concomitant immunomodulator use decreased from 65.2% in 2013 to 52.5% in 2024.

Discussion / Conclusion

Transitioning to a proactive TDM-MIPD strategy is associated with earlier monitoring and personalized dose intensification. These adjustments significantly reduce immunogenicity and LOR, leading to superior long-term treatment persistence in IBD patients.

Keywords

Inflammatory Bowel Disease

Infliimab

Model-informed precision dosing

Persistence

Loss of response

00534
Interpretable Machine Learning–Driven Exposure–Response Modeling to Optimize Infliximab Precision Dosing in Inflammatory Bowel Disease

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic drug monitoring (TDM) is widely used to guide infliximab (IFX) therapy in inflammatory bowel disease (IBD), yet optimal exposure targets remain debated and disease activity prediction remains suboptimal. Traditional exposure–response analyses often fail to account for multidimensional clinical heterogeneity. We aimed to develop and externally validate an interpretable machine learning (ML)–based pharmacokinetic exposure–response model to predict clinical remission and refine precision dosing strategies.

Materials and methods

In this multicenter real-world study, 942 IBD patients treated with IFX at Peking University Third Hospital and Tianjin Medical University General Hospital (2018–2025) were included. Patients were randomly divided into training (70%) and validation (30%) cohorts. Nine ML algorithms were evaluated, including Random Forest (RF), gradient boosting, and logistic regression. Model performance was assessed using AUC, accuracy, sensitivity, and specificity. SHapley Additive exPlanations (SHAP) were used for interpretability. Restricted cubic spline (RCS) analysis evaluated nonlinear exposure–response relationships between IFX serum concentration, IFX dosage, and disease activity risk.

Results

Among the nine algorithms, the RF model achieved the best discrimination (AUC=0.925; accuracy=0.848; sensitivity=0.846; specificity=0.848) with consistent validation performance. ESR, lesion location, fecal calprotectin, albumin, and hemoglobin were the top predictive features. Significant nonlinear exposure–response relationships were identified for IFX serum concentration (P_overall=0.021; P_nonlinear=0.033) and dosage (both P<0.001). Risk reduction plateaued when serum IFX concentrations approached approximately 7.5 μg/mL, suggesting a clinically actionable threshold for remission optimization.

Discussion / Conclusion

This large multicenter study demonstrates that interpretable ML can refine pharmacokinetic exposure–response modeling beyond conventional TDM. Integration of drug concentration with multidimensional clinical features enables individualized remission prediction and supports precision dosing strategies. Our findings provide quantitative evidence for a target IFX concentration threshold and offer a scalable framework for data-driven biologic optimization in IBD.

00571
24/7 Fully Automated Therapeutic Drug Analysis by LC MS/MS Using CLAM 2040, Nexera X3 and LCMS 8060NX

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Rapid and accurate therapeutic drug monitoring (TDM) for many drug classes is essential for research and clinical decision support. Manual sample preparation and frequent method switching, limit throughput and reproducibility. We evaluated a fully automated platform—CLAM-2040 sample preparation module coupled to Nexera X3 UHPLC and LCMS-8060NX—designed to run 14 validated LC-MS/MS methods (≈180 analytes) in random access for continuous, high-throughput TDM.

Materials and methods

14 methods (antibiotics, DOACs, antiepileptics, neuroleptics, SSRIs, TCAs, benzodiazepines, digoxin, methotrexate, DOA, etc.) were developed with unified chromatographic and MS parameters to avoid system re-equilibration. The CLAM-2040 performed automated sample handling (sample dispense, internal standard addition, protein crash, shaking, vacuum filtration) and transferred filtrates to the autosampler. Validation criteria included isobar resolution (>1), calibration accuracy (80–120%), LLOQ S/N >10, area/ratio/ion-ratio CV thresholds (≤10% LCMS, ≤15% CLAM-LC/MS), matrix factor 50–120%, carryover <30%, and ring-trial concordance (80–120%).

Results

Individual method validations met acceptance criteria for representative compounds: calibration accuracy and intra/inter-day QC area ratio CVs were within specified limits. LLOQs and matrix effects were acceptable across methods. Calibration curves remained valid for at least one week without daily recalibration. Random alternation testing (switching methods per sample) produced QC accuracies and CVs comparable to batch processing, with sample-to-sample times typically 5–6.5 minutes and time from sample receipt to result under 10 minutes.

Discussion / Conclusion

The integrated CLAM-2040 + Nexera X3/LCMS-8060NX workflow enables continuous, automated, multi-method LC-MS/MS TDM with high throughput, stable calibration, reduced hands-on time, and reliable analytical performance. The approach supports 24/7 operation and random sample arrival handling, making it suitable for large research programs and potentially routine clinical use following local regulatory guidance and method verification.

Reference(s)

CLSI guidelines; internal validation protocols.

Keywords

therapeutic drug monitoring; automation; LC-MS/MS; CLAM-2040; Nexera X3; LCMS-8060NX; high-throughput

00582
Parallel quantification and correlation of brivaracetam in paired plasma and dried blood spot samples from children with epilepsy: enabling simplified therapeutic drug monitoring via LC-MS/MS

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic drug monitoring (TDM) of brivaracetam (BRV) may be of clinical benefit if used appropriately. Accurate and accessible analytical methods are one of the prerequisites for implementing TDM, especially for some clinical application scenarios. A simple, rapid, and sensitive LC-ESI-MS/MS method for the measurement of BRV was developed and validated in both plasma and DBS matrices. Additionally, we aimed to assess the correlation between the drug concentrations measured in these two matrices

Materials and methods

The sample clean-up was performed by an easy-to-use method, protein precipitation by acetonitrile (ACN). Chromatographic separation of BRV and BRV-d3 was achieved on the SynergiTM Fusion-RP 80 Å column (2 mm × 50 mm, 4 μm) with an isocratic elution at a flow rate of 0.25 mL/min. The target analyte was completely separated by elution with 50% mobile phase B for 3 min.

Results

The method was proven to have good accuracy and precision, with high extraction recovery and without any matrix effects, and showed good linearity over the 0.005-10.0 µg/mL concentration range with a correlation coefficient r^2= 0.9991. The Passing–Bablok and Bland–Altman statistical analyses revealed a strong correlation between plasma and DBS for BRV.

Discussion / Conclusion

Moreover, these results provide a solid basis for the feasibility of BRV TDM using both plasma and DBS matrices, and provided valuable information for clinicians by monitoring plasma BRV level in clinical settings.

00588
Determining drug-antibody reflex point for therapeutic monitoring of ustekinumab in a diagnostic laboratory.

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Ustekinumab is a human monoclonal antibody targeting the p40 subunit shared by IL-12 and IL-23. As a biological agent, it is approved for use for the treatment of moderate to severe psoriasis, and more recently Crohn's disease and ulcerative colitis. Higher serum drug levels have been associated with positive clinical responses and higher rates of disease remission, however data on drug immunogenicity and antibody responses are scarce. Specifically, the reflex point for drug measurement that warrants additional antibody measurement remains unknown.

Materials and methods

In this study, we tested and evaluated serum samples spiked with ustekinumab and anti-ustekinumab antibody using the Theradiag i-Tracker assays on the IDS-iSYS platform. Serum samples were spiked with ustekinumamb (Stelara) obtained from pharmacy prescription, and commercially available anti-ustekinumab antibodies (Bio-rad) in serial dilutions.

Results

Spiking anti-ustekinumab enriched serum samples with ustekinumab resulted in a dose-dependent reduction of the measured anti-ustekinumab level. There was no single point where both drug or antibody levels could be measured on the i-Tracker assays, indicating their limited capacity in identifying a reliable reflex point.

Discussion / Conclusion

The Theradiag i-Tracker assay on the IDS-iSYS platform demonstrated reliable measurement of ustekinumab drug levels, however is limited by its capacity to determine a reliable reflex point for further anti-drug antibody testing.

00600
Towards infliximab personalized therapy in the IBD induction period: POPPK models external evaluation

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Infliximab (IFX) is highly effective for inflammatory bowel disease (IBD), yet 10–30% of patients show primary non-response and 46% discontinue therapy due to secondary loss of response or adverse events. Factors like anti-infliximab antibodies, low albumin, and high C-reactive protein (CRP) influence suboptimal outcomes. While population pharmacokinetic (POPPK) models are used for maintenance monitoring, a lack of external validation for the induction period hinders optimal exposure targeting when inflammatory burden is highest. Thus, this project aims to systematically identify and externally validate published IFX POPPK models to determine their predictive performance during the induction phase in a real-world adult IBD cohort.

Materials and methods

A retrospective study included adult IBD patients initiating IFX at a tertiary center (2013–2024). Data were collected at baseline and before infusions at weeks 2, 6, and 14. Identified models were evaluated using a priori and maximum a posteriori (MAP) estimations. Clinically acceptable performance was defined as mean individual prediction error (MIPE)≤±20% and mean absolute individual prediction error ((MAIPE)≤±30%. F20/F30 metrics and simulation-based methods were also assessed.

Results

Twenty POPPK models were identified; 65% used two-compartment structures. Common covariates included weight, sex, albumin, CRP, and immunomodulator use. The validation cohort comprised 164 patients. Although no single model met all strict acceptability criteria, several demonstrated clinically acceptable performance during induction, with MIPE, MAIPE, F20, and F30 values approaching predefined thresholds. Simulation-based methods confirmed these trends, showing consistent alignment between predicted and observed concentrations.

Discussion / Conclusion

Two-compartment POPPK models incorporating both induction and maintenance data offer acceptable predictive accuracy. These findings support implementing model-informed precision dosing (MIPD) during induction to allow proactive dose optimization, potentially reducing primary non-response and improving long-term therapeutic durability in IBD.

Keywords

Inflammatory bowel disease (IBD); infliximab; population pharmacokinetics; induction period; external evaluation

00627
Methotrexate Polyglutamates reduce Adalimumab Immunogenicity in Axial Spondyloarthritis: A prospective study

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Anti-drug antibodies (ADA) to adalimumab may compromise drug efficacy and long-term treatment maintenance. Co-administering methotrexate can reduce immunogenicity and help maintain the therapeutic effect. Methotrexate polyglutamates (MTXPG), improve adalimumab pharmacokinetics.(1) Our objective was to compare methotrexate polyglutamate (MTXPG) with the emergence of anti-drug antibodies (ADA) to adalimumab in axial spondyloarthritis.

Materials and methods

MTXPG concentrations of short (1-2) long (3) and very-long (4-5) chain lengths were measured at week 12 and week 26 in a prospective clinical trial. in which patients received adalimumab 40 mg eow with methotrexate 10 mg subcutaneously every week. (2) A descriptive statistical analysis was performed to study the correlation between MTXPG total chains (1-5) and quantitative variables, i.e age, weight, height, ASDAS and CRP and categorial variables, i.e. sex, previous TNFi and HLAB27. A logistic regression model for ADA emergence was constructed to assess the effect of covariable.

Results

Older patients had a higher MTXPG (1-5) concentration as compared with younger patients at week 12 and at week 26. MTXPG (1-5) measured at week 26 were significantly higher in women than in men and in HLAB27 negative patients than in HLAB27 positive patients. There was a relationship between MTXPG and ADA emergence. This relationship was stronger at week 12 than at week 26. Using a logistic regression model, the strongest predictors of ADA emergence were, at week 12 MTXPG (3), and, at week 26 MTXPG(1-2), MTXPG (3) and MTXPG (4-5).

Discussion / Conclusion

Methotrexate polyglutamates concentration reduces the emergence of ADA to adalimumab in axial spondyloarthritis patient receiving methotrexate co-medication. Monitoring MTXPG may be a useful tool to reduce adalimumab immunogenicity in axial spondyloarthitis.

This work is based on work from the European Cooperation in Science and Technology (COST) Action "European Network on Optimising Treatment with Therapeutic Antibodies in chronic inflammatory diseases (ENOTTA) CA 21147".

Reference(s)

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(2) Ducourau E. et al. RMD Open 2020

Keywords

Methotrexate, Adalimumab, Anti-Drug Antibodies

00644
Both CD4 and CD8 anti-CD19 CAR T-cells are involved in target depletion and clinical efficacy in B-cell malignancies – a joint CD4 and CD8 CAR T-cell kinetic-time-to-event framework

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

CD19-targeted chimeric antigen receptor (CAR) T-cells are genetically engineered receptors that redirect patients' T-cells toward recognition and elimination of CD19-positive cells. While the pharmacokinetics and exposure–response relationships of CAR T-cells have been previously described [1–4], the interplay between CAR-CD4 and CAR-CD8 kinetics, target dynamics, and progression-free survival (PFS) was not characterized. This study aimed to investigate the integrated relationship between CAR-CD4 and CAR-CD8 expansion, target depletion, and clinical efficacy in patients with B-cell malignancies.

Materials and methods

In this observational cohort, 81 patients with B-cell malignancies treated with CD19-targeted CAR T cells in Tours University Hospital between 2022 and 2025 were assessed. CD4 and CD8 CAR T-cell counts were quantified using flow cytometry. A joint mechanistic model describing CAR-CD4 (L), CAR-CD8 (C), and their (latent) target (R) kinetics was developed. CAR T-cell proliferation was assumed to follow second-order kinetics, depending on both CAR T progenitors and target counts, whereas CART-cell–mediated target depletion was modeled as a function of both circulating target cells and CAR T-cell counts. The relationship between target kinetics and PFS was assessed using joint pharmacokinetic–time-to-progression modeling. Parameters were estimated using population modeling (MONOLIXsuite®).

Results

A total of 388 CAR-CD4 and CAR-CD8 measurements were analyzed and adequately described by the model. The estimated central distribution volume was 9.1 L, with large interindividual variability (336%). The proportion of CAR-CD4 among circulating CAR T-cells was 65%. Estimated proliferation and depletion rate constants were k_R = 0.7 $mm^{-3} \cdot day^{-1}$ and k_{DL}/k_{DC} = 3.0 and 3.5 $mm^{-3} \cdot day^{-1}$, respectively. Both CAR-CD4– and CAR-CD8–mediated contributions to target depletion were significantly associated with improved PFS.

Discussion / Conclusion

This study provides the first integrated characterization of CAR-CD4 and CAR-CD8 kinetics, target dynamics, and clinical response in B-cell malignancies. Both sub-populations contributed comparably to target depletion, which was strongly associated with improved clinical outcomes.

Reference(s)

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Keywords

CAR T-cells; population pharmacokinetic modelling, anti-CD19, B-cell malignancies

00647
Quantifying the Combined Impact of Target (TNF) Binding and Anti-Drug Antibodies on Infliximab Pharmacokinetics: An Integrated "TMDD–ADAMDD" framework

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Anti-drug antibodies (ADA) against infliximab increase drug clearance and contribute to secondary treatment failure. While target-mediated drug disposition (TMDD) has been used to describe infliximab pharmacokinetics [1-2], the mechanistic contribution of ADA kinetics to infliximab disposition has not been fully characterized. This study aimed to quantify ADA-mediated infliximab elimination using an integrated population mechanistic model.

Materials and methods

In this observational cohort, 228 patients with inflammatory bowel disease (n=83), ankylosing spondylitis (n=123), or rheumatoid arthritis (n=22) treated with infliximab between 2006 and 2012 at Tours University Hospital were included; 29 patients had at least one positive ADA measurement. Infliximab pharmacokinetics was described using a previously developed one-compartment quasi-steady-state TMDD model. [1-2] Latent ADA kinetics were modeled using a five-compartment transit structure [3] with a zero-order production rate constant (k_{syn}), assumed to increase as infliximab concentrations decreased. [4]. ADA and infliximab elimination rate constants were assumed identical. ADA–infliximab interaction was described using an irreversible TMDD binding approximation. Detected ADA status was evaluated as a covariate.

Results

A total of 2612 infliximab trough concentrations were analyzed and adequately described by the model. The ADA production rate constant was estimated k_{syn}=0.78 mg/L/day with substantial interindividual variability (107%) and was significantly higher in patients with detected ADA ($p=6.9\times10^{-11}$). ADA presence was associated with markedly reduced median infliximab trough concentrations (~1 mg/L at week 22 and 0.1 mg/L at week 30). Dose escalation to 10 mg/kg did not compensate for ADA-associated clearance in more than half of patients.

Discussion / Conclusion

This study provides the first integrated characterization of target-mediated (TMDD) and ADA-mediated (“ADAMDD”) infliximab disposition. The latent ADA production rate constant may serve as an early mechanistic indicator of immunogenicity and support model-informed therapeutic monitoring.

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Keywords

infliximab; anti-drug antibodies; target-mediated drug disposition; population pharmacokinetic modeling.

00697
Utility of a Laser Diode Thermal Desorption coupled to a Mass Spectrometer (LDTD-MS) in Therapeutic Drug Monitoring of Anti-Arrhythmic Drugs.

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Cardiac arrhythmias constitute significant clinical concern. Effective pharmacological therapy requires maintaining drug concentrations within an optimal therapeutic range to ensure safety and efficacy. To facilitate Therapeutic Drug Monitoring (TDM), a rapid analytical method was developed for simultaneous determination of multiple anti-arrhythmic agents (Metoprolol, Bisoprolol, Propafenone, Eplerenone) and the active metabolite of Amiodarone (Desethylamiodarone), based on laser diode thermal desorption coupled to mass spectrometry (LDTD-MS). In the Axino system, samples placed on Domino LazzWell plates are rapidly heated using an infrared laser, enabling fast and efficient desorption of analytes.

Materials and methods

Serum samples were prepared in accordance with the following protocol. Saturated sodium chloride solution was added first, followed by extraction with acetonitrile. The upper organic layer was collected and evaporated under a nitrogen stream. The

remaining residue was re-dissolved in a dedicated reconstitution solvent to ensure effective analyte desorption from the Domino LazzWell surface. For measurement, 4 µL of the prepared sample was applied to the plate. Samples were then analyzed using AXINO (Phytronix) coupled to QTRAP 6500+ (SCIEX).

Results

Analytical procedure was successfully validated for the simultaneous quantification of selected anti-arrhythmic agents and one metabolite using LDTD-MS. Validation results confirmed linearity for all analytes ($r \geq 0.995$), accuracy within 80–120%, and good precision with %CV ≤ 15%. Validated concentration ranges were within the therapeutic ranges and were as follows: 2.5–250 ng/mL for Metoprolol and Bisoprolol, 10–250 ng/mL for Propafenone, and 25–2500 ng/mL for Eplerenone and Desethylamiodarone.

Discussion / Conclusion

The proposed method demonstrates utility of rapid, multiplex quantification of anti-arrhythmic drugs and one metabolite without limitations associated with conventional LC-MS/MS workflows. By eliminating HPLC-related requirements and reducing analysis time to only a few seconds per sample, the LDTD-MS approach offers a highly efficient and cost-effective solution for TDM, while maintaining robust linearity, accuracy, and reproducibility across the therapeutic ranges.

Keywords

TDM; LDTD-MS, anti-arrhythmic; quantification

00714
Predicting clinical response to adalimumab in juvenile idiopathic arthritis with a TDM-based multidimensional model integrating disease activity and pharmacokinetics

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Adalimumab, among TNF-inhibitors, has revolutionized the treatment of children with juvenile idiopathic arthritis (JIA). Most adalimumab-treated patients respond within months; approximately 1/3 of the patients may show lack or loss of response after continued exposure. Here, we developed a population pharmacokinetic-dynamic (PK/PD) model based on therapeutic drug monitoring (TDM) of both adalimumab (ADL) and anti-adalimumab antibodies (ADA) levels performed during routine clinical practice.

Materials and methods

Four-hundred and 45 serum samples from June 2019 to January 2024 were collected from 110 JIA patients. Adalimumab (ADL) and ADA levels were measured

as routine TDM practice by using clinically validated ELISA kits (Immundiagnostik AG). Frequency of adalimumab administration (every two weeks versus every week), dose (20 vs 40 mg) and disease activity (c-JADAS-10) were retrospectively collected. An indirect time-response PK/PD model was applied to investigate the clinical correlation between ADL and ADA levels, identifying the predictive covariates of clinical response.

Results

The median age at starting therapy was approximately 10 years [IQR 7.1-15.2]. Pharmacokinetic analysis showed a variable time-profile of both adalimumab (16.3 median micrograms/ml) and ADA titers (median 4.2 AU/ml), regardless of adalimumab dose and frequency of administration. Adalimumab clearance was influenced by 3 variables: dose, ADA titer and body weight. We observed a complete clinical response after 3 months follow-up in 65% of children, who maintain remission also at 6 and 24 months. The predicted adalimumab concentrations (Css), at the same drug dose, were on average lower in patients with mild and high disease activity score.

Discussion / Conclusion

The effect of ADA on the clinical incidence of response loss has an important impact in the clinical practise. Our findings allow to identify adalimumab target concentrations based on the exposure-clinical response relationships and highlight the utility of a proactive TDM approach that could help clinicians to recognize potential early non-responder patients, who would need different treatment strategies.

Reference(s)

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Keywords

Adalimumab; PK/PD models; pediatric patients; anti-drug antibodies; Biologics; Terapeutic Drug Monitoring (TDM).

00752
Vedolizumab Trough Concentrations Predict Fecal Calprotectin Response in Patients with Inflammatory Bowel Disease

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Therapeutic drug monitoring (TDM) of vedolizumab (VDZ) is increasingly used to optimize treatment in patients with inflammatory bowel disease (IBD), yet pharmacokinetic variability remains substantial and is partly driven by changes in disease activity. Fecal calprotectin (FCP) reflect both disease severity and response to therapy. Understanding the relationship between VDZ concentrations and FCP dynamics may inform TDM and optimize treatment.

Materials and methods

Data were obtained from adult IBD patients. Longitudinal FCP measurements were available at baseline and at weeks 6, 14. Trough VDZ concentrations at weeks 6 and 14 were used for the analysis. VDZ was administered at 300 mg according to product labeling. Data were analyzed using a linear mixed-effects model, with log-transformed FCP as the dependent variable, VDZ trough concentration as a fixed

effect, and patient ID as a random intercept to account for inter-individual variability. All analyses were performed in R (version 4.5.1).

Results

A total of 39 patients with ulcerative colitis (75% of the cohort), of whom 55.8% were male, were included in the analysis. The model included 98 observations. Inter-patient variability in baseline FCP was substantial (random intercept SD = 0.91), and residual variability within patients was 1.23. Higher VDZ concentrations were significantly associated with lower FCP (estimate = -0.0296, SE = 0.0143, t = -2.06), corresponding to an approximate 2–3% decrease in FCP per 1 mg/L increase in trough VDZ. Visual inspection of individual patient trajectories confirmed a consistent inverse relationship between VDZ concentration and FCP levels. Further analysis will focus on simultaneous pharmacokinetic-pharmacodynamic modeling using indirect-response model.

Discussion / Conclusion

FCP levels decrease in a VDZ concentration-dependent manner, highlighting the importance of pharmacokinetic exposure in modulating intestinal inflammation. These findings support the utility of TDM in optimizing VDZ therapy and suggest that early trough concentrations can inform treatment decisions in IBD patients.

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Keywords

FCP, biomarker, biologics, inflammatory bowel disease.

00767
LC MS/MS Measurement of Infliximab, Adalimumab, Ustekinumab, Vedolizumab and Anti Drug Antibodies Using mAbXmise Kits on Xevo TQ Absolute XR MS for Clinical Research

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Accurate measurement of therapeutic monoclonal antibodies (mAbs) and antidrug antibodies (ADAs) is important for understanding biologic drug exposure and immunogenicity in clinical research. Immunoassay results can be influenced by matrix effects and limited analytical specificity, motivating the use of peptide-level LC-MS/MS for more robust quantification. This study evaluates a standardized workflow using mAbXmise™ sample-preparation kits with tandem-quadrupole mass spectrometry for multiplexed measurement of infliximab, adalimumab, ustekinumab, vedolizumab and their associated ADAs.

Materials and methods

Serum samples, calibrators, and QCs were processed using mAbXmise ITDM2 and IADA1 kits following manufacturer instructions. Ten microlitres of serum were used for mAb assays and 100 µL for ADA assays, including overnight digestion at 37 °C. Peptides were separated using an 8-minute LC method and quantified by MRM on a Xevo™ TQ Absolute XR Mass Spectrometer. Calibration ranges were 0.5–100 µg/mL for mAbs and 10–400 ng/mL for ADAs. Analytical performance was characterised

using multiple QC levels and by comparing LC-MS/MS results with historical immunoassay data from seven anonymised research samples.

Results

All mAb peptides showed strong linearity ($r^2 > 0.99$) across the 0.5–100 µg/mL range, meeting ±15% accuracy criteria. QC precision was ≤10% RSD with accuracy between 94.2–114.2%. ADA assays demonstrated stable 4-parameter logistic calibration with LOQs in the low-ng/mL range, QC precision ≤10% RSD, and accuracy 90.5–105.6%. Research samples showed expected concordance with immunoassay measurements. Samples positive for ADA by immunoassay showed matching LC-MS/MS peptide responses, with method-specific differences consistent with assay format and specificity.

Discussion / Conclusion

This workflow provides sensitive, selective, and reproducible LC-MS/MS measurement of mAbs and ADAs using standardized digestion and sample-preparation kits. The results support its application for analytical characterisation and method development in clinical research laboratories.

For Research Use Only. Not for use in diagnostic procedures.

Toxicology & Environmental Health

00249
Automated LC MS/MS Verification of a CE marked Eureka Lab Division IVD Kit for Drugs of Abuse in Whole Blood on the Nexera X3/LCMS 8060RX

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Accurate detection and quantification of drugs of abuse in whole blood are essential for for forensic and clinical-forensic applications . The use of Standardized IVD kits combined with robust LC-MS/MS platforms , enables improved throughput, reproducibility, and analytical performance. In this study, the CE-marked Eureka Lab Division IVD kit for 19 drugs of abuse was verified on a Shimadzu Nexera X3 UHPLC system coupled to an LCMS 8060RX, in order to evaluate linearity, limits of quantification, precision, and accuracy.

Materials and methods

Lyophilized matrix-matched calibrators, deuterated internal standards, and QC materials from the Eureka kit were reconstituted. Sample preparation used protein crash precipitation (Reagent A/B), centrifugation, and supernatant dilution (Reagent C) from 100 µL whole blood. Chromatography employed a binary gradient (0.4

mL/min, 15 µL injection, 40 °C column oven). MS acquisition used positive-ESI MRM transitions with compound-specific parameters. Linearity and LoQ were determined from serial calibrators; acceptance criteria: accuracy 80–120% and intra-run repeatability CV <15% (≤20% near LoQ). Precision and reproducibility were evaluated across three QC levels with intra- and inter-day replicates.

Results

Calibration curves for representative analytes (amphetamine, morphine, codeine, MDA) exhibited strong linearity (R2 ≥0.989–0.999) using appropriate weighting. Reported LoQs met kit specifications. Accuracy across QC levels generally ranged 80–120%. Injection, sample-preparation, intra- and inter-day CVs were typically below 10% for most analytes; a minority approached ~11% for norbuprenorphine and buprenorphine at higher QC levels. Overall signal stability, repeatability, and quantitative behavior were consistent across evaluated ranges.

Discussion / Conclusion

Implementation of the Eureka IVD kit on the Nexera X3/LCMS 8060RX provides a robust, sensitive, and reproducible workflow for drugs of abuse analysis in whole blood. The use of lyophilized whole-blood calibrators and controls, together with deuterated internal standards, enables effective compensation of matrix effects. The streamlined analytical protocol supports high throughput and is suitable for routine use in clinical-forensic settings.

Reference(s)

References (optional) Eureka Lab Division IVD Kit documentation; Shimadzu Nexera X3/LCMS-8060RX application notes.

Keywords

drugs of abuse; whole blood; LC-MS/MS; IVD kit; Nexera X3; LCMS-8060RX; verification

00252
Carbon footprint assessment of tacrolimus blood quantification

Oral or Poster

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Healthcare activities significantly contribute to greenhouse gas emissions. Assistance Publique Hôpitaux de Paris estimates its annual emissions at 1.8 million tonnes of CO2, of which 14% are issued from laboratories. However, the impact of individual laboratory tests remains poorly characterized. Our objective was to determine the carbon footprints of two analytical techniques and identify opportunities for decarbonization.

Materials and methods

This study applied bottom-up approach by a life cycle assessment to tacrolimus assay performed using tandem mass spectrometry (LC-MS/MS) (AltisPlus, ThermoFisher) and an immunoassay on Cobas8000 (Roche) used only on weekends. Carbon footprint determination was carried out using the in-house tool Carebone® by collecting data during pre-analytical, analytical and post-analytical phases, as well as human resources, waste management, building energy consumption, digital data, and storage. After data collection and verification, emission factors were applied before result analysis.

Results

The carbon footprint of the tacrolimus assay was estimated at 2.213 and 3.925 kg CO_2e per test for LC-MS/MS and immunoassay techniques, respectively. In both cases, the analytical step accounted for the primary contributor (89% and 91%, respectively). These emissions primarily arose from the reagents (30.9% and 61.5% respectively), including calibrators and quality controls, as well as from the equipment (33.5% and 15.8%, respectively) and human resources (18.3% and 17.0% respectively). Blood collection tubes, refrigerated storage containers and digital data were the most CO2 emissive sources during the pre-analytical and post-analytical steps.

Discussion / Conclusion

Equipment and reagents account for a significant portion of CO2 emissions (46% and 70% respectively for LC-MS/MS and immunoassay). Regarding LC—MS/MS, reducing equipment costs is difficult; possible solutions include increasing the analysis volume or decreasing reagent, and consumables consumption. Regarding Cobas 8000, reagent consumption was twice higher than LC-MS/MS. Therefore, the routine use of Cobas8000—particularly during weekends—should be considered. Alternatives such as prioritizing LC-MS/MS or using a Cobas i601 module may represent lower-carbon options.

Keywords

Carbon footprint, Decarbonization, Immunoassay, Tandem mass spectrometry

00548
Miniaturized PFAS Analysis Enabled by Capillary Dried Plasma Microsampling with Integrated Plasma Separation

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Per- and polyfluoroalkyl substances (PFAS) are persistent contaminants linked to adverse health effects. Venous plasma biomonitoring poses logistical challenges, especially in large-scale studies. Capillary microsampling with plasma separation may overcome these barriers. This study aimed to develop a LC-MS/MS method to quantify 13 PFAS dried plasma spots (DPS) using the HealthID PSD device.

Materials and methods

Four drops of capillary blood were applied to plasma separation devices, generating dried plasma spots (DPS). Six 6-mm disks were extracted using aqueous buffer with 0.1% BSA, followed by protein precipitation and weak anion-exchange solid-phase extraction. Chloride quantification was used to estimate recovered plasma volume and correct PFAS concentrations. Chromatographic separation was achieved on an Acquity UPLC HSS T3 column coupled to a Xevo TQ-S Micro triple quadrupole mass spectrometer operating in negative ESI mode. The assay was validated (0.5–20 ng/mL) according to international bioanalytical guidelines. Hematocrit and applied blood volume effects were evaluated. Clinical application included 76 paired venous plasma and DPS samples.

Results

All analytes showed linearity (r>0.99). Intra- and inter-assay precision ranged from 3.58–14.2% and 0.39–11.5%, respectively, with accuracy between 93.2–115.2%. Matrix effects were 0.38–2.49%). Most analytes were stable for 21 days at 40 °C. Hematocrit influence was acceptable except for PFDA and N-MeFOSAA at low concentration levels. Blood volume variations (160–240 µL) did not significantly affect chloride-corrected concentrations. In clinical samples, PFOS was the only compound quantified in all volunteers (1.19–18.7 ng/mL). DPS and plasma concentrations of PFOS in volunteers were highly correlated (r=0.959), meeting incurred sample reanalysis criteria.

Discussion / Conclusion

A method for the determination of PFAS determination in capillary dried plasma was validated. The analytes were highly stable in non-refrigerated conditions, and measurements had strong agreement with venous plasma. Capillary DPS sampling represents a valuable alternative for PFAS biomonitoring, particularly in limited-resource settings.

Keywords

PFAS. LC-MS/MS. Capillary dried plasma. Microsampling. Analytical validation. Human Biomonitoring.

00592
From Phycotoxins to Bioactive Metabolites: An Integrative Approach to Assess Cutaneous Risks and Benefits of Marine Microalgae

Poster only

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Introduction - Structured abstract in 300 words in English (excluding title, references and keywords

Marine microalgae represent an extremely diverse group of organisms, shaped by over a billion years of evolution. Their chemically diverse metabolites exhibit bioactivities in humans, placing them at the crossroads of environmental toxicology and medical bioprospecting.

Harmful species such as Ostreopsis cf. ovata and Vulcanodinium rugosum are associated with cutaneous symptoms during blooms, whereas taxa including Dunaliella salina, Tetraselmis suecica, and Cylindrotheca fusiformis produce metabolites with beneficial skin properties. This work aimed to develop an integrated chemical–biological workflow to characterize both the cutaneous hazards and the bioactive potential.

Materials and methods

Ethanolic extracts from freeze-dried biomass of selected bioactive microalgae were fractionated by semi-preparative RP-C18 chromatography following a bio-guided strategy. Fractions were screened in human keratinocytes for cytotoxicity (MTT), pro-inflammatory cytokine release (ELISA) and ROS production (DCFH-DA) under stress

conditions. Active fractions were further sub-fractionated and analyzed by high-resolution MS/MS coupled to feature-based molecular networking for dereplication (GNPS). For toxic species, crude extracts and purified ovatoxin analogues or portimine A were assessed. Mechanistic investigations assessed ribotoxic stress signaling, ZAKα and p38 activation, NLRP1 inflammasome assembly, and IL-1β/IL-18 release.

Results

Cytotoxicity of O. cf. ovata extracts correlated with ovatoxin content, with purified analogues displaying sub-nanomolar potency. Extracts of V. rugosum containing portimine A induced ribosomal stress, triggering ZAKα- and p38-dependent activation of the NLRP1 inflammasome, leading to IL-1β/IL-18 release and inflammatory cell death.

Conversely, fractions from beneficial microalgae reduced ROS production and pro-inflammatory cytokine release (TNF-α and IL-8). Bio-guided fractionation and dereplication of C. fusiformis extract highlighted N-acyl amino acids as candidate mediators of anti-inflammatory activity.

Discussion / Conclusion

This integrative approach bridges mechanistic toxicology and marine bioprospecting. It refines the risk assessment of emerging phycotoxins while enabling the identification of bioactive metabolites with dermatological potential; illustrating that hazard characterization and bioprospecting can be addressed within a unified experimental framework.

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