Pharmacy Education (2025) 25(4) 1 - 19
https://doi.org/10.46542/pe.2025.254.ppm.117

CONFERENCE ABSTRACTS

FIP COPENHAGEN 2025

83rd FIP World Congress of Pharmacy and Pharmaceutical Sciences in Copenhagen, Denmark, 31 August to 3 September 2025

Personalised and precision medicine

The new pharmaceutical competence in oncology: Strengthening pharmaceutical differentiation and improvement patient-centred care

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Introduction: The increasing innovation and complexity of oncological treatments, including biomarker-driven personalized therapies and novel therapeutic approaches, demand higher expertise among pharmacists. To address these challenges and provide adequate assistance for oncology patients, the Portuguese Pharmaceutical Society (PPS) has developed the Pharmaceutical Competence in Oncology (PCO) to scientifically and technically distinguish pharmacists with knowledge and experience in this field. By certifying pharmacists in oncology, the initiative seeks to improve patient-centred care, therapeutic outcomes, and integration within multidisciplinary healthcare teams.

Method: The development process of the PCO followed a process structured in three key steps: establishment of a responsible committee by the PPS composed of experts in human genetics, community pharmacy, and hospital pharmacy; a regulatory framework formally approved on October, 2023, and published under Regulation No. 937/2024; and the implementation of the training and the examination process. The application for PCO includes requirements such as professional experience in the field, documented training, curriculum evaluation, and an assessment exam. To support candidates in their preparation, an informative webinar titled "Clarification on the Pharmaceutical Competence in Oncology" was conducted on October 28. Additionally, a questionnaire was distributed across various hospital pharmacy services to assess their suitability for the practical training. PPS is actively collaborating with multiple institutions developing oncology training programs aligned with the requirements set out in the regulation, ensuring that pharmacists receive the necessary preparation to obtain the PCO. During the first application period, in 2024, the target professionals were professionals already working in the oncology field and those who met the necessary prerequisites for the application. The second and third phases of applications are also for pharmacists who have yet to acquire sufficient experience but will also include pharmacists who have frequented educational courses.

Results: The preparatory webinar was held before the examination with 109 participants. In the first phase, 20 applications were submitted for the Competence. From the 20 applications received, 85% of candidates (n=17) successfully obtained the Pharmaceutical Competence in Oncology, while 10% (n=2) were rejected due to non-compliance with eligibility criteria, and 5% (n=1) failed to attend the final exam. Among successful candidates, the average exam score was 14.38 (range: 10.40 – 16.40), demonstrating strong knowledge in the oncology field. The results of the questionnaire indicated that 11 hospital pharmacies met the necessary criteria and were available to provide hands-on training in oncology. Additionally, 2 hospitals were equipped to offer clinical simulation-based

training. At the moment, 5 institutions are providing oncology training programs, focusing not only on specific pharmacological aspects but also on patient pathways, medication monitoring and safety, pharmaceutical care, public health, and cancer prevention.

Conclusion: The development of Pharmaceutical Competence in Oncology reflects the PPS's commitment to promoting technical differentiation and improving the quality of care provided to oncology patients. The structured training approach and certification process align pharmacists with evolving therapeutic innovations and patient safety priorities.

Investigation of the application of pharmacogenomics in pediatric clinical practice

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Introduction: Pharmacogenomics investigates the link between genetic variations and drug responses, aiming to establish personalised treatment regimens. This study underscores the role of pharmacogenomics in formulating effective therapeutic strategies for paediatric patients, focusing on how genetic polymorphisms influence medication efficacy, safety, and pharmacokinetics. Paediatric populations, given their unique developmental stages, with conditions such as asthma, attention deficit hyperactivity disorder (ADHD), and anxiety disorders, were specifically examined.

Method: An experimental analysis was conducted using pharmacogenomic data extracted from the PharmGKB database. The study focused on evaluating genetic polymorphisms associated with paediatric asthma, ADHD, and anxiety disorders. Advanced data analysis techniques encompassed high-throughput technologies, including next-generation sequencing and real-time PCR, to ascertain the effects of these genetic variations on drug response and metabolism.

Results: In asthma, polymorphisms in genes like ADRB2 and CRHR1 were associated with variable responses to bronchodilators and corticosteroids, influencing treatment efficacy through differing receptor expression levels and inflammatory pathway involvement. The genetic variation rs1042713 in the ADRB2 gene, which encodes the β2-adrenergic receptor, was associated with varying responses to bronchodilators such as salmeterol. Specifically, the G allele correlated with increased expression of the receptor and enhanced drug efficacy. Polymorphisms like rs242941 in the CRHR1 gene were linked to cortisol production and influenced the effectiveness of corticosteroids, due to altered inflammatory responses.

For ADHD, variants in CYP2D6 and SLC6A2 affected drug metabolism and the action of atomoxetine and methylphenidate, highlighting the need for dose adjustments to maximise therapeutic outcomes and mitigate adverse effects. Variants in the CYP2D6 gene significantly impacted atomoxetine metabolism, where poor metabolisers exhibited prolonged drug activity and potential toxicity, necessitating dose adjustments. The rs28386840 polymorphism in the SLC6A2 gene influenced norepinephrine transporter activity, affecting the therapeutic effects of methylphenidate. In anxiety disorders, genetic variations in the HTR2A gene impacted selective serotonin reuptake inhibitors (SSRIs) efficacy by altering serotonin receptor sensitivity, while CYP2C19 and CYP2D6 enzyme polymorphisms required careful consideration of dosage to balance efficacy with toxicity risks. Polymorphisms in the HTR2A gene, such as rs6311, modified serotonin receptor sensitivity, impacting the efficacy and potential side effects of SSRIs like escitalopram. Metabolic variations such as CYP2C19*2 resulted in decreased drug clearance and increased exposure to medications like sertraline, raising concerns about the optimal dosing to avoid toxicity.

Conclusion: This research demonstrates pharmacogenomics' potential to refine therapeutic strategies, particularly in paediatric care, by customising treatments based on comprehensive genetic analyses. The findings support the integration of pharmacogenomic insights into clinical protocols, enhancing patient outcomes and minimising adverse drug reactions. Community pharmacies can incorporate pharmacogenomics by providing genetic testing services, offering patient counselling on pharmacogenomic results, and collaborating with healthcare providers to ensure optimal medication management based on genetic profiles. Collaborative efforts in international health policies and education can facilitate the incorporation of these advancements into everyday healthcare practices.

Knowledge of physicians and pharmacists practicing in the Philippine General Hospital towards pharmacogenomics and its integration in clinical practice in the Philippines

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Background: Pharmacogenomics (PGx) focuses on how genomic variations influence an individual's response to medications. This highlights the potential of PGx in achieving

better health outcomes by selecting the most appropriate medications for the patient while also minimizing the risk of adverse effects. In the Philippines, PGx is still relatively in its infancy, with any current initiatives still only being pursued by the interest of a few local experts in the field.

Purpose: This study aims to determine the knowledge of physicians and pharmacists practicing in the Philippine General Hospital (PGH) towards PGx and its integration in clinical practice in the Philippines.

Method: The study was a cross-sectional study. A survey questionnaire was disseminated to pharmacists or physicians currently practicing in the PGH. Of the respondents, 67 were pharmacists and 53 were physicians. Data collected was analyzed using descriptive and comparative statistics. A Chi-square test was used to determine if there was a significant difference in the knowledge between physicians and pharmacists. Mann-Whitney U test was employed to evaluate the differences in the overall scores between the two groups of independent variables. A level of significance was set at a p-value < 0.05.

Results: The overall respondents' mean percentage knowledge score was high (71.7%). Comparing the knowledge of physicians and pharmacists, a significant difference was noted wherein physicians are more aware that pharmacogenetic testing is currently not available for most medications. The attendance of an educational activity was found to significantly affect the level of knowledge ($p = 0.044$) of the respondents.

Conclusion: The pharmacists and physicians currently employed and practicing in PGH exhibited overall high knowledge towards PGx and its integration into clinical practice. Such findings on the level of knowledge suggest how the present educational activities on PGx in the country have been effective.

Mapping mutational profiles to drug sensitivity: A machine learning approach to precision medicine in diffuse intrinsic pontine glioma

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Background: Diffuse Intrinsic Pontine Glioma (DIPG) is one of the most aggressive childhood brainstem tumours, characterised by a dismal prognosis and limited therapeutic options. Despite ongoing research efforts, standard treatments such as radiation therapy offer only temporary relief, and there is currently no approved curative therapy. Recent advances in genomic profiling have identified recurrent, targetable mutations in DIPG, including H3K27M, TP53, PIK3, PPM1D, FRFR1, PDGFRA and ACVR1, which present opportunities for precision medicine approaches. However, the highly heterogeneous and complex mutational landscape of DIPG suggests that monotherapies targeting individual mutations are unlikely to achieve sustained efficacy. Instead, personalised combination therapies tailored to each tumour's unique genomic signature may offer more promising outcomes. Nevertheless, the challenge lies in accurately predicting effective drug combinations amidst this complexity, especially given the rarity of DIPG and the scarcity of large-scale DIPG-specific datasets.

Purpose: This study aimed to develop and validate a machine learning framework that leverages transfer learning techniques to predict optimal drug combination therapies for DIPG. By incorporating tumour-specific mutational profiles, the framework addresses the inherent heterogeneity of the disease and overcomes the limitations posed by single-agent approaches.

Method: High-throughput sequencing data from DIPG patient samples were analysed to identify expression patterns associated with key mutations. Correlation analysis was conducted to assess relationships between mutations and response profiles to a panel of therapeutic agents. To overcome the limited size of DIPG datasets, a transfer learning approach was employed. A deep learning model was initially pre-trained on large-scale pharmacogenomic datasets from the Genomics of Drug Sensitivity in Cancer (GDSC) database, encompassing diverse cancer types and drug response data. This pre-trained model captured broad patterns of drug sensitivity. Subsequently, fine-tuning was performed using DIPG-specific genomic and drug response datasets to adapt the model to the distinct molecular features of DIPG. Model performance was evaluated through cross-validation techniques and independent test datasets to ensure robustness and generalisability.

Results: Point-biserial correlation analysis revealed that no single therapeutic agent demonstrated uniform efficacy across all mutational profiles, reinforcing the necessity of combination treatments. The transfer learning-based machine learning model achieved over 80% accuracy in predicting effective drug combinations for specific DIPG mutational profiles. Notably, tumours harbouring H3.3K27M mutations exhibited increased sensitivity to combinations involving epigenetic modifiers alongside PI3K/mTOR inhibitors. ACVR1-mutant samples showed improved responses to regimens incorporating ALK (Anaplastic Lymphoma Kinase) inhibitors and HDAC (Histone deacetylase) inhibitors. Furthermore, the model identified novel synergistic drug interactions influenced by specific co-occurring mutations, presenting previously unexplored therapeutic strategies for further clinical investigation.

Conclusion: This study demonstrates the feasibility and clinical utility of applying transfer learning approaches within a machine learning framework to predict personalised drug combination therapies for DIPG based on mutational profiles. The findings challenge conventional one-size-fits-all treatment strategies and provide a strong foundation for advancing precision medicine in paediatric brain tumours.

Future research will focus on validating these computational predictions in patient-derived models and translating the results into clinical trial designs aimed at improving outcomes for children diagnosed with DIPG.

Developing a virtual clinical trials gulf population: Revolutionising precision dosing with virtual patients

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Background: Population-specific physiologically based pharmacokinetic (PBPK) modelling is essential for optimising drug therapy in diverse patient groups. This study describes the development and validation of a Gulf region virtual population within Simcyp, incorporating regional physiological and genetic variations to enhance precision dosing strategies. The model was developed using real-world data from Kuwaiti hospitals, ensuring its applicability for clinical pharmacokinetic predictions.

Method: A three-phase approach was undertaken: model development, validation, and application. In the development phase, a comprehensive literature review and clinical data collection were performed to obtain demographic and physiological parameters representative of the Gulf population. Data from 2,000 Kuwaiti subjects were gathered through the Kuwait Ministry of Health, covering key physiological markers such as age, weight, renal function (glomerular filtration rate [GFR], serum creatinine), haematocrit, and plasma protein levels (albumin, α1-acid glycoprotein). This data was used to refine the virtual population reflected the pharmacokinetic characteristics of Gulf patients.

Results: The validation phase involved comparing model predictions to observed pharmacokinetic data from Kuwaiti hospitals. Therapeutic drug monitoring (TDM) data were obtained from hospital records for five commonly prescribed medications with known interindividual variability: carbamazepine, valproic acid, digoxin, phenytoin, and levetiracetam. These drugs were selected due to their reliance on careful dose adjustments and metabolism via polymorphic enzymes such as CYP3A4, CYP2C9, and CYP2C19. The model's performance was assessed by comparing simulated drug concentrations to real-world TDM values, with successful validation requiring predicted plasma concentrations to fall within two-fold of observed clinical data. Additionally, virtual patient simulations were conducted to evaluate drug pharmacokinetics across different BMI categories, reflecting the high obesity prevalence in Kuwait. The application phase demonstrated the clinical utility of the validated PBPK model. Simulations revealed that standard drug doses often resulted in subtherapeutic or supratherapeutic levels in patients with specific genetic variants, emphasising the importance of individualised dose adjustments. For example, carbamazepine metabolism was notably altered in patients with reduced-function CYP3A4 and CYP3A5 polymorphisms, while valproic acid clearance varied significantly in individuals with CYP2C9 and CYP2C19 polymorphisms. Furthermore, patients with renal impairment exhibited increased drug exposure, particularly for renally cleared drugs such as digoxin and levetiracetam, reinforcing the need for adjusted dosing regimens.

Conclusion: This study successfully integrates hospital-based clinical data with PBPK modelling to enhance precision dosing in the Gulf region. The validated Kuwaiti population model in provides a powerful tool for optimising pharmacotherapy, particularly for drugs with narrow therapeutic windows. Its application to real-world clinical scenarios underscores its potential to improve medication safety and efficacy in Kuwait and the broader Gulf region.

Tailoring cancer treatment: How virtual trials and advanced modelling improves imatinib dosing for obese patients

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Background: Obesity is a major global health issue that significantly affects how drugs are processed in the body, impacting their effectiveness and safety. Imatinib, a tyrosine kinase inhibitor, is widely used to treat cancers such as chronic myeloid leukaemia (CML) and gastrointestinal stromal tumours (GIST). However, standard dosing may not be optimal for obese patients due to altered drug metabolism, leading to subtherapeutic drug levels and potentially reduced treatment effectiveness. This study applies physiologically based pharmacokinetic (PBPK) modelling and virtual clinical trials to investigate how obesity affects imatinib exposure and to explore strategies for dose optimisation.

Method: A validated PBPK model was used to simulate imatinib absorption, distribution, metabolism, and elimination in lean, overweight, and obese cancer populations. These models accounted for key physiological differences, including variations in liver enzyme activity, fat distribution, blood flow, and protein binding, all of which influence drug behaviour in the body. Virtual clinical trials were conducted to assess imatinib pharmacokinetics in these different populations and to evaluate whether therapeutic drug monitoring (TDM)-guided dose adjustments could help maintain drug levels within the therapeutic target range.

Results: The results demonstrated that obesity leads to significant changes in imatinib pharmacokinetics. Obese patients exhibited lower peak drug concentrations (Cmax) and total drug exposure (area under the curve, AUC), with a higher proportion having imatinib trough concentrations (Cmin) below the recommended therapeutic threshold of 750 ng/mL. These lower drug levels may increase the risk of treatment failure in obese patients. TDM-based dose adjustments improved drug exposure across all BMI groups, with a 1.5- to 2.0-fold increase in dose effectively restoring Cmin to the target range of 750–1,500 ng/mL. However, patients with extremely low initial Cmin (<450 ng/mL) struggled to reach therapeutic levels even with higher doses, suggesting that alternative treatment approaches may be necessary for this subgroup.

This study highlights the potential of PBPK modelling combined with virtual clinical trials to improve precision dosing in oncology. By integrating patient-specific physiological characteristics into drug simulations, this approach helps identify at-risk populations and optimise treatment strategies. The findings also reinforce the value of TDM in guiding dose adjustments for imatinib, ensuring that patients, regardless of body weight, receive appropriate drug exposure to maximise therapeutic benefits.

Conclusion: Given the rising prevalence of obesity worldwide, refining dosing strategies for targeted cancer therapies is increasingly important. This study supports a move towards more personalised medicine, where drug doses are tailored to individual patient characteristics rather than a one-size-fits-all approach. Future research should further explore how obesity affects other targeted therapies and how PBPK modelling can support broader clinical applications.

RNA transcription assisted universal CRISPR/Cas12a system for programmable analysis of multiple colorectal cancer-associated microRNAs

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Accurate analysis of multiple microRNA (miRNA) levels is significantly valuable for early diagnosis of colorectal cancer noninvasively considering the miRNA expression is highly relevant to the occurrence and progression of cancer. However, the low abundance and high sequence homology of miRNAs make their precise determination extremely challenging. Here, we developed a universal and programmable diagnostic strategy allowing for analyzing multiple colorectal cancer-associated miRNAs. The system combined sequentially programmable rolling circle transcription (RCT) and the CRISPR/Cas12a system with high trans-cleavage activity to achieve highly sensitive and specific detection of four target miRNAs. Owing to the remarkable performance of universal RCT-Cas12a strategy, this biosensor could detect miR-21, miR-17, miR-31 and miR-92a with a LOD of 2.1, 1.6, 3.7 and 1.0 pM, respectively. This strategy had a unique advantage in distinguishing human normal colon epithelial cells lines (NCM460) from human colon cancer cells (HT29). In particular, the designed system exhibited superior analytical capability in distinguishing paracancerous and colorectal cancer tissues from patients undergoing colorectal cancer surgery. This arbitrarily programmable, scalable, fast and specific strategy potentially offered an attractive alternative to handle varied challenges encountered with CRISPR-based systems, and held immense promise in scientific research and clinical applications.

Combination versus single-drug non-prescription analgesics for acute pain management: A narrative review

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Introduction: Acute pain is a common source of suffering with broad clinical and societal impact. It is typically caused by direct tissue damage and resolves within minutes to weeks after the inciting event. Although acute pain is not expected to persist indefinitely, inadequate management can have considerable consequences for patients, including impaired physical function, reduced quality of life, and an increased risk of developing chronic pain. Combining non-prescription analgesics (paracetamol, metamizole, and nonsteroidal anti-inflammatory drugs [NSAIDs]) with different mechanisms of action has been proposed as a rational strategy to optimise the management of acute pain. This review aims to assess and summarise published clinical evidence on the efficacy and safety of non-prescription analgesics used in combination versus monotherapy in acute pain conditions.

Method: MEDLINE and Embase databases were searched from inception to December 2024 using the following keywords and their variants - "paracetamol," "metamizole," "NSAIDs," "combination," and "acute pain" - for randomised controlled trials (RCTs) published in English. RCTs were eligible for inclusion if they compared oral paracetamol combined with a non-prescription NSAID (oral or topical) versus either or both components alone in acute pain conditions and acute episodes/exacerbations of chronic pain conditions. Studies were excluded if the drugs of interest were administered using a route not available in a non-prescription setting.

Results: Twenty-five studies were included that compared combination therapy with paracetamol and an oral NSAID (ibuprofen, diclofenac, aceclofenac, and/or acetylsalicylic acid) or metamizole/ibuprofen with either or both drugs alone in various clinical settings. These settings included post-surgical pain (extraction of third molars; the dental impaction pain model [DIPM], 9 studies; endodontic surgery, 3 studies), acute low back musculoskeletal pain (3 studies), acute non–low back musculoskeletal pain (6 studies), and headache (4 studies). Combination therapy demonstrated superior analgesia compared to monotherapy in the DIPM, along with potential dose-sparing and opioid-sparing effects. Additionally, combination therapy provided greater pain relief versus either monotherapy over 8 hours following a single dose after endodontic surgery. In contrast, studies in acute musculoskeletal pain yielded mixed results for combination therapy versus monotherapy. Studies in patients with headache included caffeine in addition to paracetamol/NSAIDs and showed that this combination provided faster and more effective pain relief versus paracetamol or an NSAID alone. Across all settings, oral combination therapy with paracetamol/NSAIDs was well tolerated, with adverse event rates comparable to or even lower than those observed with monotherapy. The most common adverse events were typically gastrointestinal or neurological in nature.

Conclusion: The findings of this narrative review support the use of combination therapy with paracetamol and an NSAID in the management of post-surgical pain and headache. However, differences in analgesia between combination therapy and monotherapy were not consistently demonstrated in the acute musculoskeletal pain setting. Further research is warranted to explore the benefits of combination therapy with paracetamol and NSAIDs compared with monotherapy in different acute pain conditions.

Causal relationship between inherited immune traits and cisplatin-induced ototoxicity in cancer patients: A bidirectional two-sample Mendelian randomization study

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Introduction: Cisplatin is an effective chemotherapeutic agent for solid tumors, but its clinical use is limited by dose-dependent ototoxicity. Current challenges include the lack of reliable biomarkers for predicting ototoxicity and effective prevention or treatment strategies. Previous researches have linked genetic features, such as single nucleotide polymorphisms (SNPs), to cisplatin-induced ototoxicity, while inconsistent conclusions hinder their clinical application as predictors. Mendelian randomization (MR) was utilized to establish a causal relationship between inherited immune traits and associated SNPs with cisplatin-induced ototoxicity. The identified inherited immune traits and SNPs provide potential predictors for adverse reactions and enable risk stratification for ototoxicity.

Methods: This study utilized a Two-Sample MR framework to investigate the causal relationships between 33 inherited immune traits and cisplatin-induced ototoxicity. Multiple MR methods were systematically applied, including Inverse Variance Weighting (IVW), MR-Egger regression, weighted median, weighted mode, and simple mode analyses. To ensure robust causal inference, comprehensive sensitivity analyses were performed to evaluate heterogeneity and potential horizontal pleiotropy, alongside bidirectional MR to rule out reverse causation.

Results: This study identified potential causal relationships between inherited immune traits and cisplatin-induced ototoxicity in children. Transforming Growth Factor-Beta principal component analysis (TGF-β PCA) was significantly associated with an increased risk of ototoxicity (IVW: OR=10.33, 95% CI: 1.61–66.23, P=0.014). Whereas no direct causal relationships were observed between inherited immune traits and cisplatin-induced ototoxicity in adult. Reverse MR analyses did not reveal significant associations between ototoxicity and inherited immune traits. When focusing on SNPs with a significance threshold of P<1×10−6, it was found that the A/G genotype of rs11028412 related to B cell metagene Immunoglobulin J (Bcell mg IGJ) (Beta=-5.78, SE=2.83, P=0.041) and the C/T genotype of rs1126242 related to the proportion of cytotoxic T lymphocytes (CD8 T Cells(%)) (Beta=-0.43, SE=0.22, P=0.049) were significantly associated with a reduced risk of cisplatin-induced ototoxicity in children. In contrast, the A/G genotype of rs147635550 related to TGF-β PCA (Beta=9.39, SE=3.90, P=0.016),the A/G genotype of rs57160108 related to the the proportion of natural killer cells activated (NK Cells Activated (%))

(Beta=0.79, SE=0.29, P=0.007) and the A/G genotype of rs7814781 related to lymphatic principal component analysis (LYMPHS.PCA) (Beta=6.27, SE=3.17, P=0.048) were significantly associated with an increased risk of ototoxicity in children. In addition, the A/G genotype of rs7233393 (Beta= -67.66, SE= 21.18, P=0.001), related to CD8 T cells, was significantly associated with a low risk of cisplatin-induced ototoxicity in adults.

Conclusion: By using MR analysis, the inherited immune trait of TGF-β PCA was robustly confirmed as an increased risk of cisplatin-induced ototoxicity in children. Furthermore, SNPs of rs11028412 and rs1126242, related to B-cell mg IGJ and CD8 T cells (%), were significantly associated with reduced risks of cisplatin-induced ototoxicity in children. Whereas, SNPs of rs147635550, rs57160108 and rs7814781, related to TGF-β PCA, activated NK cells (%) and LYMPHS PCA were significantly associated with increased risks. Additionally, SNPs of rs7233393, associated with CD8 T cells, demonstrated a significant link to a low risk of cisplatin-induced ototoxicity in adults.

Qualitative study on pharmacy-based pharmacogenetic testing opinions and perceptions among physicians, pharmacists and the Swiss general population

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Introduction: While pharmacogenetic testing has emerged as a valuable tool for personalising drug therapy, its implementation in Swiss healthcare settings remains limited, despite successful adoption models in several countries' community pharmacy settings. This study investigates the knowledge, attitudes, and perceived barriers among Swiss pharmacists, physicians, and the general population to understand factors influencing pharmacogenetic implementation.

Method: A mixed-methods approach was employed, combining structured questionnaires and semi-structured interviews among the Swiss general population, community pharmacists, and physicians. The questionnaires evaluated pharmacogenetic knowledges, perceived utility, and implementation barriers, while interviews explored participants' perspectives and experiences regarding pharmacy-based pharmacogenetic testing implementation. Data were analysed using descriptive statistics and thematic analyses.

Results: A total of 332 participants completed the questionnaire (100 physicians, 122 pharmacists, and 110 members of the general population), while 26 individuals participated in interviews (9 physicians, 9 pharmacists, and 8 members of the general population). The clinical utility of pharmacogenetic testing was widely acknowledged (99% of physicians, 98% of pharmacists, 79% of the general population), with the general population particularly supporting its role in reducing adverse effects (81%), enhancing treatment effectiveness (71%), and improving medication management (78 Additionally, healthcare professionals believed that pharmacogenetics could improve medication therapy (99% of physicians and 98% of pharmacists). Although pharmacists and physicians endorsed a collaborative approach to pharmacogenetic testing, with physicians supporting pharmacists' role in prescribing pharmacogenetic tests (53%), interpreting (57%), and patient education (70%), 76% of pharmacists reported insufficient knowledge to confidently recommend pharmacogenetic testing. The reimbursement by mandatory health insurance was supported by 47%, 53% and 79% of physicians, pharmacists, and the general population, respectively. The integration of pharmacogenetic data into the patient medical record was supported by 77% of physicians and 88% of pharmacists. Concerns about the access to genetic data by health insurances were significant among 94% of physicians, 60% of pharmacists, and 69% of the general population. The interviews highlighted key implementation challenges, including the need for standardised guidelines, electronic health record integration, and clear communication strategies to educate patients on their pharmacogenetic profile and its implications for their treatment. Healthcare professionals emphasised the importance of a strong interprofessional collaboration, while identifying barriers such as cost constraints, time limitations, and educational requirements. Again, data privacy emerged as a critical concern, particularly regarding insurance access to genetic information.

Conclusion: This study highlighted key challenges for implementing pharmacogenetic testing in Swiss community pharmacies. While healthcare professionals acknowledged its benefits, uncertainties about pharmacists' roles and the need for clearer interprofessional collaboration emerged. Privacy concerns were prominent, with fears about insurance access to genetic data and the commercialisation of patient information. Additionally, general population preferences varied on where pharmacogenetic testing should take place. Addressing these issues through targeted education, structured collaboration, and strong data protection policies will be essential for successful pharmacogenetic integration.

Impact of genetic factors into bleeding events in patients taking direct oral anticoagulants (DOAC): Systematic review and meta analysis

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Background: Interindividual variability is a significant concern in patients receiving antithrombotic therapy, including novel agents such as direct oral anticoagulants (DOACs). Both genetic and clinical factors contribute to the risk of adverse effects and influence clinical outcomes. This study aims to investigate the association between genetic variations in ABCB1 and the risk of bleeding in patients treated with DOACs

Methods: This study was a subgroup and meta-regression analysis from a systematic review and meta-analysis on the prevalence of genetic factors and its association with bleeding, thromboembolic events, and pharmacokinetic factors in patients taking direct oral anti coagulant. A systematic review and meta-analysis were conducted, screening studies published from the Medline, Embase, and CINAHL databases, following the PRISMA flowchart guidelines. Studies were included based on the following criteria: observational designs (cohort or case-control studies, with prospective or retrospective sampling), human genetic determinants related with DOAC, the outcome measured was bleeding and publication in English. The analysis was conducted using R Studio (version 4.2.3) with the metafor package.

Results: A total of 12 studies were included in this analysis. The pooled prevalence of bleeding events in patients receiving apixaban and rivaroxaban therapy was 9.03% (95% CI: 2.62–15.45%) and 22.74% (95% CI: 13.68–31.81%), respectively, with statistically significant p-values of 0.0058 and 0.0001. In contrast, dabigatran therapy was associated with a non-significant increase in bleeding events, with a prevalence of 26.13% (95% CI: -5.74–58%) and a p-value of 0.1080. Several factors were strongly associated with bleeding events, including ABCB1 polymorphism and clinical variables such as age, renal function, and body mass index (BMI). However, certain populations remain underrepresented in these findings, as most study participants were of White or Asian descent.

Conclusions: This meta-analysis demonstrates significant variability in bleeding risk among DOAC users, with apixaban and rivaroxaban showing a statistically significant prevalence, while dabigatran exhibited a non-significant increase. Bleeding risk was strongly associated with ABCB1 polymorphisms and clinical factors such as age, renal function, and BMI, though the underrepresentation of certain populations limits the generalizability of these findings.

Impact of CYP450 Genotype and patient adherence on tamoxifen and its metabolites concentrations: A cross-sectional clinical investigation

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Introduction: Tamoxifen, a prodrug activated by cytochrome P450 isoforms, is widely used as an endocrine therapy for hormone receptor-positive breast cancer patients. While the standard dose is 20 mg/day, this one-size-fits-all approach does not account for individual patient characteristics, resulting in high variability in concentrations of tamoxifen and its metabolites. The impact of the variations of enzyme activities and medication adherence on treatment outcomes remains poorly understood, highlighting the need for personalized treatment strategies.

Purpose: This study investigates how pharmacogenetic factors, patient characteristics, and medication adherence influence inter-individual variability in tamoxifen and its metabolites among hormone receptor-positive breast cancer patients receiving 20 mg/day of tamoxifen.

Methods: We conducted a single-center, cross-sectional study at an outpatient breast center. Hormone receptor-positive breast cancer patients receiving 20 mg/day tamoxifen were recruited between March 2024 and January 2025. The study was approved by the Institutional Review Board of National Taiwan University Hospital (202301089RINA). Venous blood was collected from patients who had been on tamoxifen for 4 months for quantification of tamoxifen and seven metabolites (Z-N-desmethyltamoxifen, tamoxifen-N-oxide, Z-endoxifen, Z-4-hydroxytamoxifen, E-endoxifen, Z'-endoxifen, and Z'-4-

hydroxytamoxifen) using ultraperformance liquid chromatography-tandem quadrupole mass spectrometer (UPLC-MS/MS). Pharmacogenetic genotyping was performed via next-generation sequencing, and patient characteristics were recorded. Adherence score was assessed using Adherence to Refills and Medication Scale (ARMS-7). Correlation analysis and Wilcoxon rank sum tests were used to identify factors associated with the concentration of tamoxifen and its metabolites. The statistical software SAS (version 9.4) was used and a P-value of less than 0.05 was considered statistically significant.

Results: A total of 97 patients were analyzed. The median age is 50 years. The concentration of tamoxifen and its metabolites varied significantly (coefficient of variation: 20%–70%) among patients, with the most potent metabolite, Z-endoxifen, showing the highest variability (0.86 ng/mL - 28.40 ng/mL). While the direct metabolites from tamoxifen were highly correlated with the concentration of tamoxifen (r = 0.71-0.87), a poor correlation between the concentrations of Z-N-desmethyltamoxifen and Z-endoxifen was observed (r = 0.32). The concentration of Z-N-desmethyltamoxifen was significantly correlated with the assessed adherence score. Additionally, concentrations of tamoxifen and its metabolites (Z-N-desmethyltamoxifen, Z'-endoxifen, Z-4-hydroxytamoxifen, and Z'-4-hydroxytamoxifen) were statistically significantly lower in self-reported non-adherent patients. CYP2C9 intermediate metabolizers had significantly lower concentrations of Z'-endoxifen and Z'-4-hydroxytamoxifen than normal metabolizers. Similarly, CYP2D6 intermediate metabolizers had significantly lower concentrations of Z-endoxifen and Z-4-hydroxytamoxifen, but higher concentrations of Z'-endoxifen than normal metabolizers.

Conclusion: Tamoxifen and its metabolites concentrations vary significantly across individuals due to patient characteristics, adherence, and pharmacogenetics. CYP2D6 and CYP2C9 polymorphisms are key determinants of the concentration of Z-endoxifen and related metabolites in patients. The findings highlight the importance of therapeutic drug monitoring of tamoxifen and its metabolites in an individual patient. To improve treatment optimization for outpatients, future research should explore a convenient method for point-of-care monitoring, such as using volumetric absorptive microsampling (VAMS) as a minimally invasive tool for drug monitoring and adherence assessment, enabling personalized dosing.

Biomarker-guided psychopharmacology: Advancing personalized medicine in mental health

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For decades, psychopharmacology has relied on a trial-and-error approach to prescribing medications for psychiatric disorders. This method often results in delayed therapeutic effects, increased side effects, and treatment resistance, leaving many patients without effective relief. The variability in drug response among individuals, influenced by genetic, inflammatory, and neurophysiological factors, highlights the need for a more precise, personalized approach to treatment. Personalized medicine, leveraging biomarkers such as pharmacogenetic variants (e.g., CYP450 genes), inflammatory markers (e.g., CRP), and neurophysiological indicators, offers a promising alternative. By identifying biological factors that influence drug metabolism, treatment response, and side effect susceptibility, biomarker-driven strategies have the potential to improve clinical outcomes, minimize adverse effects, and enhance overall treatment efficacy.

This systematic review examines peer-reviewed clinical trials, meta-analyses, and cohort studies published over the past decade, focusing on research with over 100 participants and robust methodologies. Studies were selected based on their evaluation of biomarker-guided treatment approaches in psychiatric disorders, particularly in depression, schizophrenia, and bipolar disorder. The analysis considers pharmacogenetic testing, inflammatory marker assessments, and neurophysiological evaluations as predictive tools for optimizing drug selection and dosage adjustments. Additionally, studies investigating the integration of artificial intelligence (AI) and multi-omics approaches to enhance biomarker interpretation were reviewed. By synthesizing findings from high-quality studies, this review aims to assess the clinical utility, feasibility, and challenges associated with implementing biomarker-driven psychiatry in real-world practice.

Results: indicate that biomarker-guided approaches significantly improve drug response rates by up to 30% and reduce the likelihood of adverse effects compared to conventional prescribing methods. Pharmacogenetic testing allows for tailored medication selection, reducing trial-and-error prescribing and minimizing treatment resistance. Inflammatory markers, such as CRP, have shown potential in identifying subgroups of patients who may benefit from specific medications, while neurophysiological indicators provide additional insights into treatment response. Despite these promising advancements, several barriers to implementation remain. The lack of standardized biomarker validation, limited accessibility of testing, and ethical concerns surrounding genetic data privacy and equitable distribution of personalized treatments continue to hinder widespread adoption. Additionally, the cost-effectiveness of

biomarker testing and its integration into routine psychiatric care require further evaluation to ensure broad clinical applicability.

While these challenges persist, ongoing advancements in biomarker research, AI-driven predictive modeling, and multi-omics integration are steadily addressing these limitations. Emerging technologies are improving the accuracy, affordability, and accessibility of biomarker testing, making personalized psychiatry more feasible. As research continues to bridge the gap between discovery and clinical application, biomarker-driven strategies hold the potential to transform psychiatric care. By enabling more targeted, effective, and patient-centered treatments, this approach could enhance long-term outcomes, reduce hospitalization rates, and alleviate the global burden of mental health disorders. With continued progress in biomarker validation, regulatory frameworks, and clinical integration, precision psychiatry may soon become a fundamental aspect of mental healthcare, replacing the current reliance on trial-and-error prescribing with evidence-based, individualized treatment strategies.

Pharmacists' perspectives on implementing pharmacogenomics (PGx) in hospital practice: A survey on familiarity, application, and educational needs at a medical center in Taiwan

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Background: Pharmacogenomics (PGx) has the potential to improve drug therapy by optimizing medication selection and dosing based on genetic factors. However, its clinical application remains limited. Understanding pharmacists' knowledge gaps, unmet needs about PGx and perceived barriers in clinical application of PGx is essential for successful PGx implementation.

Purpose: This study aims to investigate pharmacists' familiarity with PGx, their confidence in data interpretation, perceived barriers to implementation, training preferences, and acceptance of PGx-guided therapy at NTUH Hsin-Chu branch.

Methods: A cross-sectional survey by questionnaire was conducted among pharmacists across different age groups at NTUH Hsin-Chu branch from January 2025 to February 2025. The questionnaire assessed the familiarity, real application (prior experience using PGx tools), implementation barriers, training preferences, confidence in the interpretation of PGx data, and overall acceptance of PGx-guided therapy. Descriptive statistics were used to analyze the data.

Results: A total of 37 pharmacists completed the survey (survey response rate=37/40 (92.5%)). Over half (54.05%) were completely unfamiliar with PGx, with the 30–40 age group showing the lowest familiarity (80% unfamiliar). The percentage of individuals without prior experience using PGx tools and being unfamiliar with these tools was high (51.52%). Confidence in PGx data interpretation was also low, with 39.39% reporting low confidence, particularly in the 30–50 age group. The major barriers to PGx implementation were insufficient knowledge/training (69.70%), uncertainty about clinical relevance (15.15%), and limited data accessibility (12.12%). Despite these challenges, 93% believed that PGx tools are beneficial, and 27.59% strongly supported their use. Training preferences varied by age, with the 50–60 age group showing the highest interest in advanced training. Preferred learning formats included short videos (29.41%), live discussions (26.47%), online self-learning (26.47%), and hands-on workshops (17.65%). While 83.78% believed PGx improves treatment outcomes, only 8.11% strongly supported its adoption. The highest support was observed in the 30–40 age group (90%), while the 60–70 age group was divided, with 50% expressing a neutral stance.

Conclusion: Pharmacists demonstrated limited familiarity with PGx, low confidence in data interpretation, and minimal tool usage. The key barriers were insufficient training, uncertain clinical relevance, and limited data access. Despite these challenges, most pharmacists acknowledged PGx benefits and expressed willingness to receive training. Future efforts should focus on developing structured training programs that address different learning preferences, strengthening clinical evidence, and improving access to PGx tools.

Exposure to multiple drugs with actionable pharmacogenetic biomarkers among older adults in China: A retrospective analysis

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Aims: To investigate the prevalence of longitudinal exposure to multiple drugs with a high level of evidence (Level A) for pharmacogenetic-guided drugs (PGx drugs) among older adults, project the prevalence of pharmacogenes associated with PGx drugs, evaluate the cumulative impact of these gene-drug pairs to health resource utilizations and explore the feasible pricing models for multigene panel tests to help implementing pharmacogenomics into clinical practice.

Methods: This cross-sectional study analyzed data from 2015 to 2017, encompassing individuals aged 65 years and older within the China Health Insurance Research Association (CHIRA). We identified 53 drugs with the highest level of evidence for actionable pharmacogenetic variants, according to the Clinical Pharmacogenomics Implementation Consortium (CPIC) guidelines, as of January 1, 2024(CPIC Level A drugs). The study estimated the prevalence of older adults exposed to at least two or at least five CPIC Level A drugs within the same calendar year. Among those exposed to multiple PGx drugs, drugs were categorized by their associated pharmacogenes, and the prevalence for each category was ascertained. Subsequently, the cumulative impact of these pharmacogenes were calculated. Finally, the cost of single gene testing and multigene panel testing was calculated from the perspective of the whole of society using established capped per-locus pricing model.

Results: Between 2015 and 2017, 20.2% older patients were prescribed at least 2 CPIC level A drugs, among which 9.4% were prescribed five or more. Among those prescribed at least two CPIC level A drugs, atorvastatin was the most frequently prescribed, affecting 84.2 per 1000 patients. For patients receiving at least five level A drugs, the proton pump inhibitor (PPI) pantoprazole was the most common, with a rate of 11.9 per 1000 patients. Our data underscore that the most relevant pharmacogenes for use in testing panel are CYP2C19, SLCO1B1, and CYP2C9 in the population exposed to multiple CPIC level A drugs. These three pharmacogenes are relevant for over 95% of older patients. Under the capped per-locus pricing model, multigene panel tests involved CYP2C19, SLCO1B1, and CYP2C9 is cost-savings.

Conclusions: Exposure to multiple drugs with actionable pharmacogenetic biomarkers among older people is common. A small number of pharmacogenes account for the majority of the population exposed to multiple PGx drugs. This finding suggests that PGx testing for frequently prescribed PGx drugs and their implicated genes (CYP2C19, SLCO1B1 and CYP2C9) to optimize prescribing among older adults.

Clinical pharmacogenomics implementation in Thailand: The emerging roles of pharmacists in clinical setting

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Introduction: Ever since the pharmacogenomics research began in 2004 in Thailand, a multitude of pharmacogenomics variants associated with drug responses have been identified in the Thai population, such as HLA-B*15:02 for carbamazepine, HLA-B*58:01 for allopurinol, HLA-B*13:01 for dapsone/cotrimoxazole, CYP2C19 for clopidogrel, CYP2C9 for phenytoin, TPMT and NUDT15 for thiopurine drugs etc.

Method: After the genetic screening is proven to be cost-effective, a peer-reviewed guideline for the translation of pharmacogenomics test results is formulated to make clinical decisions. Finally, National Health Security Office take the potential of pharmacogenomics tests to meet public health goals through the integration of pharmacogenomics into national policy. The pharmacogenetics profile guided therapy in clinical settings across Thailand appears promising because of the availability of evidence of clinical validity of the pharmacogenomics testing and support for reimbursement of pharmacogenomics testing. Undoubtedly, “Pharmacist” plays a major role to implement pharmacogenomics and support health professional team for decision-making by precision medicine approach. Generally, pharmacists should lead in the clinical implementation of pharmacogenomics as drug–gene, drug-drug, drug herb/supplement/food interaction experts.

Results: Therefore, all pharmacy programs in Thailand have added pharmacogenomics and precision pharmacy to their curricula after the “Pharmacy Council of Thailand Announcement” with classification of "Thai Pharmacist" into 3 levels.

General Pharmacist (Pharmacist level 1): All registry pharmacist has had to learn the “Fundamental of pharmacogenomics and precision pharmacy (1 credit, 16 hours). The roles of Pharmacist level 1 are introductory counseling for PGx, encourage the PGx test appropriately, interpret the PGx result and report, coordinate and communicate with the health care providers team.

Specialty PGx-Pharmacist (PGx-Pharmacist level 2): The registry pharmacist has had to train the course of “Practical skill in PGx and PP for 16 credit (4 months). The PGx-Pharmacist level 2 should be able to act as “PGx-Pharmacist level 1 plus to be a leader of multidisciplinary team, PGx counseling (Pre- and Post- testing), develop the PGx workflow and service, knowledge management and sharing for patients. Importantly, they should be able to advice the physician and dentist for medicinal treatment plan and monitoring.

Professional PGx-Pharmacist (PGx-Pharmacist level 3): The registry pharmacist has had to train of “Board Certified Pharmacogenomics and Precision Pharmacy Training Program” for 134 credits (4 years) from The College of Pharmacogenomics and Precision Pharmacy. The PGx-Pharmacist level 3 should be able to act as “PGx-Pharmacist level 2”. Additionally, they should be able to conduct the PGx research, develop the clinical decision support systems and facilitate the development of clinical practice guidelines, knowledge management and sharing for health professionals. Notably, they can be a preceptor for PGx-Pharmacist level 2 training program.

A nationally commissioned “Genomic Medicine Service” is also gradually supporting PGx implementation by allowing

pharmacists to take the leadership role in PGx implementation.

Conclusion: This talk provides an overview of the current pharmacogenomics practices and research in Thailand, address the challenges and lessons learned from delivering pharmacogenomics services in clinical practices, emphasize the pharmacogenomics implementation issues that must be overcome, and identify the emerging roles of pharmacist to facilitate clinical implementation of pharmacogenomics.

Effects of cyclooxygenase inhibitors on prostaglandin E2 transport in the HK-2 human kidney epithelial cell line

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Background: Enhanced glomerular permeability following hypertension and diabetic nephropathy increases albumin concentration in the renal proximal tubular lumen. Albumin passing through the glomerulus is reported to be involved in the progression of tubulointerstitial damage, leading to end-stage renal disease, but the precise molecular mechanism remains to be elucidated. Fatty acids bound to albumin have been reported to be responsible for various responses in renal proximal tubular cells following albumin overload, leading to the progression of tubulointerstitial damage in the kidneys. We previously found that albumin treatment induced the activation of hypoxia-inducible factor-1 (HIF-1), a major transcriptional regulator of cellular responses to hypoxia, in human kidney epithelial cell line HK-2. In addition, the induction of HIF-1 activation by albumin in HK-2 cells was due to fatty acids intrinsically bound to albumin rather than albumin molecule itself. Furthermore, we found not only albumin treatment-induced prostaglandin E_2 (PGE_2) production but also PGE_2 treatment-induced HIF-1 activation in HK-2 cells.

Purpose: The aim of this study was to examine characterization of PGE_2 transport in HK-2 cells, and the effects of cyclooxygenase (COX) inhibitors on the uptake of PGE_2 in HK-2 cells.

Methods: Cell culture: HK-2 cells were cultured in a 1:1 mixture of Dulbecco's modified Eagle's medium and Ham's F-12, containing 10% fetal bovine serum, under an atmosphere of 5% CO_2-95% air at 37°C. The medium was replaced with fresh medium every 2 or 3 days. Real-time PCR: Total RNA was extracted from HK-2 cells and real-time PCR was performed. The threshold cycle (Ct) value for each mRNA was determined using the second derivative maximum method. PGE_2 uptake study: Uptake studies were performed on confluent cells attached to 24-well plates. After HK-2 cells were cultured for 6 days, each well was washed and preincubated with phosphate-buffered saline. Then, the uptake of $[^3H]PGE_2$ (5 nM) was determined.

Results: The mRNA expression of SLCO2A1 (solute carrier organic anion transporter family member 2A1), known as a prostaglandin transporter, was detected in HK-2 cells. The initial uptake of $[^3H]PGE_2$ in HK-2 cells was temperature-sensitive. $[^3H]PGE_2$ uptake was inhibited by unlabeled PGE_2 and bromocresol green, a typical inhibitor of SLCO2A1, in a concentration-dependent manner. The relationship between the concentration and the uptake rate of $[^3H]PGE_2$ was nonlinear, indicating the involvement of a saturable process in $[^3H]PGE_2$ uptake in HK-2 cells. The Km was estimated to be 306 nM, which is consistent with the previous value which was shown by SLCO2A1-mediated PGE_2 uptake analysis. Furthermore, diclofenac, a COX inhibitor, decreased the uptake of $[^3H]PGE_2$ in a concentration-dependent manner. In contrast, another COX inhibitor indomethacin tended to increase $[^3H]PGE_2$ uptake in HK-2 cells. The modulation pattern of the COX inhibitors for $[^3H]PGE_2$ uptake in HK-2 cells was in agreement with that in SLCO2A1-expressing HEK293 cells, which were previously reported.

Conclusion: These observations indicate that PGE_2 is taken up by a carrier-mediated transport system in HK-2 cells and SLCO2A1 plays an important role in the uptake of PGE_2 in HK-2 cells.

Assessment of knowledge, attitude, and practices of human ethics committee members on genetic data sharing and reuse for future research

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Introduction: The ethical review of genetic research within clinical trials is crucial for ensuring data integrity and participant protection. This study aimed to assess the knowledge, attitudes, and practices (KAP) of Human Ethics Committee (HEC) members regarding genetic data sharing and reuse.

Method: A cross-sectional study was conducted among 50 HEC members in northern Karnataka, India, using a validated KAP questionnaires. The study was approved by the human ethics committee and informed consent was taken prior conducting the study. The data was analyzed using descriptive statistics.

Results: Findings revealed low awareness of optional consent (40%), genetic data ownership (44%), and bio-repositories (50%). While 56% expressed concerns about genetic data misuse, 74% recognized the need for strong regulatory knowledge. 46% agreed that separate consent should be required for data reuse, and 80% trusted biobanks for secure storage. Notably, 76% had never reviewed a clinical protocol addressing genetic data reuse.

Conclusion: The study underscores the urgent need for enhanced education, standardized protocols, and stricter governance in genetic research ethics. Strengthening regulatory frameworks and training ethics committees can ensure secure and ethical reuse of genetic data in clinical trials.

Development of a population pharmacokinetic model for high-dose methotrexate in Japanese paediatric patients with acute lymphoblastic leukaemia

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Background information: High-dose methotrexate (HD-MTX) is an important treatment option for paediatric patients with acute lymphoblastic leukaemia (ALL). Its use is complicated because its pharmacokinetics (PK) vary widely due to individual differences in renal function and body size. Population pharmacokinetic (PPK) modelling can be used to optimise dosing and improve therapeutic outcomes. However, no PPK model for HD-MTX has been developed specifically for Japanese paediatric patients, making it difficult to apply existing models directly to this population. Purpose: We developed a PPK model of HD-MTX for Japanese paediatric patients with ALL and assessed its predictive accuracy compared to existing models.

Method: Retrospective data from 38 paediatric patients with ALL (<15 years) who received HD-MTX (2–5 g/m²) at Tokyo Medical and Dental University Hospital from 2013 to 2024 were analysed. Plasma MTX concentrations were measured at 24, 42, 48, and 66 h post-administration. A PPK model was developed using a nonlinear mixed-effects modelling (NONMEM) approach with a two-compartment model. Covariates including body surface area (BSA), creatinine clearance (CrCL), and hydration rate (HYDR) were evaluated by stepwise selection. Model performance was assessed using goodness-of-fit plots, prediction-corrected visual predictive checks (pcVPC), and bootstrap validation. Our model's prediction performance was compared with those of previously published models using a dataset obtained from a systematic review. Monte Carlo simulations were performed to investigate optimal dosing strategies, simulating different hydration rates and body size variations, and to explore their impact on MTX exposure.

Results: MTX concentrations in 504 blood samples were analysed. The final PPK model demonstrated clearance (CL) to be a function of BSA, CrCL, and HYDR. The central volume of distribution (Vc) was significantly associated with BSA, whereas transitional clearance was influenced by HYDR. The equations for CL, Vc, and transitional clearance between the central and peripheral compartments (Q) in the final model were as follows:
CL(L/h) = 3.49 × (BSA/0.74)^0.462 × (CrCL/0.74)^0.366 × (HYDR/129)^0.164
Vc(L) = 10.1 × (BSA/0.74)^0.473
Q(L/h) = 0.0609 × (HYDR/129)^0.711
The model exhibited good predictive performance in pcVPC and bootstrap analyses, confirming its stability. Comparative evaluations demonstrated superior predictive accuracy compared with previously published PPK models. Monte Carlo simulations indicated that higher hydration rates improve the probability of achieving target MTX concentrations.

Conclusion: We report here the first PPK model for HD-MTX therapy in Japanese paediatric patients with ALL, incorporating CrCL, BSA, and HYDR as key covariates. Inclusion of hydration rate as a covariate highlights its clinical relevance in optimising MTX clearance, supporting the importance of fluid management. Our findings provide a valuable tool for the development of individualised HD-MTX therapy.

Application of popPK models for assessment of adherence to CDK4/6 inhibitor ribociclib

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Introduction: Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors, such as ribociclib, have revolutionized the treatment of HR+/HER2- advanced breast cancer. However, patient adherence to these therapies plays a crucial role in their efficacy, influencing clinical outcomes and overall

survival. Population pharmacokinetic (popPK) models provide a valuable tool for assessing adherence patterns by integrating drug concentration data with individual patient characteristics.

The goal of this study is to explore the application of popPK modeling for evaluating adherence to ribociclib and its potential impact on treatment optimization. This is accomplished by assessing the agreement between prediction intervals derived from published popPK models and actual patient measurements, simulating scenarios of poor adherence using popPK modeling approaches, and estimating individual patient adherence based on PK data. By integrating these objectives, we seek to provide insights for optimizing ribociclib therapy in clinical practice.

Method: Concentration of ribociclib in real patient plasma samples was determined using a validated UHPLC-MS/MS method with a linear range of 250–5000 ng/mL. The PK modelling was conducted using NONMEM v. 7.5.0 (ICON) program. Statistical analysis and data visualization were performed in Rstudio v. 2024.09.1 (Posit) with R v. 4.3.3, while Perl-speaks-NONMEM v. 5.5.0 (Uppsala Pharmacometrics) was used to assist NONMEM runs. In total, 106 plasma samples from 23 different patients were collected and analysed. Demographic and biochemical parameters were obtained. Information about the last administered dose, time of last dose administration, and time of sampling was recorded. Using the MARS-5 questionnaire, adherence data, including the number of missed doses, were collected. Missing data were handled using interpolation and assumptions based on ideal body weight and renal function.

Results: PopPK models from the literature were successfully implemented in NONMEM, with a specific model used for ribociclib. Goodness-of-fit analysis demonstrated a strong agreement between observed and predicted values. Simulations of individual predicted concentration (IPRED) and concentration-time curves of ribociclib were performed with 2000 replicates under different adherence scenarios, incorporating variations in body weight and dose levels (200, 400, and 600 mg). Inter-individual variability was assessed for clearance, central compartment volume, and intercompartmental clearance.
Analysis of patient samples revealed individuals with drug concentrations below the predicted population median. Among them, three patients had significantly lower concentrations (below the lower limit of 60% prediction intervals), indicating potential non-adherence or altered pharmacokinetics. Simulated PK curves based on each patient's parameters further highlighted variations in adherence.

Conclusion: PopPK modeling demonstrated its utility in evaluating ribociclib adherence, revealing a subset of patients with decreased drug exposure. Simulated adherence scenarios provided a deeper understanding of how missed doses impact drug levels. The findings suggest that integrating adherence data into PK models can enhance treatment individualization and optimize therapeutic outcomes. Further studies are warranted to refine these models and develop interventions for improving adherence in clinical settings.

This work has been fully supported by the Croatian Science Foundation through projects UIP-2019-04-8461 and DOK-2021-02-4595, and the European Regional Development Fund, project Farminova, KK.01.1.1.02.0021.

Development of personalized fixed-dose anti-tuberculosis 3D printlets using selective laser sintering (SLS) additive manufacturing

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Background information: The bioavailability issue of RIF in FDCs arises because of the rapid decomposition of RIF in the presence of INH under gastric pH conditions. This causes a direct decline in the RIF dose below the subtherapeutic level after FDC administration of these two drugs, as confirmed by our previous research.

Purpose: To address this issue, we explored selective laser sintering (SLS)-mediated powder bed fusion 3D printing (3DP) technology using advanced polymers, SmartEx QD 100 and Eudragit L 100-55, which were validated in our earlier studies. This novel approach allows the compartmentalized delivery of INH and RIF, preventing RIF decomposition in the gastric environment and ensuring its targeted release in the intestine.

Method: We successfully fabricated FDCs bilayer tablets of INH and RIF using SLS-mediated 3DP. The bilayer tablets underwent official and unofficial pharmacopeial tests, and their physico technological characteristics were thoroughly evaluated.

Results: Dimensional measurements (16.02 ± 0.21, 8.01 ± 0.04, and 4.03 ± 0.14 mm), weight variation (255.23 ± 3.38 mg), friability (<1%) and hardness (34.61 ± 2.77 N) were all within acceptable ranges. Scanning electron microscopy with energy dispersive x-ray spectroscopy (SEM-EDX) confirmed the uniform distribution of INH and RIF in the bilayer tablet, while Raman mapping verified the presence of each drug in distinct layers. The breaking force, analyzed using a texture analyzer, was determined to be 39 N, and the drug content was 94.56 ± 2.02% for INH and 95.15 ± 3.21% for RIF. The 3D-printed FDC bilayer tablet has proven its efficacy in delivering optimal in vitro release of INH (in the stomach at pH-1.2) and RIF (in the intestine at pH-6.8) in separate compartments. Furthermore, in vivo pharmacokinetic examination of sintered FDC bilayer tablets showed promising results.

Conclusion: Considering this finding, advanced SLS-mediated 3DP technology offers a promising option for addressing the bioavailability issues associated with FDCs of RIF and INH, thus providing a promising solution for the future formulation development and delivery of RIF and INH in separate compartments.

AI-driven precision medicine: Transforming pharmacy practice in Asia

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Background Information: Asia is home to a diverse and rapidly evolving healthcare landscape, encompassing both advanced technologies in developed countries and significant challenges in resource-limited settings. The integration of artificial intelligence (AI) into personalised and precision medicine (PPM) offers transformative opportunities for pharmacy practice. Pharmacists, as essential healthcare providers, are uniquely positioned to utilise AI-driven tools to optimise medication safety, enhance treatment adherence, and improve patient outcomes. Nevertheless, various challenges, such as disparities in digital infrastructure, regulatory hurdles, and insufficient training in AI, impede the full realisation of these benefits. These challenges necessitate comprehensive strategies to bridge the gaps and enable equitable access to AI technologies across diverse settings.

Purpose: This study aims to evaluate the roles of pharmacists in adopting AI-driven precision medicine across Asia, identify challenges and gaps in implementation, and propose strategies to enable pharmacists to lead this transformation.

Method: A comprehensive review of 57 peer-reviewed studies (2018–2024) was conducted to assess the impact of AI-driven PPM in Asian healthcare systems. The analysis focused on the contributions of pharmacists, regional disparities in technology adoption, and strategies for overcoming barriers. Particular attention was given to the applications of AI in pharmacogenomics, clinical decision support systems (CDSS), telepharmacy, and medication adherence interventions. Case studies highlighting successful integration of AI tools were also examined.

Results: Pharmacists in Asia have demonstrated significant contributions to the implementation of AI-driven PPM. Key findings include:
•Improved Outcomes: AI-powered CDSS reduced medication errors by 30% and increased treatment adherence by 25% in urban healthcare settings. These improvements underscore the potential of AI to significantly enhance patient safety and treatment success rates.
•Technological Advancements: Countries like Japan, Singapore, and South Korea have developed AI tools for pharmacogenomic testing and personalised treatment plans, setting benchmarks for the region.
•Identified Barriers: Limited access to digital health tools, inconsistent regulatory frameworks, and insufficient training programs were noted, particularly in low- and middle-income countries. These barriers highlight the urgent need for targeted investments and policy reforms.
•Emerging Opportunities: Pharmacists are increasingly integral to interdisciplinary teams, contributing to pharmacogenomics integration, patient education, and medication management in precision medicine.

Conclusion: AI-driven precision medicine has the potential to transform pharmacy practice across Asia, paving the way for improved healthcare outcomes and enhanced system efficiency. Empowering pharmacists through targeted education, supportive policies, and expanded access to technology is essential to ensuring their pivotal role in this transformation. National strategies should prioritise investments in digital innovation, harmonisation of regulatory frameworks, and collaborative models to establish equitable and effective healthcare systems. By addressing disparities and building capacity, Asia can position itself as a leader in the global movement towards precision medicine. Topic Area: Personalised and precision medicine.

Integrating hypoxia-related gene signatures and machine learning to predict cetuximab resistance in colorectal cancer

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Introduction: Cetuximab resistance is the major obstacle in the treatment of colorectal cancer (CRC), with hypoxia-related mechanisms playing a critical role. This study aims to identify hypoxia-related genes associated with cetuximab resistance and develop a predictive model to optimize therapeutic strategies for CRC patients.

Method: Transcriptomic and proteomic data were analyzed to identify differentially expressed hypoxia-related genes in CRC. Gene enrichment, pathway analysis, and immune infiltration analysis were conducted to investigate their functional roles. Machine learning models, including support vector machines (SVM) and k-nearest neighbors (KNN), were developed using hypoxia-related gene features to predict cetuximab efficacy. Model performance was evaluated using metrics such as accuracy, and F1-score.

Results: Sixteen hypoxia-related genes were identified, including SLC2A1, TGFBI, and MIF, which promote tumor

progression, and NEDD4L, PCK1, and SELENBP1, which exhibit tumor-suppressive effects. Upregulated genes, such as SLC2A1, correlated positively with immunosuppressive cells (macrophages, iTregs) and negatively with cytotoxic cells (CD8+ T cells). In contrast, downregulated genes like NEDD4L and MT2A were linked to weakened immune surveillance. The SVM model achieved exceptional performance in predicting cetuximab efficacy, with 100% accuracy, and F1-score = 1, significantly outperforming the KNN model.

Conclusion: Hypoxia-related genes play pivotal roles in cetuximab resistance by driving metabolic reprogramming, immune suppression, and oncogenic signaling. The SVM-based predictive model provides a robust tool for identifying CRC patients likely to benefit from cetuximab and supports the development of personalized therapeutic strategies.

Development of a 3D-3 co-culture microbead consisting of cancer-associated fibroblasts and human umbilical vein endothelial cells for the anti-tumor drug assessment of lung cancer

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Introduction: Drug resistance is a major challenge in the treatment of lung cancer. Increasing evidence indicates that the tumor microenvironment (TME), including cancer-associated fibroblasts (CAFs) and tumor endothelial cells (TECs), plays a significant role in determining the tumor sensitivity to therapeutic agents. There is, however, a dearth of models, two-dimensional (2D) or three-dimensional (3D), that represent the in vivo interaction of tumor and stromal components in the TME. The purpose of this study was to use conditionally reprogrammed lung cancer cells (CRLCs), and then use sodium alginate (Alg) and hyaluronic acid (HA) as a hydrogel matrix to establish an in vitro 3D model for co-culture of CRLCs, CAFs, and human umbilical vein endothelial cells (HUVECs). The application of this model in the sensitivity testing of anti-tumor drugs and the mechanism of drug resistance were studied, providing new means and ideas for individualized precise anti-tumor treatment and the development of new anti-tumor drugs.

Methods: We established direct 3D micro-beads of primary lung cancer using conditional reprogramming technology and co-cultured them with CAFs and HUVECs to evaluate the effect of the TME compartment on tumor sensitivity to chemotherapeutic agents and tyrosine kinase inhibitors (TKIs). RNA sequencing (RNA-seq) was performed on the 3D micro-beads in tissue, mono-culture, and co-culture conditions to uncover transcriptional changes induced by tumor-stroma interaction.

Results: The storage modulus of 3D hydrogel microbeads was shown to be 12 kPa, which is similar to that of lung tumor tissue and demonstrates good biocompatibility, making it suitable for constructing in vitro tumor models. RNA-seq data indicated that the co-culture of CAFs and HUVECs can upregulate the pathways related to extracellular matrix (ECM) remodeling, cell adhesion molecules, ECM-receptor interactions, cancer pathways, and the PI3K-Akt signaling pathway. Moreover, the results also showed that after co-culturing CRLCs with CAFs and HUVECs, the cytotoxicity induced by chemotherapeutic agents (cisplatin, paclitaxel, vinorelbine, and gemcitabine) as well as TKIs (gefitinib, afatinib) was reduced. Furthermore, protein expression analysis confirmed that cells seeded on 3D-3 co-culture models significantly overexpressed most of the stemness promoters tested compared to mono cell culture, including ALDH1A1, NANOG, and SOX9.

Conclusions: These findings suggest that the patient-derived in vitro 3D-3 co-culture model, which highlighted the close association between tumor cell resistance and the TME, offers innovative ideas and methods for addressing treatment resistance in lung cancer patients. By closely mirroring human lung tumors, this model not only enhances our understanding of the disease but also paves the way for the development of more effective and personalized therapeutic strategies.

Synergizing artificial intelligence and telemedicine in pharmacotherapy of HIV-associated neurological disorders: A review from 2014-2024

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Background: Since the introduction of antiretroviral therapies (ARTs), the incidence of severe complications such as HIV-associated dementia and CNS malignancies has progressively declined. However, milder forms of HIV-associated neurocognitive disorders (HAND) remain highly prevalent, affecting approximately 50% of patients with HIV on ART. Patients with HIV take ART regimens, which involve combining multiple drugs. This intricate condition

necessitates optimal therapeutic monitoring to minimize side effects of ART such as HAND. Recent studies have examined the significance of telemedicine and artificial intelligence (AI) in the pharmacotherapy of HIV. However, they have not yet explored the outcome of combining the two interventions.

Purpose: To review and analyze the significance of combining AI and telemedicine in the therapeutic management of HIV patients with neurological conditions.

Methods: Previous articles were retrieved from PubMed, MEDLINE, ScienceDirect, and Embase throughout November 2024. The search strategy employed keywords such as "HIV care", "HAND", "artificial intelligence", "AI", "telemedicine", "personalized medicine", "neurological disorders", and "drug-drug interaction" combined with Boolean operators: "AND", "OR". Titles and abstracts of the retrieved articles were screened based on whether they contained the keywords. To ensure up-to-date and adequate information, only articles published in the English language from 2014 to 2024 and having their full texts were considered. Thereafter, data was extracted from full texts of relevant articles. A narrative synthesis was then employed to prepare this review after cross-checking all extracted data. A total of 73 articles were considered in this review.

Results: Telehealth innovations such as remote consultations significantly improve medication adherence, care efficiency, viral suppression, and treatment continuity. With the adoption of telehealth, 65.7% of patients maintained an undetectable viral load, while 86.9% had a CD4 count of 200 or more cells per cubic millimeter of blood, indicating well-managed HIV treatment. Meanwhile, AI accelerates drug discovery, predicts long-term complications, and identifies drug interactions in ART. It also identifies patients with the greatest risk of not achieving viral suppression after a year in care. AI-powered chatbots enhance patients' education, and virtual scenarios strengthen their mental resilience and cognitive functions. Chatbots have also shown success in HIV care, such as the Nolwazi bot, which was developed to encourage HIV testing in sub-Saharan Africa and resulted in 79.2% of participants reporting a positive counseling experience, compared to traditional counseling.

Conclusion: AI and telemedicine have revolutionized HIV management, showing great potential for further advancements. By combining both technologies, healthcare providers can adopt highly personalized and proactive strategies to improve care for HAND. However, implementation of this approach faces ethical, financial, and legal concerns, along with global technological inequalities. Further extensive research, large-scale trials, and policy improvements are crucial to maximizing their benefits and ensuring safe and equitable access to optimal treatment among patients living with HIV.

A point-of-care (POC) quantitative non-invasive test for liver dysfunction: Insights from animal and clinical trials

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Background & Aims: A non-invasive point-of-care approach can help clinicians manage liver dysfunction. The galactose composition for an oral liver function test and a method to increase oral absorption of galactose for assessment of effective hepatic blood flow and enzyme activity are needed. We developed a convenient oral galactose single-point test from the i.v. test and determined its potential to quantitatively assess various types of liver dysfunction.

Methods: Galactose and oral galactose single-point tests were performed on animals with liver impairment induced by acetaminophen, carbon tetrachloride, alcohol, or a high-fat diet. The tests' predictive validity was prospectively evaluated in 167 healthy participants and patients with steatohepatitis or decompensated cirrhosis at Tri-Service General Hospital, Taipei, Taiwan.

Results: The oral galactose single-point cutoff values for participants with normal (<343 μg/mL), mild/moderate (343–650 μg/mL), and severe (>650 μg/mL) liver dysfunction were appropriately defined. The tests' sensitivity and specificity suggested good agreement with conventional clinical diagnoses arising from the misrepresentation of the actual hepatic reserve by conventional diagnostics. The galactose and oral galactose single-point tests effectively identified patients with liver dysfunction. Both tests significantly correlated with biochemical parameters and the Model for End-Stage Liver Disease and Child-Pugh scores for severe liver impairment ($p<0.005$).

Conclusions: Point-of-care galactose single-point tests evaluated various degrees of liver function reserve in humans and animals. The test has approved by Taiwan FAD, used clinically or at home. The oral galactose single-point test is suitable for rapid screening and the i.v. galactose single-point test for precise assessment, assisting in screening, assessment, follow-up, and management of liver dysfunction.

Treatment modifiers and predictors of risperidone response in individuals with dementia: An individual participant meta-analysis of six randomised controlled trials

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Introduction: Up to 90% of people with dementia experience behavioural and psychological symptoms of dementia (BPSD). While risperidone is approved for managing BPSD in some countries, its efficacy is modest and varies between symptoms. Given the risks of risperidone use in dementia, identifying subgroups most likely to benefit and predictors of therapeutic response is crucial for personalised treatment.

Objective: To identify BPSD symptoms most responsive to risperidone, explore subgroups with better or poorer treatment response, and investigate predictors of therapeutic response.

Method: An individual participant data meta-analysis (IPD-MA) was conducted from six clinical trials of risperidone in BPSD. Baseline characteristics, symptoms, treatment-emergent factors, and outcomes at weeks 4 and 8 were compiled into a master dataset for one-stage IPD-MA. Symptoms were assessed using the Behavioural Pathology in Alzheimer's Disease (BEHAVE-AD) scale, comprising seven subscales (psychosis, activity disturbance, aggression, sleep disturbance, affective disturbance, anxiety/phobias, and a global rating). Therapeutic response was defined as a ≥30% reduction in total BEHAVE-AD scores. Mixed-effects logistic and linear regression evaluated treatment effects, modifiers, and predictors of response to risperidone.

Results: Overall, 1,720 participants (711 placebo, 1,009 risperidone), 70% female, with a mean age (SD) of 83 (7), all resided in nursing homes. Risperidone did not improve therapeutic response compared to placebo (odds ratio, OR: 1.26; 95% CI: 0.97–1.63) but reduced total BEHAVE-AD scores (mean difference, MD: -1.6; 95% CI: -2.44 to -0.76) and global rating scores (MD: -0.14; 95% CI: -0.24 to -0.04) after 8 weeks. Symptom-specific analyses indicated significant benefits in people with baseline aggression (Week 8 MD: -0.61; 95% CI: -0.95 to -0.26), psychosis (Week 8 MD: -0.9; 95% CI: -1.46 to -0.34), and sleep disturbances (Week 4 MD: -0.17; 95% CI: -0.33 to -0.01). Participants with baseline anxiety had higher scores at week 4 (MD: 0.26; 95% CI: 0.01 to 0.50) but improved at week 8 (MD: -0.26; 95% CI: -0.49 to -0.02). No significant effects were observed for subgroups with baseline activity or affective disturbances. Subgroup analyses revealed greater reductions in BEHAVE-AD total scores among those with a normal body mass index (Week 4 MD: -1.84; 95% CI: -2.89 to -0.79) and neurological diseases (Week 8 MD: -2.87; 95% CI: -4.58 to -1.16). Predictors of treatment response included achieving an early response at week 2, strongly predicting sustained responses at week 4 (OR: 9.04; 95% CI: 6.10–13.39) and 8 (OR: 4.46; 95% CI: 3.00–6.62). Early symptom improvement also predicted later improvement in corresponding subscales. Higher baseline MMSE scores predicted lower total BEHAVE-AD (MD: -0.11; 95% CI: -0.18 to -0.04), and aggression (MD: -0.07; 95% CI: -0.10 to -0.05), but higher psychosis scores (MD: 0.08; 95% CI: 0.05 to 0.11) at week 8.

Conclusion: Risperidone showed potential symptom-specific benefits at different time points, particularly for aggression, psychosis, and sleep disturbances. Subgroup analyses identified specific baseline characteristics influencing treatment efficacy, while early response and baseline cognitive function predicted sustained improvement. These findings support a more individualised approach to treating BPSD. Further research is needed to optimise the risk-benefit balance across subgroups.

Physiologically based pharmacokinetic modeling of lamotrigine to predict drug-disposition using GastroPlusTM

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Lamotrigine is an antiepileptic drug that is mainly eliminated via metabolic degradation by uridine diphosphate glucuronosyltransferase (UGT) enzymes. Therefore, hepatic impairment and enzyme-mediated drug-drug interactions may influence lamotrigine clearance. Physiologically based pharmacokinetic modeling (PBPK) modeling was used to investigate lamotrigine exposure in clinical situations in which drug clearance may be impacted. A PBPK model for lamotrigine was developed using physicochemical properties and pharmacokinetic data from reported clinical trials. Hepatic impairment was simulated by adjusting disease-specific parameters, and co-administration of valproic acid and rifampicin was simulated using the DDI module of GastroPlusTM. Pharmacokinetic predictions in virtual populations were compared with clinical observations from selected trials. The model performed well when used to predict lamotrigine pharmacokinetics in hepatic impairment; all predicted Cmax and AUC ratios fell within 2.0 times of the observed values. Mild hepatic impairment had a minor impact on lamotrigine exposure; however, the effects of moderate to severe hepatic impairment on lamotrigine

exposure were pronounced. A PBPK model for valproic acid was also developed and validated using data from several clinical studies. Use of the PBPK models for lamotrigine and valproic acid in the DDI module predicted an increase in lamotrigine exposure by 1.96- to 2.16-fold caused by valproic acid co-administration, reflecting UGT inhibition by valproic acid. Co-administration of rifampicin (using the standard PBPK model for this drug in GastroPlusTM) reduced lamotrigine exposure by 0.61-fold, reflecting the UGT induction effect of rifampicin. In conclusion, development of PBPK models of lamotrigine and valproic acid permitted prediction of exposure to lamotrigine under different conditions. This approach can be extended to utilization of lamotrigine in different patient populations, including in malnourished patients, and may be useful for choice of dosage regimens in these patients.

Population pharmacokinetic model of linezolid and its metabolite PNU-142300 in critically ill patients

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Introduction: Previous research suggested that linezolid trough concentration (Cmin) and concentration of its metabolite (PNU-142300) was independently associated with development of linezolid-induced thrombocytopenia in critically ill patients by multiple regression analysis. Therefore, clarifying population pharmacokinetic characteristic (PPK) of linezolid and PNU-142300 in critically ill patients is of great importance. The purpose of the study was to establish a PPK model of linezolid and PNU-142300 in critically ill patients to facilitate in implementing strategies to prevent linezolid-induced thrombocytopenia.

Method: Critically ill patients aged 18 years or older who were administrated with linezolid for suspected or confirmed infections were eligible for study inclusion. The exclusion criteria were as follows: (1) pregnant women; (2) underwent renal replacement therapy; (2) with covariate data missing or incomplete, such as demographic data (sex, age, etc.), laboratory values (hemoglobin, platelet, etc.). Concentrations of linezolid and PNU-142300 were measured by liquid chromatography–tandem mass spectrometry. One and two compartments with linear elimination were evaluated as the potential structural base model for linezolid and PNU-142300. Additive, proportional, and combined additive and proportional error models were assessed to account for residual variability. Potential covariates affecting pharmacokinetic parameters were incorporated into the final model by a stepwise forward inclusion followed by backward elimination approach. The final model was assessed based on goodness-of-fit plots, prediction-corrected visual predictive check plots, and a nonparametric bootstrap approach. Monte Carlo simulations were performed using the final PPK model with 1,000 virtual participants. Simulated dosing regimens included once-daily (300 mg, 400 mg, 600 mg, 800 mg), 12-hourly (200 mg, 300 mg, 400 mg, 600 mg), and 8-hourly (200 mg, 300 mg) administrations.

Results: A total of 150 linezolid and PNU-142300 concentrations were obtained from 114 critically ill patients. For both linezolid and PNU-142300, pharmacokinetics was adequately described by a one-compartment model. The model that best characterized interindividual variability and residual variability was the exponential model and additive error model, respectively. CrCL were identified as significant covariates that affect clearance of linezolid and PNU-142300. The mean population estimates of clearance for linezolid and PNU-142300 was 2.02 L and 1.57 L, respectively. The mean population estimates for volume of distribution of linezolid and PNU-142300 were 31.17 L. The model demonstrated good stability, robustness and predictive performance. Linezolid and PNU-142300 concentration gradually increased as the renal function declined. For patients with CrCL ranging from 15 to 29 mL/min, a dosage regimen of 200 mg every 12 hours achieved optimal target exposure of linezolid, with a 78.6% probability of maintaining PNU-142300 levels below the toxicity threshold. Whereas for patients with CrCL values of 30–59 mL/min or 60–89 mL/min, 200 mg every 8 hours most likely achieved the therapeutic Cmin of linezolid, while maintaining PNU-142300 levels below the threshold with >80% probability.

Conclusion: This is the first study to develop a PPK model of linezolid and PNU-142300 in critically ill patients, which may facilitate in designing the optimal individual dosage regime to prevent linezolid-induced thrombocytopenia. Linezolid dose reduction may be necessary in critical ill patients with renal impairment.