

## CONFERENCE ABSTRACTS

# FIP Brisbane 2023

81<sup>st</sup> FIP World Congress of Pharmacy and Pharmaceutical Sciences in Brisbane, Australia,  
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## *Personalised and precision medicine*

### **Oncological patients' perception of biological medicines switching by a physician**

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**Background:** Biological medicines play an essential role in oncology. Their increasing costs can be curbed by using less expensive biosimilars which are similar and interchangeable biological medicines. Patients' perceptions of biosimilars and biological medicines switching may affect treatment adherence, outcomes and costs.

**Purpose:** To study adult oncological patients' perceptions of biological medicines switching conducted by a physician and the predictors of the perceptions. The recognition of terms of biological medicine and biosimilar, and sources of medicines information are studied.

**Methods:** A cross-sectional survey with statements with a 5-point Likert scale and structural background questions were used. Invitations for the survey were delivered to University Pharmacy's loyalty customers via email and through communication channels of the Association of Cancer Patients in January 2021. The primary outcome variable (sum variable containing 7 statements with a 1-5 scale, 5=most positive perception) was constructed. Bivariate and multivariate analyses were conducted.

**Results:** On average, the patients had a positive perception of biological medicines switching by a physician (average value of sum variable: 3.29/5.00; 95% CI 3.20-3.38) but it

was widely associated with uncertainty. The positive perception was associated with patients' positive perception of biosimilars and generic medicines, such as efficacy, safety and usability, as well as with patients' higher education level and having less concerns about their medication. Most respondents (72 %) recognized the term biological medicine while biosimilar was recognized less frequently (18 %). The most frequently used sources of medicines information were healthcare professionals (48-88%) and a package leaflet (80%).

**Conclusions:** Oncological patients' perceptions of biological medicines switching by a physician were influenced by several factors such as perceptions of biosimilars. Although several patients on average had a positive perception of the switching it was often accompanied with uncertainty. The results suggest the need of appropriate medicines information to enhance rational use of biosimilars.

### **Clinical efficacy and safety of tigecycline based on therapeutic drug monitoring for carbapenem-resistant gram-negative bacterium pneumonia in intensive care units**

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**Objective:** We investigated the associations between the different dose of tigecycline, its efficacy and safety, and the role of tigecycline therapeutic drug monitoring for patients in intensive care unit (ICU).

**Methods:** This was a single-center cohort study including patients with Multidrug-Resistant *Acinetobacter baumannii* (MDR-AB) and Multidrug-Resistant *Klebsiella pneumoniae*(MDR-KP) pulmonary infections admitted to the ICU between October 2020 and December 2021. The steady-state plasma concentration after tigecycline administration

was determined by the High Performance Liquid Chromatography (HPLC) method. Multivariate analysis of the clinical efficacy and safety of tigecycline were performed to control confounding factors.

**Results:** This study included 45 patients, and a total of 45 blood samples were collected to determine steady-state trough concentrations of tigecycline. All patients were divided into High Dose (HD) group and Standard Dose (SD) group. The median trough concentration of tigecycline was 0.56µg/mL in the HD group, which was higher than in the SD group(0.21µg/mL), $p=0.000$ . There was no significant difference between the two groups of patients in terms of bacterial eradication rate, mortality rate and clinical efficacy. Multiple regression analysis showed that SFOA score was correlated with mortality, OR 1.414 (1.001-1.997)  $p = 0.050$ . High dose of tigecycline was one of the factors affecting the clinical efficacy (OR 0.029(0.001-0.839)  $p=0.039$ ). The level of fibrinogen decline in the HD group was significantly higher than that in the SD group( $-3.05\pm 1.67$  vs  $-1.75\pm 1.90$ ), $p=0.038$ . Age and days of tigecycline use were identified as influencing factors for fibrinogen decline.

**Conclusion:** Tigecycline plasma concentrations are significantly increased when using a high dose. However, the plasma concentration of tigecycline is not correlated with clinical efficacy and adverse reactions. Fibrinogen decline appears to be related to patient age and days of tigecycline. Large sample data are still needed to confirm the clinical guidance significance of tigecycline TDM.

### Assessing the readability of discharge medication records prepared at The Prince Charles Hospital: A retrospective study

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#### Background

To be understood by patients at all literacy levels, health information written by pharmacists in Discharge Medication Records should be written at a reading level of grade 8 or lower. However, it is unclear if current discharge information is written to be thus accessible to all patients, which may affect their health outcomes.

#### Purpose

This project aimed to understand the average reading level of pharmacist-written information in patient Discharge Medication Records from the cardiothoracic surgery service

at The Prince Charles Hospital, to inform future interventions.

#### Method

In October 2022, Discharge Medication Records (DMRs) provided to patients between January and June 2022 were retrospectively assessed. Digital free-text fields in these DMRs were extracted for evaluation. This data was screened using the Sydney Health Literacy Lab (SHELL) Editor to determine reading level scores for each medication. For each DMR, reading levels for pharmacist free-text input was averaged. Words and phrasing that contribute to more difficult reading levels was also collected.

#### Results

462 DMRs were included for review. DMRs were, on average, at a grade 9 reading level. The five most common medications documented (and respective reading grade level ranges) were paracetamol (3.1-14.6), oxycodone (3.1-14.6), warfarin (3.1-19.3), docusate/senna (3.1-18.2) and potassium (3.1-14.6). Words that contributed to more difficult scores were identified.

#### Conclusion

The average reading level of pharmacist-written information in DMRs was higher than the recommended score of grade 8. Differing patient complexity and clinician preferences may explain the considerable variability across commonly prescribed medications. The findings will inform an intervention to improve the readability of pharmacist-written discharge information.

### Analysis of the rate of formation of 4-hydroxycyclophosphamide in dried blood spot of breast cancer patients in Indonesia after administration of cyclophosphamide

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**Background:** Cyclophosphamide (CP) is an anticancer alkylating group (nitrogen mustard) and a prodrug that will be metabolized to form its active metabolite, 4-hydroxycyclophosphamide (4-OHCP). The various enzymes involved in its bioactivation can cause a wide range of CP expression and activity among patients, and ultimately affect the metabolism, efficacy and toxicity of this drug. The effectiveness of CP therapy can be determined by 4-OHCP level in Dried Blood Spot (DBS).

**Aim:** The purpose of this study was to conduct the phenotyping of CP 4-hydroxylation rate in cancer patients of some ethnicities in Indonesia.

**Method:** Phenotyping study of CP 4-hydroxylation rate to 83 subjects of Indonesian cancer patients was done based on the value of its bioactivity ratio (4-OHCP to CP levels). The

analysis of CP and 4-OHCP was conducted using liquid chromatography tandem mass spectrometry.

**Result:** The results shown the cyclophosphamide 4-hydroxylation rate of Malay cancer patients was 80% (n = 32) subjects as ultrarapid metabolizer (UM) and 20% (n = 8) as poor metabolizer (PM). While the other ethnicity was 53% (n = 23) subjects as ultrarapid metabolizers, and 47% (n = 20) as poor metabolizers.

**Conclusion:** Phenotyping study of CP 4-hydroxylation in Indonesian cancer patients can be conducted by quantifying CP bioactivity ratio (4-OHCP to CP level) in dried blood spot. In majority of Indonesian cancer patients, cyclophosphamide would be bioactivated through 4-hydroxylation in liver rapidly as indicated by the high value of the bioactivity ratio or the increased CP clearance and 4-OHCP level.

### How to dose edoxaban when taking ritonavir-boosted medications for COVID-19 infections in different patient populations

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#### Background

Edoxaban is an oral anticoagulant frequently used for stroke prevention in patients with atrial fibrillation. The drug is mainly eliminated via renal excretion, and its therapeutic efficacy is highly dependent on maintaining consistent plasma concentrations. By modulating multiple drug metabolizing enzymes and transporters, ritonavir (co-formulated with Nirmatrevir or Simnotrelvir for coronavirus) is expected to fluctuate edoxaban's exposure in addition to interindividual variations in physiological function (including renal/hepatic function), hindering precision dosing strategies in clinical practice. To date, there is limited clinical data on the magnitude of the interaction between these two drugs, and precision dosing for patients with varying degrees of comorbidities remains a challenge.

#### Purpose

Herein, guided by physiologically-based pharmacokinetics (PBPK) modeling and simulation, we aim to provide a comprehensive and quantitative evaluation of drug-drug interactions (DDIs) between edoxaban with ritonavir in patients with different populations.

#### Method

The models and simulations were performed and implemented within the population-based Simcyp Simulator (version 21, Sheffield, UK). Population profiles for renal impairment/hepatic impairment/geriatrics/obesity/cancer were directly adopted from the Simcyp library. The edoxaban and ritonavir models were optimized based on previous studies and clinical data. To verify the performance of the modified model, we first simulated the

pharmacokinetic profiles of ritonavir/edoxaban following multiple oral dose administrations. The modified model was further validated using clinically available studies to assess its liability for DDIs simulations against different enzymes and transporters. Each final simulation was designed as a total size of 100 subjects (10 trials with 10 subjects for each). Peak concentrations (C<sub>max</sub>), the area under the curve (AUC), and the ratio of the values with/without ritonavir were obtained for marginal comparison.

#### Results

PBPK-DDI models were successfully established and verified, followed by performing prospective ritonavir-perpetrating simulations with edoxaban in different populations. Elevated C<sub>max</sub> and AUC were observed in ritonavir-boosted treatment, where the magnitudes were more profound among subjects with mild to severe hepatic impairment (Child-Pugh Class A to C) and severe renal impairment (2.01, 2.57, 3.11, and 2.65-fold increases in AUC change, and 1.59, 1.88, 2.14, and 1.74-fold elevations in C<sub>max</sub> change, respectively). Mild renal impairment and obesity appeared less significant, with their interaction ratios smaller than 1.5. Cancer, geriatric, and patients with moderate renal impairment were estimated to have 1.74, 1.77, and 1.87-fold greater interactions in AUC elevation, and 1.40, 1.42, and 1.40-fold changes in C<sub>max</sub> increase, respectively.

#### Conclusion

Our PBPK-based simulations assessed clinically meaningful yet uncertain DDIs between edoxaban and ritonavir-boosted anti-coronavirus regimens. These findings may highlight the importance of precision dosing and careful monitoring of edoxaban plasma concentrations, particularly in patients with compromised renal/hepatic functions. Quantitative results are expected to support clinical judgment in selecting proper anticoagulation management for cardiovascular patients infected with COVID-19.

### Study of rivaroxaban and crizotinib drug-drug interaction and dose recommendation based on PBPK model

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#### Background

Rivaroxaban is an effective anticoagulant for the treatment of cancer-associated venous thromboembolism. Combination with anticancer drugs cannot be avoided in cancer patients. Rivaroxaban is mainly metabolized by CYP3A4, CYP2J2 and p-gp. Crizotinib is a moderate CYP3A4 inhibitor and P-gp inhibitor. When combined with rivaroxaban, it will lead to increased exposure to rivaroxaban, which may increase the risk of bleeding.

#### Purpose

The purpose of this study was to evaluate the effect of combined application of crizotinib and rivaroxaban on the pharmacokinetics of rivaroxaban in cancer patients with

renal impairment by using PBPK model, and to explore the reasonable dosage of rivaroxaban.

#### Method

PK-Sim is used for modeling and simulation. The parameters required for modeling rivaroxaban and crizotinib were collected from the literature. The reported drug-drug interactions between rivaroxaban and CYP3A4 and P-gp inhibitors, crizotinib and CYP3A4 substrates were used to validate the developed PBPK models of rivaroxaban and crizotinib. The model was used to evaluate the effect of crizotinib on exposure in cancer patients with renal impairment.

DDIs precipitating major bleeding risks of rivaroxaban were assessed using exposure-response analyses derived from literature.

#### Results

- (1) Cancer patients with mild renal impairment: When the dose of rivaroxaban was 10 mg QD, 15 mg QD, 20 mg QD and 15 mg BID, the AUC of rivaroxaban increased by 1.30, 1.57, 1.73 and 1.88 times, respectively. The risk of bleeding was 2.95%, 4.25%, 5.84% and 5.35%, respectively.
- (2) Cancer population with moderate renal impairment: When the dosage of rivaroxaban was 10 mg QD, 15 mg QD, 20 mg QD and 15 mg BID, the AUC of rivaroxaban increased by 1.41, 2.11, 2.14 and 2.48 times, and the bleeding risk was 3.07%, 5.72%, 7.71% and 7.58%, respectively.

#### Conclusion

Coadministration of crizotinib resulted in increased exposure and an increased risk of bleeding in cancer patients with renal impairment. In cancer patients with mild renal impairment, it is recommended that the daily dose of rivaroxaban should not exceed 15 mg, and in cancer patients with moderate renal impairment, it is recommended that the daily dose should not exceed 10 mg, which provides a reference for clinical medication.

### Lansoprazole as a promising concomitant agent ameliorating cisplatin-induced ototoxicity

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**Background:** Cisplatin (CDDP) is widely used drug in various cancer chemotherapy. Because CDDP-induced ototoxicity limits its clinical application, the development of ototoxicity strategies during chemotherapy of CDDP is an urgent matter to be solved. CDDP-induced ototoxicity is caused by CDDP accumulation in the inner ear cochlea via organic cation transporter 2 (OCT2). Since lansoprazole (LPZ), which is a

proton pump inhibitor, is known to inhibit OCT2-mediated transport of CDDP, LPZ might ameliorate CDDP-induced ototoxicity.

**Purpose:** We examined the effect of LPZ against CDDP-induced ototoxicity using in vivo fluorescence imaging of auditory hair cells in zebrafish. Moreover, the clinical impact of concomitant LPZ against CDDP-induced ototoxicity was examined by retrospective chart review of the hospitalized patients who received CDDP, and database analysis using the Food and Drug Administration Adverse Event Reporting System (FAERS).

**Methods:** We examined the co-treatment of LPZ (0.5  $\mu$ M) on the CDDP (250  $\mu$ M)-induced ototoxicity through in vivo fluorescence imaging of the zebrafish neuromast hair cells stained with YO-PRO1 dye. Using oct2 knock out zebrafish generated by CRISPER/Cas9 system, we investigated the role of OCT2 on the CDDP-induced ototoxicity. Moreover, we retrospectively investigated the impact of LPZ on the development of ototoxicity in 289 patients receiving CDDP therapy. Ototoxicity was defined as hearing loss, sensorineural hearing loss, or tinnitus following CDDP treatment. Using FAERS database, 29,976 patients who experienced ototoxicity following CDDP treatment were extracted. We analyzed reporting ratio of CDDP-induced ototoxicity, reporting odds ratio (ROR), and 95% confidence interval (CI). The clinical study was approved by the Ethics Committee of Mie University Graduate School of Medicine and Faculty of Medicine (No.2021-170).

**Results:** CDDP treatment to zebrafish significantly decreased the fluorescence intensities of hair cells (approximately 50% of those of control zebrafish). Co-treatment of LPZ or knockout of oct2 significantly suppressed the reduction of fluorescence intensities by CDDP (approximately 75% of those of control zebrafish). The protective effect of LPZ was not observed in oct2-knockout zebrafish. In the retrospective study, the rate of concomitant LPZ in patients without ototoxicity (88 out of 260 patients, 34%) was significantly higher than that in patients with ototoxicity (2 out of 29 patients, 7%,  $P=0.002$ ). FAERS database analysis revealed that the reporting odds ratio of LPZ for CDDP-induced ototoxicity was 0.37 (95% CI: 0.14-0.99,  $P=0.039$ ).

**Conclusion:** These findings suggest that LPZ should ameliorate CDDP-induced ototoxicity by inhibition of OCT2. Therefore, concomitant administration of LPZ would be promising therapy against CDDP-induced ototoxicity.

### Potential benefits of local radiotherapy in addition to adjuvant chemotherapy in female patients with triple negative breast cancer in the absence of distant metastases: A SEER database analysis

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**Background:** There is no consensus on the advisability of additional supplementation with local radiotherapy in non-metastatic triple negative breast cancer (TNBC) patients.

**Purpose:** The present study is the first analysis to construct a risk-scoring model to determine prognosis for TNBC without distant metastases with a view to identifying those groups for whom local radiotherapy would be of benefit.

**Methods:** Cases of female patients diagnosed with non-metastases TNBC patients who received adjuvant chemotherapy were extracted from Surveillance Epidemiology and End Results (SEER) database. Breast cancer-specific death (BCSD) was used as the primary prognostic indicator; Sub-distribution hazard ratio (sHR) with 95% confidence intervals (CI) were used to analyze the effect of radiotherapy with risk-stratification. Differences were considered statistically significant if  $P \leq 0.05$ .

**Results:** A total of 19,371 patients were enrolled. Multivariable function of BCSD showed that year of diagnosis, race, grade, N stage, primary site, lymph node ratio and tumor size were all associated with the probability of cancer-specific death ( $P < 0.05$ ). As regards BCSD, there was no survival benefit in receiving radiotherapy for low-risk (Score  $\leq 122$ ) patients (sHR = 0.839; 95% CI: 0.69-1.02;  $P = 0.08$ ), but radiotherapy improved survival for medium and high risk (Score  $> 122$ ) groups (medium risk: sHR = 0.801; 95% CI: 0.682-0.941;  $P = 0.007$ ; high risk: sHR = 0.618; 95% CI: 0.516-0.74;  $P < 0.001$ ).

**Conclusion:** A novel risk scoring system was constructed based on the results of the survival nomogram to screen for medium-high risk patients for whom radiotherapy may bring additional benefit.

### Pharmacokinetic/pharmacodynamic target attainment of tigecycline in patients with hepatic impairment in a real-world setting

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#### Background:

To date, several studies have used population pharmacokinetic (PPK) and Monte Carlo simulation to evaluate tigecycline dosing in patients with different hepatic

functions. However, it has not been verified whether the simulated probability of achieving the pharmacokinetic/pharmacodynamic (PK/PD) target is consistent with the actual condition of the patients.

#### Purpose:

This study aimed to investigate the PK/PD targets attainment of various tigecycline (TGC) dosing regimens in real-world patients with impaired liver function.

#### Methods:

The clinical data and serum concentrations of TGC were extracted from the patients' electronic medical records. Patients were divided into groups Child-Pugh A, Child-Pugh B and Child-Pugh C according to classify liver impairment. Then, minimum inhibition concentration (MIC) distribution and the pharmacokinetic/pharmacodynamic (PK/PD) targets of TGC from the literature were used to obtain a proportion of PK/PD targets attainment of various TGC dosing regimens in different infected sites.

#### Results:

The pharmacokinetic curves revealed significantly higher values in moderate and severe liver failure (groups Child-Pugh B and Child-Pugh C). Considering the target  $AUC_{0-24}/MIC \geq 4.5$  for patients with pulmonary infection, most patients with high-dose (100 mg, q12h) or standard-dose (50 mg, q12h) for TGC achieved target in groups Child-Pugh A, B and C. Considering the target  $AUC_{0-24}/MIC \geq 6.96$  for patients with intra-abdominal infection, when  $MIC \leq 1$  mg/L, more than 80% of patients achieved the target. For an MIC of 2 - 4 mg/L, only patients with high-dose TGC in groups Child-Pugh B and C may attain the treatment target. Patients experienced a reduction in fibrinogen values after treatment with tigecycline. In group Child-Pugh C, all six patients developed hypofibrinogenemia.

#### Conclusions:

Severe hepatic impairment may attain higher PK/PD targets attainment, but carries a high risk of adverse reactions.

### The role of a clinical pharmacist in the treatment and management of psychotic and bipolar disorders

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**Background:** Clinical pharmacists play an important role in optimising psychiatric treatment by applying their psychopharmacology expertise to improve medication management and compliance with psychotropic medications. This study aimed to investigate the role of a clinical pharmacist in the pharmacological treatment of psychotic and bipolar disorders at a tertiary academic hospital in South Africa by evaluating medication-related problems, comparing prescribing patterns against treatment guidelines, and describing clinical pharmacist-led

interventions. Despite the importance of clinical pharmacists in psychiatry settings, their role in South Africa has not been adequately studied.

**Methods:** A quantitative, descriptive study design was followed to identify medication-related problems and suggest appropriate interventions. The study population included all patients (>18 years) admitted to the psychiatry or internal medicine wards diagnosed with psychotic and/or bipolar disorder. Non-probability purposive sampling was used to obtain a sample size of 52, calculated using Raosoft®. The data-collection instrument was the previously validated pharmaceutical care form. The data was analysed descriptively, using Statistical Package for the Social Sciences (SPSS). Ethical clearance was granted from Sefako Makgatho University Research Ethics Committee (SMUREC) and permission obtained from Hospital chief executive officer (CEO).

**Results:** A sample of n=60 patients with various psychotic and/or bipolar disorders was obtained, which was more than the sample size of 52 calculated. Males and females represented 38% and 61% of the population respectively, with an average age of 37 years. The sample consisted of patients with a range of diagnoses, including schizophrenia (31%), schizophrenia with other psychotic disorders (10%), bipolar type-1 disorder (28%), bipolar type-2 disorder (1%), bipolar type-1 disorder with other psychotic disorders (15%), and stimulant-induced psychosis amongst other psychotic disorders (20%). Sixty-two medication-related problems were identified, leading to 56 interventions being recommended, with 60% of those being implemented. Most prescriptions adhered to the South African Standard Treatment Guidelines, with a few adhering to the NICE and APA guidelines.

**Conclusions:** The study concludes that there is a need for pharmacist-led interventions in the treatment of mental health disorders such as psychotic and bipolar disorder. Medication-related problems occurs, and through pharmacist-led interventions, errors can be reduced, and side effects mitigated.

### Risk factors associated with unplanned acute care in outpatient chemotherapy with oral anticancer drugs as monotherapy or combination therapy with injectable anticancer drugs

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**Background/Purpose:** In recent years, the number of cancer patients receiving outpatient chemotherapy using oral anticancer drugs has increased, but the current outpatient cancer chemotherapy is not safer than before yet. The purpose of this study is to identify the risk factors associated with unplanned acute care (UAC) that require outpatient chemotherapy related consultation and hospitalization. Patients and

**Methods:** We conducted a case-control study in 1,674 patients who received oral anticancer drug alone treatment or combination treatment with injectable anticancer drugs at the National Cancer Center Hospital East in Japan, from December 1, 2014 to November 30, 2015.

**Results:** We found body mass index (BMI) a risk factor for UAC during chemotherapy. And patients with BMI<18.5 classified as underweight in WHO classification of nutritional status had a significantly higher risk of UAC.

**Conclusion:** During outpatient chemotherapy with oral anticancer drugs, it is necessary to pay attention to the underweight patients.

### Audit on use of zuclopenthixol acetate for acute behavioural disturbance management in mental health in-patients

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#### Background:

The 10th National Seclusion and Restraint Reduction Forum highlighted lack of current national data sources that support the documentation, analysis and reporting of chemical restraint. The Australian Mental Health Commission urged for this subject to be pursued with a focus on use of acute injectable medications. Zuclopenthixol acetate (Acuphase) is one potentially toxic preparation with very little published information to support its use.

Presently, it is reserved for prolonged or sustained disturbed behaviour management and is not recommended for

routine use in Acute Behavioural Disturbance Management (ABDM).

**Purpose:**

To establish the proportion of Acuphase usage that deviates from local ABDM guidelines.

**Objectives:**

Determine adherence to ABDM guidelines regarding appropriateness.

Identify dose, dosage interval and total dose prescribed within a two-week period.

Determine adherence to post-injection monitoring guidelines.

**Methods:**

A 12-month retrospective study was conducted to identify adults prescribed Acuphase.

**Data collected:**

Dose/s administered including time interval between doses  
Appropriateness of zuclopenthixol acetate, including how it was prescribed

Post-injection monitoring adherence

**Results:**

Forty-nine doses of Acuphase were given to 29 patients. On average, patients received 1.7 doses of Acuphase over an interval of 6.3days. The average dose was 96.85mg.

There were no apparent contraindications to Acuphase administration, although there were some guideline deviations.

These included;

No clear documentation of agitation in notes prior to administration (n=7, 24%)

Minimal or no use of first line ABDM medication prior to Acuphase usage (n=5, 17%)

Prescribed "in advance" or as "PRN" (n=4, 8%)

Administered as a test dose for zuclopenthixol decanoate or as a top up (n=2, 4%)

Exceeded 400mg over 2 weeks (n=1, 2%)

Post-injection monitoring, including daily ECGs, recording of sedation scale and extrapyramidal side effects (EPSEs) were not always completed. ECGs were completed for 31 out of 49 doses. Post-injection sedation was recorded for 78% doses, with patients refusing 11% of the time, the remaining 11% was not recorded. EPSEs, or lack of, was not explicitly stated for all patients.

**Conclusion:**

Acuphase is mostly being used in accordance with ABDM guidelines for dosing however, there is a trend of low adherence to post injection monitoring, namely ECGs and EPSEs. This could be attributed to the patient population refusing or remaining agitated post injection. The creation of a monitoring form, initiated by the pharmacist after the first Acuphase dose, could close this gap.

There was also some deviation with charting as well as the use of Acuphase in conjunction with zuclopenthixol decanoate depots.

## Preparation of medicines by three-dimensional printing and personalization of therapy in compounding pharmacies: A case study

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3D printing (3DP) is an innovative approach to manufacturing personalized medicines. The incorporation of 3DP in the pharmaceutical compounding landscape is expected to promote flexibility, efficiency, safety, and quality [1] of existing medicines.

This work aims to identify the most relevant requirements impacting the use of Fused Deposition Modelling (FDM) to compound medicines. This should be achieved by identifying the main challenges that a pharmacist faces prior to defining the strategies to be considered for the successful implementation of this 3DP technology in the daily practice of compounding pharmacies. For this purpose, a case study where paroxetine (PRX), an antidepressant drug needing regular dose readjustments and pharmaceutical intervention for therapy compliance, is presented. The work was conducted in a research pharmaceutical laboratory, mimicking the dedicated manipulation areas present in community pharmacies.

PRX-loaded tablets were printed using FDM. The polymer-based filaments required to feed the printer were previously prepared by Hot-Melt Extrusion (HME), from powder mixtures of raw materials (PRX, hydroxypropylcellulose and other adjuvants, such as dicalcium dihydrate phosphate, magnesium stearate and triethylcitrate) [2]. In this work, the coupling of HME-FDM manufacturing process for the production of PRX tablets has proven to be expedite, provided that the optimal mechanical and thermal properties of the filaments were ensured. It has been also demonstrated that the storage of filaments under controlled environmental conditions was critical for the successful printing of tablets. In fact, filaments kept in a controlled atmosphere (desiccator) were printable, while those stored in higher humidity conditions failed to successfully feed the 3DP printer's gears and die. Post-treatment drying of the filaments (e.g. microwave, oven) was also explored in this work. While the removal of water was slow under a dried atmosphere (desiccator), it was speeded up when active drying methods were considered. Microwave-mediated drying seems to have been the method that brought the greatest benefit since it streamlined the 3DP process with an increase in the dissolution rate of PRX. Noteworthy is that microwave drying must be carried out under well-controlled instrumental conditions, considering the larger variability of results, by comparison to oven drying. Complementary studies involving drugs and polymers with different physicochemical properties will enable the construction of models that will speed up the design and manufacture of

new medicines supporting the compounding pharmacies in implementing this manufacturing process.

Overall, prior production of the filaments with adequate properties for printing may be a limiting step for using FDM in compounding at the point of care. As an alternative, filaments may be manufactured in a facility that would centralize their manufacture, and supplied as intermediate materials to community pharmacies, which are expected to be able to convert different combinations of filaments into personalized medicines, based on individual prescriptions, to fulfil the patient's needs. This approach, not only presents irrefutable benefits for the patient's health, minimizing waste of medicines, but also repositions and strengthens the role of the pharmacy and the pharmacist in health care provision to the population.

### The impact of ABCB1 and CES1 polymorphisms on dabigatran pharmacokinetics and pharmacodynamics in patients with atrial fibrillation

**Prof Xiaoye Li**<sup>1</sup>, Dr Zi Wang<sup>1</sup>, Prof. Qing Xu<sup>1</sup>, Prof. Xiaoyu Li<sup>1</sup>, Prof. Qianzhou Lv<sup>1</sup>

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**Aims** Our study aimed to determine the impact of genetic polymorphisms of ABCB1 and CES1 on the pharmacokinetics(PK) and pharmacodynamics(PD) of dabigatran in patients with non-valvular atrial fibrillation(NVAF).

**Methods** We conducted a prospective study and enrolled NVAF patients treated with dabigatran. Blood samples were obtained from each patient and used for genotyping and determination of plasma dabigatran concentration(PDC) and coagulation parameters including activated partial thromboplastin time(APTT) and thrombin time(TT). Patients' demographics and clinical outcomes from scheduled follow-up visits were all recorded. Statistical analysis was performed to identify the impact of genetic polymorphisms on the PK/PD and bleeding risk of dabigatran.

**Results** A total of 198 patients was included in analysis. For the ABCB1 polymorphisms rs4148738 and rs1045642, no significant association was found with dabigatran PK/PD. For the CES1 polymorphism rs8192935, the minor allele(C) carriers had higher peak and trough levels of PDC (P=0.028 for peak level; P<0.001 for trough level) along with higher APTT values at trough level(P=0.015)than non-carriers. For the CES1 polymorphism rs2244613, the minor allele(A) on rs2244613 was associated with a 6~7% increase in trough PDC per allele(P<0.001) and with an increased risk for minor bleeding(P=0.034; OR=2.71, 95% CI 1.05-7.00).

**Conclusions** Our study indicated that the minor allele(C) on the CES1 SNP rs8192935 was associated with higher peak and trough PDCs along with higher APTT value at trough

level, and the minor allele(A) on the CES1 SNP rs2244613 were associated with increased trough PDC and higher risk for minor bleeding in NVAF patients treated with dabigatran.

### Clopidogrel-associated genetic variants on inhibition of platelet activity and clinical outcome for acute coronary syndrome patients

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Acute coronary syndrome (ACS) has become a vital disease with high mortality worldwide. A combined anti-platelet therapy (aspirin and a P2Y12 antagonist) is commonly used to prevent re-infarction in ACS patients who have undergone percutaneous coronary intervention (PCI). Clopidogrel, a P2Y12 antagonist, plays an important role in the inhibition of platelet aggregation (IPA). However, it is a pro-drug requiring bio-transformation by cytochrome P450 (CYP450). The aim of this study is to unravel the effect of clopidogrel-associated genetic variants on inhibition of platelet activity and clinical outcomes in ACS patients. In our study, a total of 196 patients with metabolic gene polymorphism of clopidogrel were enrolled, and their anti-platelet effect as well as their cardiovascular events were collected. Approximately 2 ml of venous blood samples were used for genotype detection and another 4 ml were collected for platelet reactivity with thrombelastography. The primary clinical endpoint was defined as a combination of cardiovascular mortality and revascularization for targeted vascular lesion. Based on the results of IPA, the prevalence of high on-treatment platelet reactivity (HPR) was 17.3% and the majority of patients (82.7%) obtained normal on-treatment platelet reactivity (NPR). The HPR group had significantly higher body mass index (BMI) and lower arachidonic acid (AA) induced IPA (P < 0.05). Therapy including Glycoprotein (GP) IIb / IIIa antagonist increased IPA (P < 0.05). ADP-induced IPA effect was lower with the presence of CYP2C19\*2, \*3 and paraoxonase (PON)1 Q192R loss-of-function (LOF) alleles, respectively (P < 0.05). Multivariate logistic regression analysis demonstrated that aspirin resistance (AA-induced IPA < 50%) had a greater risk of the occurrence of major adverse cardiovascular events (MACE) (OR = 3.817; 95%CI: 1.672-8.700; P = 0.002). CYP2C19\*2 LOF alleles were associated with high risk of MACE in 1-year post PCI operations (OR = 2.571; 95%CI: 1.143-5.780; P = 0.030). For the ACS patients, presence of CYP2C19\*2 and PON1 Q192R LOF alleles were the major drivers of HPR.



### Exploring G-protein coupled receptors as specific targeting sites for drug delivery into ovarian cancer cells

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**Background:** Genetic heterogeneity in ovarian cancer (OvCa) indicates the need of personalised treatment approaches. Currently, only very few G-protein coupled receptors (GPCRs) have been investigated for active targeting with drug loaded nanoparticles (NPs), highlighting a neglected potential to develop case-by-case personalised treatment. To address the genetic heterogeneity of OvCa, a personalised approach will include the identification of overexpressed GPCRs in cancer biopsies, matched with a personalised GPCR-targeted NP drug carrier platform, for the delivery of lethal drugs to tumour tissue before, during and after surgery as an intraperitoneal therapy.

**Purpose:** To explore personalized treatment of OvCa via active targeting of overexpressed GPCRs in OvCa tissue, using NPs as ligand-guided drug carriers.

**Method:** Public RNA-Seq data of OvCa tissues were retrieved from the GEO database (NCBI/NIH). Gene expression assemblies were generated using the Lasergene software and highly expressed receptors were shortlisted. Subsequently, gene expression was analysed in OvCa cell lines, using quantitative polymerase chain reaction (qPCR) and Western blotting.

**Results:** A systematic gene expression analysis led to prioritisation of three different receptor types, namely lipid receptors (e.g., lysophosphatidic acid receptor 3), ion activated receptors (e.g., G protein-coupled receptor 39) and peptide activated receptors (e.g., parathyroid hormone 2 receptor, C-X-C motif chemokine receptor 4 and coagulation factor II thrombin receptor). Expression of these receptors has been confirmed in five OvCa cell lines (ES-2, OVCAR3, CaOV3, COV504 and SKOV3), using qPCR. The selected cell lines will be established as potential in vitro models to study NP uptake. Further validation for candidate target receptors will be carried out on patient-derived samples using qPCR, Western blotting, and flow cytometry.

**Conclusion:** Our data indicate overexpression of several GPCRs in OvCa. The expression levels showed high variability between various samples, therefore indicating the need of a case-to-case personalised targeting approach. Our findings need to be further consolidated with patient-derived OvCa tissues, to confirm the expression levels and frequencies of future targeting receptors, to be exploited with ligand-furnished NPs.

### Assessment of cefepime toxicodynamics: Comprehensive examination of pharmacokinetic/pharmacodynamic targets for cefepime-induced neurotoxicity and evaluation of current dosing guidelines

**Ms Cindy Lau**<sup>1,2</sup>, Prof Deborah Marriott<sup>3,4</sup>, Dr Hayley Shultz<sup>5</sup>, Dr Michael Gould<sup>6</sup>, Dr David Andresen<sup>3,6</sup>, Prof Sebastian Wicha<sup>7</sup>, Prof Jan-Willem Alffenaar<sup>2,8,9</sup>, Dr Jonathan Penm<sup>2,10</sup>, A/Prof Stephanie Reuter Lange<sup>5</sup>

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**Background:** Cefepime-induced neurotoxicity is a serious adverse event causing symptoms such as drowsiness, confusion, seizures and encephalopathy. Regardless of increasing reports of cefepime-induced neurotoxicity, cefepime is still an essential antimicrobial required for the treatment of severe infections. Cefepime therapeutic drug monitoring has been utilised in clinical settings to optimise antibacterial efficacy and minimise risk of toxicity, however the toxicity threshold remains unclear.

**Purpose:** This study was conducted to provide a comprehensive examination of the most appropriate threshold for cefepime-induced neurotoxicity. The secondary objective was to evaluate the ability of current dosing regimens to attain therapeutic targets while avoiding potential neurotoxicity.

**Methods:** Data of the incidence of cefepime-induced neurotoxicity and cefepime plasma concentrations were collected retrospectively from patients administered cefepime in a tertiary hospital setting between October 2017 and May 2018. Patients requiring any form of renal replacement therapy were excluded. Population pharmacokinetic modelling was used to determine daily cefepime trough concentrations (C<sub>min</sub>), maximum serum cefepime concentration and cefepime area under the concentration–time curve. The ability of each pharmacokinetic parameter to predict cefepime-induced neurotoxicity was evaluated using receiver operating characteristic (ROC) curves, from which optimal toxicity thresholds were determined. Monte Carlo simulation was used to evaluate the ability of cefepime dosing guidelines to meet established efficacy targets, whilst maintaining

exposure below the determined cefepime-induced neurotoxicity threshold.

**Results:** In total, 102 cefepime courses were evaluated, with cefepime-induced neurotoxicity reported in 10 courses. ROC analyses showed that all cefepime pharmacokinetic parameters were strongly predictive of cefepime-induced neurotoxicity. C<sub>min</sub> of 49 mg/L was identified as the optimal toxicity target, based on its predictive ability (0.88, 95% confidence interval 0.758–0.999, P<0.001) and ease of clinical use. Assessment of cefepime dosing regimens predicted that only 29% of simulated patients achieve therapeutic targets, with patients with impaired renal function more likely to exhibit subtherapeutic concentrations (89%), and patients with normal renal function likely to have potentially toxic exposure (64%).

**Conclusions:** The findings from this study provide evidence that cefepime exposure is highly predictive of cefepime-induced neurotoxicity, with C<sub>min</sub> of 49 mg/L being the most appropriate toxicity threshold. Further research is required to optimise cefepime dosing in the context of this therapeutic target.

### **A systematic review of knowledge, attitudes, perspectives and education needs in oncology pharmacogenomics among healthcare professionals and consumers**

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#### **Background:**

A significant number of medicines utilised for the treatment and supportive care of individuals with cancer have pharmacogenomic (PGx) recommendations outlined in international PGx clinical guidelines. However, clinical implementation of PGx-guided prescribing in oncology still lags behind research evidence and guideline publications. Understanding PGx perspectives of oncology healthcare professional (HCPs) and consumers could inform strategies for implementation of routine PGx screening in practice.

#### **Purpose:**

The purpose of this systematic review was to identify oncology HCPs' and consumers' knowledge, attitudes, perspectives and education needs for PGx.

#### **Methods:**

A systematic review of original articles indexed in EMBASE, EMCARE, MEDLINE and PsycInfo from January 2012 till June 2022 was conducted using PRISMA guidelines. Article quality was assessed using the Mixed Methods Appraisal Tool. This study was registered with PROSPERO, registration number CRD42022352348.

#### **Results:**

The initial search identified 1442 articles. Twenty-three articles met the inclusion criteria and 87% were of high quality. Of these, twelve exclusively reported on HCPs, eight were exclusive to consumers and three reported on a mixed population inclusive of both HCPs and consumers. The majority of the identified studies were conducted in the USA and included multiple cancer types.

A total of six barriers and six enablers were identified through content analysis. Barriers to routine implementation of PGx in oncology included 1. Cost, lack of insurance coverage and resources; 2. Lack of PGx clinical guidelines and perceived benefits; 3. Lack of PGx knowledge, skills and education; 4. Complex PGx test ordering systems and a long processing time; 5. Health inequity, discrimination and privacy concerns; and 6. Health beliefs and self-efficacy. Enablers which could promote adoption of PGx in oncology were 1. Oncology PGx education; 2. Evidence-based PGx guidelines with clear clinical impact; 3. Streamlined and regulated PGx testing; 4. Funding and access to resources; 5. Patient requests and professional engagement; and 6. Effective communication with consumers.

#### **Conclusions:**

Both HCPs and consumers appreciated the value of PGx in personalised medicine. Continuing education for HCPs, standardised PGx clinical guidelines, streamlined PGx testing procedures and insurance coverage for testing have been identified as key facilitators to support increased PGx uptake in oncology practice.

### **Pharmacogenetics of warfarin dosing in Chinese adults with nonvalvular atrial fibrillation**

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fibrillation (AF) is still lacking.

**Aim** We aimed to evaluate whether genotype-guided warfarin dosing is superior to conventional clinical dosing for the outcomes of interest in Chinese patients.

**Method** Our study consisted of 508 newly recruited and 471 existing Chinese AF patients. Among the total 979 patients, 585 patients received their dose of warfarin determined by a genetic and clinical factor (gene group), while the remaining 394 patients whose dosing was determined empirically in control group. We incorporated CYP2C9 and VKORC1 genotypes into the gene group. The international normalized ratio (INR) measurement and standard protocols were used

for further dose adjustment in both groups. The primary outcomes were the percentage of time in the therapeutic range (%TTR) and INR during 12-month follow-up. Secondary safety outcome included bleeding and thrombotic events.

**Results** Compared with the control group, the average TTR of the gene group was higher [68.4 ± 20.6% vs 48.5 ± 21.6%,  $P < 0.001$ ]. The average INR monitoring times to reach the therapeutic time in the gene group was lower ( $P < 0.001$ ). The risk ratios (RR) for cumulative incidence of total bleeding events, minor bleeding events, gastrointestinal bleeding, and intracerebral bleeding events were not significantly different between the two groups ( $P > 0.05$ ). Comparing to the analysis using existing 471 patients, the analysis using total 979 patients showed that the gene group experienced a lower (RR 0.4 [95% CI 0.2 to 0.8],  $P = 0.008$ ) incidence of cumulative ischemic stroke.

**Conclusion** Genotype-guided warfarin administration increases the average TTR, reaches higher TTR levels in the early anticoagulant phase, and significantly reduces the risk of ischemic stroke events.

### **FIRTECH, a novel infrared patch for the non-pharmacological management of acute mild-to-moderate low back pain: Data from randomized phase 1 and 3 trials**

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**Background:** Some guidelines recommend non-pharmacological interventions for patients with acute low back pain (LBP). Bioceramic infrared therapy patch (FIRTECH) absorbs body heat and maintains enough temperature to re-emit infrared radiation that promotes self-healing through antioxidant, anti-inflammatory, and vasodilatory mechanisms.

**Purpose:** To evaluate safety of FIRTECH patch as a novel non-pharmacological therapy in healthy participants (Phase 1) and efficacy and safety in participants with acute mild-to-moderate LBP (Phase 3).

**Methods:** Two randomized, open-label trials (Phase 1 and 3) compared FIRTECH vs no-patch groups in healthy participants ( $\geq 18$ – $< 55$  years) and those with acute mild-to-moderate LBP ( $\geq 18$ – $< 65$  years) with an intensity of  $\leq 6$  on 0–10 Numerical Rating Scale (NRS). Phase 1: Primary endpoint: increase in baseline perfusion during treatment on the upper back; secondary endpoints: change in baseline perfusion, oxygen consumption and temperature of FIRTECH vs no-patch areas. Statistical analyses were according to the plan written before database unblinding. Phase 3: Primary endpoint: NRS-responder rate (Day [D] 5) by no difference (between group) hypothesis using Fisher's exact test. Key secondary endpoints: Normalized Sum of Pain Intensity Difference (SPID0-5) over 5D, percentage change in Roland-Morris Disability Questionnaire (RMDQ) score, change in mobility evaluation (Schober's Test) from baseline to D5; and time to reach acceptable pain. Baseline assessments, e-Diary activation and patch application on LBP site (D1) and final evaluations with patch removal (D5) with an additional follow-up day. Descriptive (95%CI) and inferential analyses were performed.

**Results:** Phase 1: No significant difference in primary endpoint between treated and non-treated areas. The baseline perfusion (PU) on the forearm (Least Square Mean [LSM] difference [95%CI]: 2.63 [0.97,4.28]), oxygen consumption (AU): (0.42 [0.04,0.81]) and skin temperature: (0.35°C [0.16,0.6]) were significantly higher in treated vs non-treated areas following exploratory analyses. Among 8 (40%) reporting mild and transient adverse events (AEs), 1 (5%) participant reported treatment-related AEs (TEAEs) and no serious AEs.

Phase 3: There was a significantly higher NRS-responder rate (95%CI) in FIRTECH (N=66/91) (72.5%; 62.2,81.4) vs no-patch (N=44/89) (49.4%; 38.7,60.3;  $p=0.002$ ) groups at D5. FIRTECH showed (LSM difference [95%CI]) a significant decrease in normalized SPID0-5 (-0.5 [-0.817,-0.137];  $p=0.015$ ); improvement in mobility evaluation (1.0 [0.511,1.581];  $p<0.001$ ) at 5D; whereas RMDQ scores (-32.2% vs -16.3%;  $p=0.103$ ) and median time to reach acceptable pain (9.62 h vs 8.65 h) showed no significant change vs no-patch. Difference in pain perception from baseline to D5 were significant for average pain (-0.4 [-0.835,-0.003];  $p=0.048$ ) and worst pain (-0.5 [-1.017,-0.013];  $p=0.044$ ); but not for least pain (-0.4 [-0.847,0.079];  $p=0.103$ ). 59% of subjects retained their patch for  $\geq 5$  days and 70.5% were overall patch use compliant. TEAEs were reported in FIRTECH (18/114) and no-patch groups (7/107). Among the total device related TEAEs reported (10.5%), application site pruritus (6.1%) was the most common followed by application site pain and erythema (1.8% each).

**Conclusion:** FIRTECH patch was effective against acute LBP with favorable safety profile (Phase 3) and improved vascular response (Phase 1). Thus, IR therapy can be an effective non-pharmacological intervention in pain

management and enhancing body's natural Self-Healing potential.

### Personalised dose titration regimens through 3D printing medicines

**Dr Jared Miles<sup>1</sup>**, Mr Liam Krueger<sup>1</sup>, Zheng Zheng<sup>1</sup>, Jason Ward<sup>1</sup>, Prof Amirali Popat<sup>1</sup>

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Three-dimensional (3D) printing medicines is an exciting new area of pharmaceutical manufacturing. In particular, 3D printed medications have the potential to revolutionise personalised medicine. 3D printing is a form of additive manufacturing which allows for many parameters of solid oral dosage forms to be customised with ease. Every aspect from dose and release rate, to colour and surface identifiers can be adjusted, and this could potentially be performed at the point of care. This opens the door for custom doses, formulations, and polypills to be 3D printed for each patient according to their specific needs.

One of the many options for customisation involves dose titration, allowing for gradual weaning of a medication at smaller dose intervals than is available commercially. This presentation will demonstrate 3D printing of custom dose titration regimens of clinically relevant medicines in our laboratory. It will cover aspects of formulation, quality control, and release studies, as well as provide perspectives on clinical applications in the future.

### Using machine learning algorithm to predict the occurrence of nephrotoxicity with tacrolimus

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**Background:** When administering tacrolimus, therapeutic drug monitoring is recommended to prevent adverse events such as nephrotoxicity. However, even when tacrolimus is administered in the standard recommended range of whole blood concentration, nephrotoxicity occurs in some patients. Risk factors other than drug exposure were reported to be associated with tacrolimus-induced nephrotoxicity. Therefore, it is necessary to establish a therapeutic range of tacrolimus for each individual patient to avoid nephrotoxicity.

**Purpose:** We aimed to develop a machine learning model that can predict the nephrotoxicity of tacrolimus for each patient.

**Method:** From existing medical records, we collected the data of patients who took oral tacrolimus. Patient data at tacrolimus initiation, such as age, laboratory test data, concomitant drugs, and tacrolimus concentration were used. Nephrotoxicity was defined as 1.5 times baseline or 0.3 mg/dL increase of serum creatinine levels in the 60 days after tacrolimus initiation. The conventional model identified patients with above 10 ng/mL whole blood concentration of tacrolimus as those with nephrotoxicity. We built 13 prediction models for tacrolimus-induced nephrotoxicity based on the following five machine learning algorithms: logistic regression model, support vector machine, gradient boosting trees, random forest, and neural network. The best-performing model was compared with the conventional model.

**Results:** We used the data of 163 patients to build models, and that of 41 patients to evaluate the best-performing model. Most of the patients in this study were diagnosed with inflammatory or autoimmune diseases. Among our 13 models, support vector machine showed the best prediction performance; the model utilized 10 features, including tacrolimus concentration, hemoglobin level, and lymphocyte count. Our model showed the higher F2-score of 0.750 and outperformed the conventional model (0.500).

**Conclusion:** We found that the machine learning model that used tacrolimus whole blood concentration and other patient data from the medical records performed better than the conventional model that used only tacrolimus concentration to predict nephrotoxicity. Our model can help in identifying high-risk patients who require individualized target therapeutic concentrations of tacrolimus prior to initiation, to prevent nephrotoxicity. In the future, efforts may be directed towards further evaluation of this model with more data and other features.

### Trimethoprim-sulfamethoxazole pharmacokinetic evaluation in adult kidney transplant recipients

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**Background:** Pneumocystis jiroveci pneumonia (PJP) is a potentially life-threatening opportunistic infection seen in immunosuppressed patients. Effective prophylaxis of PJP is essential with the drug combination trimethoprim-sulfamethoxazole currently used as first-line therapy in

kidney transplant patients. Little is known about the pharmacokinetics of trimethoprim-sulfamethoxazole in this cohort and whether there is any association between drug exposure and patient outcomes.

**Aim:** A prospective, observational study was conducted to characterise the pharmacokinetics of trimethoprim-sulfamethoxazole in adult kidney transplant patients during its use for PJP prophylaxis.

**Methods:** Pharmacokinetic profiling was performed in 19 adult, kidney transplant patients prescribed 80mg/400mg prophylactic dose of trimethoprim-sulfamethoxazole respectively for at least 10 weeks. Serial blood samples were taken pre-dose (0) and 0.5, 1, 2, 4 and 8-hours post-dose on a single occasion for measurement in plasma using high performance liquid chromatography. Trimethoprim-sulfamethoxazole minimum concentration (C<sub>min</sub>), maximum concentration (C<sub>max</sub>), and area-under-the concentration-time-curve from 0 to 8 hours post-dose (AUC<sub>0-8</sub>) were estimated using the trapezoidal method.

**Results:** Large variation in exposure was evident. Mean ( $\pm$ SD) trimethoprim C<sub>min</sub> was 0.4 ( $\pm$ 0.3) mg/L and C<sub>max</sub> was 1.1 mg/L ( $\pm$ 0.54) mg/L. Mean ( $\pm$ SD) sulfamethoxazole C<sub>min</sub> was 8.58 ( $\pm$ 4.5) mg/L and mean C<sub>max</sub> concentration was 26 mg/L ( $\pm$ 8.3mg/L). The mean AUC<sub>0-8</sub> for trimethoprim was 6.7 mg.hr/L (range 2.1-18.7 mg/L) and sulfamethoxazole was 148.6 mg/L (range 52.8-209.2mg.hr/L). Large between-subject pharmacokinetic variability was evident with a 4-fold difference in AUC<sub>0-8</sub> across the cohort.

**Conclusions:** Our findings suggest a considerable variation in patient blood concentrations which warrants further investigation into optimising treatment based on patient outcomes in relation to PJP prophylaxis and other infections that can be treated with trimethoprim-sulfamethoxazole.

### Measuring adherence in patients with metastatic breast cancer on CDK4/6 inhibitors therapy using the MARS-5 questionnaire and LC-MS/MS

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Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-related deaths in women worldwide. As oral anti-cancer medications (OAMs) are becoming common treatment in breast cancer and could be

prescribed for many years, long-term adherence becomes a critical aspect of continued care. Literature shows that adherence with long-term OAMs is suboptimal and decreases over time. For the newly approved cyclin-dependent kinase 4/6 inhibitors (CDKIs) indicated in metastatic breast cancer, knowledge on adherence is scarce. This is a pilot study aiming to measure adherence to CDKIs using two different methods – indirect (self-reported adherence on a validated scale) and direct (quantifying drug concentrations in plasma).

We randomly selected three participants from a larger observational, cross-sectional study on adherence that included adult patients with advanced breast cancer at the Department of Oncology, University Hospital Centre Zagreb, Croatia. The patients were diagnosed with stage IV breast cancer, with no cognitive impairment and on oral anticancer combination therapy with CDKIs.

Adherence was measured using MARS-5 scale and plasma concentrations of CDKIs determination using LC-MS/MS method.

MARS-5 questionnaire comprised 5 items that describe the range of non-adherent behaviour. Each item is rated on a five-point scale and total scale scores ranged from 5 (lowest adherence) to 25 points (highest adherence). The questionnaire was adapted to Croatian language in accordance with Principles of good practice for translation and cultural adaptation process for patient reported outcome measures and was approved by Horne. Quantitative determination of the CDKIs was performed using LC-MS/MS. The patients' plasma samples were deproteinized, evaporated and redissolved in 65% methanol. The analyses were performed on a biphenyl column (150 × 4.6 mm, 2.6  $\mu$ m) with mobile phase consisting of water and acetonitrile containing 0.1% formic acid in gradient elution on an Agilent 1290 Infinity II UHPLC system coupled to a QTOF MS, by a previously developed method (1). Pharmacokinetic data (C<sub>min</sub>, C<sub>max</sub>, T<sub>max</sub>, AUC<sub>0-24 h</sub>) were analyzed with the PK solver Excel extension, using the linear trapezoidal model for non-compartmental analysis of plasma data after extravascular input.

Patients were women, aged 79, 44 and 40 years on the combination of endocrine therapy (aromatase inhibitors) and CDKI (two on ribociclib, one on palbociclib). The obtained results show that all three patients' plasma concentrations were within the expected ranges as reported in the literature (2); C<sub>max</sub> for ribociclib samples were 2392.0 and 2782.2 ng/ml, and for palbociclib 133.2 ng/ml, while AUC<sub>0-24 h</sub> for ribociclib were 49954.6 and 54075.0 ng×h/mL, and for palbociclib 2604.1 ng×h/mL. All patients were in high-adherence group (scored 25 on MARS scale) which is in accordance with the results obtained by the LC-MS/MS.

This pilot study shows that the direct and indirect adherence measurements are in concordance. The LC-MS/MS drug plasma quantification results confirmed the self-reported adherence. The adherence in three randomly selected patients with advanced breast cancer was very high.

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### Validating a novel three-times weekly post-haemodialysis cefazolin regimen in Indigenous Australian patients—A population pharmacokinetic study

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**Objective:** To describe the total and unbound population pharmacokinetics of a 2-g three-times weekly post-dialysis cefazolin regimen in Indigenous Australian patients requiring intermittent haemodialysis.

**Methods:** A pharmacokinetic study was carried out in the dialysis unit of a remote Australian hospital. Adult Indigenous patients on intermittent haemodialysis (using high-flux dialyzer) and treated with a 2-g three-times weekly cefazolin regimen were recruited. Plasma samples were serially collected over two dosing intervals and assayed using a validated methodology. Population pharmacokinetic analysis and Monte Carlo simulations were performed using Pmetrics in R. Probability of pharmacokinetic/pharmacodynamic target attainment (PTA) was simulated for cefazolin concentrations achieved in plasma (target: unbound trough concentrations  $\geq 4$  mg/L for 100% of a 3-day dose interval) and bone (target: trough total concentrations  $\geq 4$  mg/L for 100% of a 3-day dose interval)

with a bone penetration ratio of 0.18) against various dosing strategies. The target of  $>4$  mg/L was selected as it is the clinical breakpoint for methicillin-sensitive *Staphylococcus aureus* (MSSA) infections, for which cefazolin is most commonly indicated.

**Results:** Total and unbound concentrations were measured in 122 plasma samples collected from 16 patients (14 female) with median (IQR) age 51 (39-62) years and weight 70 (59-76) kg. The median pre-dialysis unbound cefazolin concentration for a 3-day dose interval trough was 17.7 (13.5-31.4) mg/L. The median unbound fraction was 38.3 (32.1-45.9). A three-compartment model comprising a complex albumin binding component adequately described the data. No tested demographic or clinical data significantly improved the final pharmacokinetic model. In the dosing simulation, the 2 g three-times weekly regimen achieved a 99.2% probability to maintain plasma unbound cefazolin concentrations  $\geq 4$  mg/L for 100% of the 72-h dose interval. The simulated regimen of 1g three-times weekly achieved a 97.3% PTA in the plasma. The 2g three-times weekly model also achieved a PTA of 99% in the bone penetration model. Mean cefazolin clearance during dialysis vs non-dialysis period was  $15.4 \pm 3.5$  L/h vs  $0.48 \pm 0.28$  L/h.

**Conclusions:** A 2-g three-times weekly post-dialysis cefazolin regimen can be recommended for MSSA infections. Future studies may be needed to validate cefazolin penetration in the bone with this dosing regimen for the treatment of staphylococcal osteomyelitis.

### Study the individual differences of patients with rheumatoid arthritis to methotrexate therapy based on metabolomics

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**Objective:** To find out the biomarkers associated with the response to methotrexate (MTX) therapy in rheumatoid arthritis (RA), and explain the individual differences of MTX therapy from the perspectives of metabolomics.

**Methods:** Ultra-performance liquid chromatography-quadrupole/time-of-flight mass spectrometry was adopted to acquire the serum profiles of the effective (n=22) and non-effective (n=17) groups of RA patients receiving MTX treatment. Clinical response to MTX was defined by a clinically meaningful reduction in disease activity score in 28 joints (DAS28-ESR) of greater than 1.2. Then principal component analysis and partial least squares-discriminant analysis were conducted to find out the biomarkers and metabolic pathways associated with the response to MTX therapy.

**Results:** There existed obvious difference of the metabolic profiles between the effective and non-effective groups. A total of thirty-nine differential metabolites were identified.

Briefly speaking, 12 differential metabolites, including myristic acid, palmitic acid, tryptophan, and uridine, showed a significant increase, while 22 differential metabolites, including glycine cholic acid, sphingosine 1-phosphate, lysophosphatidylcholine, and lysophosphatidylethanolamine, showed a significant decrease, in the non-effective group when compared with those of the effective group. These differential metabolites participated in phenylalanine, tyrosine and tryptophan biosynthesis, tryptophan metabolism, tyrosine metabolism and so on.

**Conclusion:** Our study revealed the metabolites associated with the response to MTX therapy in RA, which would provide data support for the individualized therapy of MTX.

### The impact of nicotine metabolism on smoking cessation during pregnancy: A review

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**Background:** Smoking during pregnancy is detrimental to the foetus, but quitting smoking is challenging for pregnant women. This is especially relevant to Australian Indigenous families, for whom 43% of mothers smoke compared with 7.5% by non-Indigenous mothers. The nicotine metabolite ratio (NMR), which is the ratio of the nicotine metabolites 3-hydroxycotinine/cotinine, is used to indicate the relative rate of nicotine metabolism, with a higher value indicating faster metabolism. The NMR has been shown to be a useful tool for predicting smoking behaviours and guiding smoking cessation efforts; individuals with higher NMR values are more likely to have greater nicotine dependence and withdrawal symptoms, and are more likely to opt for varenicline or bupropion to quit smoking rather than nicotine replacement therapy, as compared to those with slower NMR values.

**Purpose:** To examine what is known about NMR during pregnancy, and its impact on smoking cessation in relation to Australian Indigenous populations.

**Method:** A literature search was conducted using PubMed, EMBASE, CINAHL, PsycINFO and Google Scholar for studies reporting NMR (nicotine metabolite ratio) or CYP2A6 activity, and smoking or nicotine in pregnancy.

**Results:** Nine studies were identified to have investigated the relationship between NMR values and pregnancy. Two studies conducted in Canada and one in the UK demonstrated that NMR values increase during pregnancy and decrease again after birth. Two studies in the US found that despite increases in NMR values during pregnancy, self-reported cigarette usage remained similar, and suggested that pregnant women may feel social pressure to underreport their smoking habits. Moreover, one study in

the UK showed that pregnant women with higher NMR values are less likely to quit smoking. Additionally, two US-based studies, which included White, African, and Hispanic/Latina participants, found that opioid use can also increase NMR values, and greater nicotine dependence is observed in pregnant women with higher NMR values. In terms of pregnancy outcomes, only one study considered this aspect; this US study concluded that women with lower NMR values are more likely to have low birth weight babies than those with higher NMR values. In seven out of nine studies, 89% or more of participants were White, and none of the studies were conducted in the Southern hemisphere.

**Conclusion:** NMR values can predict smoking behaviours, and tend to increase during pregnancy, making it more difficult for women to quit smoking. However, the range of ethnic backgrounds involved in the studies on NMR values during pregnancy is very limited. Ethnicity is known to affect NMR, for example White and Hispanic people have higher NMR values than African American and Asian populations. Due to the large proportion of Australian Indigenous women smoking during pregnancy, further studies are needed to better understand NMR values in populations in the Western Pacific and South-East Asian regions.

### Impact of supportive care crugs on treatment effectiveness in cancer chemotherapy

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#### Background and Purpose

Numerous supportive care agents have been used in cancer therapy. However, the ability of every support care drug in augmenting the effect of cancer chemotherapy drugs has not been elucidated. Vascular endothelial growth factor (VEGF) is a protein secreted by various tissues in the body that increases vascular permeability and promotes angiogenesis. VEGF is an essential treatment target for many diseases. Angiogenesis by VEGF is known in oncology to be a poor prognostic factor because it is associated with cancer progression and metastasis, making it one of the therapeutic targets for cancer treatment. We found that proton pump inhibitors (PPIs), which inhibit gastric acid secretion and are used in palliative care, may attenuate the efficacy of cancer therapy by inducing VEGF secretion in colorectal cancer. onoprazan, on the other hand, which has the same gastric acid secretion inhibitory action as PPIs, did not induce VEGF

secretion. We found that estrogen receptors may play a role in the distinction between these effects. Therefore, in this study, we compared the effects of PPIs and vonoprazan on the therapeutic efficacy of cancer drugs from both clinical and basic points of view across cancer types.

### Methods

We investigated the relationship between the duration of bevacizumab (Bev) treatment and administration of vonoprazan or PPIs in patients with cancer. In addition, we used cancer cell lines to investigate differences in the expression of the VEGF gene induced by PPIs or vonoprazan and to study the contribution of estrogen in different cancer types. We studied the drugs that may affect VEGF expression similar to the effect of PPIs by employing extensive data analysis.

### Results

The PPI group included 190 patients and the vonoprazan group had 32, with no significant differences in patient background (age, gender, cancer type). Patients in the vonoprazan group received Bev treatment for a longer duration than those in the PPI group. However, when analyzed by cancer type, the duration of Bev treatment was 227 days longer in the vonoprazan group than in the PPI group for breast, lung, brain, and ovarian cancer but 102 days longer in the PPI group for colorectal cancer ( $p < 0.05$ ). Therefore, we investigated the effects of VEGF induction by PPI and vonoprazan in cancer cells other than colorectal cancer. PPI exposure increased VEGF gene expression in several cancer cell lines as opposed to vonoprazan. The induction of VEGF expression by PPIs was suppressed by estrogen receptor inhibitors in colorectal cancer cell lines but not in non-colorectal cancer cell lines. Moreover, among the drugs used in clinic, several drugs other than PPIs may also have VEGF induction effects.

### Discussion

Our results indicate that an appropriate selection of gastric acid secretion inhibitors may improve cancer therapy efficacy. However, since the possibility of an estrogen-independent VEGF induction mechanism has been demonstrated, further validation is needed for each cancer type. Furthermore, additional research is needed for drugs other than PPIs that may exhibit VEGF-inducing effects.

## Revolutionizing patient care through pharmacogenomics: Opportunities, challenges and a call to action for pharmacists, pharmacy regulators and educators: A narrative review

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RFMO-03 - Rapid Fire Session Monday, M1-M2, September 25, 2023, 2:30 PM - 4:00 PM

**Background:** A groundbreaking article published in the Lancet in February 2023, revolutionized the narrative around

the evidence for pharmacogenomics implementation in clinical practice. Based on the findings of the open-label, multicenter, controlled, cluster-randomized crossover implementation study, Swen *et al.* concluded that "a 12-gene pharmacogenetic panel significantly reduced the incidence of clinically relevant adverse drug reactions and was feasible across diverse European health-care system organizations and settings. Large-scale implementation could help to make drug therapy increasingly safe." Despite the significance of this evidence, pharmacogenomics implementation is lagging, leading to undesirable outcomes for patients and unnecessary costs for healthcare systems. This necessitates identifying and mitigating the underlying barriers that are impeding pharmacogenomics from becoming mainstream clinical pharmacy practice.

**Purpose:** This narrative review aims to explore the opportunities and challenges of implementing pharmacogenomics and provide a call to action for pharmacists, pharmacy regulators, and educators. The hypothesis is that the integration of pharmacogenomics into patient care has the potential to improve patient outcomes and reduce healthcare costs, but it requires a concerted effort from pharmacists, regulators, and educators to become mainstream. The review aims to provide a thematic analysis of these opportunities and barriers for pharmacists, educators, regulators, and mitigators to address any barriers identified.

**Methods:** A narrative review of the literature was conducted using PubMed, Scopus, and Web of Science databases. The search terms included pharmacogenomics, personalized medicine, precision medicine, patient care, pharmacists, pharmacy regulators, educators, institutions, competence standards, opportunity, and challenge. The articles included in this review were published between 2010 and 2022. 56 articles were screened based on their relevance to the objectives of the review.

Qualitative data was extracted and thematically categorized into:

- Opportunities and challenges of implementing pharmacogenomics into pharmacy education
- Identify action taken by regulators to embed precision medicine into professional competence standards
- Pharmacists' role and attitudes towards pharmacogenomics implementation

**Results:** Thematic analysis of the eligible literature highlights that pharmacists are in the best position to lead pharmacogenomics implementation as medicine experts, and providers of medication review services. Pharmacist attitudes were favorable and supportive of pharmacogenomics implementation. However, the findings highlight a significant gap in integrating pharmacogenomics education into curricula as part of undergraduate programs and the need for institutional support globally. There is also a lack of competency frameworks by regulators for consistent application of pharmacogenomics principles in practice, which flows into institutional curricula, and consequently affects pharmacist uptake, competence, and confidence in pharmacogenomics implementation.



**Conclusion:** The findings highlight a call to action for pharmacists to play a key role as patient advocates and medication safety champions in catalyzing the adoption of pharmacogenomics into clinical practice. For regulatory bodies, a call to action to embed pharmacogenomics into competence standards based on the significant available evidence for its applicability to patient care, and for institutions to ensure pharmacogenomics education is integrated into curricula. The International Pharmaceutical Federation, as an international pharmacy organization, has a significant role in leading this work. Further research could explore barriers to creating standardized global competencies for safe pharmacogenomics implementation.

### Development and validation of a machine learning algorithm to optimise the dosing of unfractionated heparin

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RFMO-03 - Rapid Fire Session Monday, M1-M2, September 25, 2023, 2:30 PM - 4:00 PM

#### Background

Unfractionated heparin (UFH) is considered a high-risk medication, with complex dosing. An excessive dose can cause bleeding, while an insufficient dose can lead to a recurrent embolic event. Following initiation of intravenous (IV) UFH therapy, the therapeutic response is monitored using a measure of blood clotting, the activated partial thromboplastin time (aPTT). Clinicians iteratively adjust the dose of UFH to a target aPTT therapeutic range, with the local range between 60 to 100 seconds. Unfortunately, dose estimation for UFH is difficult due to pronounced intra- and inter-patient variability in the pharmacodynamic response. Data across four metropolitan tertiary Australian hospitals showed only 23% of patients were reaching the target aPTT range after the first dose. New dosing methods are required, and advances in the development of machine learning (ML) algorithms offers an exciting opportunity to optimise the dosing of UFH.

#### Purpose

The aim of this study was to develop and validate a ML algorithm to predict, aPTT within 12 hours after a specified bolus and maintenance dose of UFH.

#### Method

This was a retrospective cohort study of data obtained over 3-years. The patient population was adult general medicine and surgical patients being administered UFH for an embolic event such as deep vein thrombosis or pulmonary embolism, or for the prevention of embolic events due to atrial fibrillation. Data was collected from electronic health

records of five hospitals in Queensland, Australia. Data from four hospitals were used to build and test ensemble models using cross validation, while the data from the fifth hospital was used for external validation. Modelling was performed using H2O Driverless AI® an automated ML tool.

#### Results

A total of 2691 patients were included from 3019 episodes of care. 17 different experiments were conducted in an iterative process to optimise model accuracy. In predicting aPTT, the best performing experiment produced an ensemble with 4x LightGBM models with a root mean square error (RMSE) of 31.35 (standard deviation (SD)=1.37). This model relied on 93 features. The dataset was re-purposed as a multi-classification task (sub-therapeutic, therapeutic, and supra-therapeutic aPTT result) and achieved a 0.599 (SD=0.029) accuracy and area under the receiver operating characteristic curve (AUC) of 0.735. External validation yielded similar results: RMSE of 30.52 (SD = 1.29) for the prediction model, and accuracy of 0.568 (SD=0.032) and AUC of 0.724 (95% CI 0.714-0.734) for the multi-classification model.

#### Conclusion

To our knowledge, this is the first ML model applied to IV UFH dosing that has been developed and externally validated in a multisite adult general medical and surgical inpatient setting. The algorithm will be embedded into an application and evaluated in a prospective clinical trial.

### The impact of ABCB1, CYP3A4/5 and ABCG2 gene polymorphisms on rivaroxaban trough concentrations and bleeding events in patients with non-valvular atrial fibrillation

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RFMO-03 - Rapid Fire Session Monday, M1-M2, September 25, 2023, 2:30 PM - 4:00 PM

**Background:** The influence of genetic factors on the pharmacokinetics and clinical outcomes of rivaroxaban in patients with non-valvular atrial fibrillation (NVAf) is poorly understood. This study aimed to explore the effects of CYP3A4/5, ABCB1, and ABCG2 gene polymorphisms on the trough concentrations and the bleeding risk of rivaroxaban in NVAf patients.

**Patients and Methods:** This study is a prospective multicenter study. The patient's blood samples were collected to detect the steady-state trough concentrations of rivaroxaban and gene polymorphisms. We visited the patients regularly at month 1, 3, 6, and 12 to record bleeding events and medications.

**Results:** A total of 95 patients were enrolled in this study, and 9 gene loci were detected. For the dose-adjusted trough

concentration ratio (C<sub>trough</sub>/D) of rivaroxaban, the homozygous mutant type was significantly lower than wild type at ABCB1 rs4148738 locus (TT vs. CC, P=0.033), and the mutant type was significantly lower than the wild type at ABCB1 rs4728709 locus (AA+GA vs. GG, P=0.008). ABCB1 (rs1045642, rs1128503), CYP3A4 (rs2242480, rs4646437), CYP3A5 (rs776746), and ABCG2 (rs2231137, rs2231142) gene polymorphisms had no significant effect on the C<sub>trough</sub>/D of rivaroxaban. For the bleeding events, we found that there were no significant differences among genotypes of all gene loci.

**Conclusion:** This study found for the first time that ABCB1 rs4148738 and rs4728709 gene polymorphisms had a significant impact on the C<sub>trough</sub>/D of rivaroxaban in NNAV patients. CYP3A4/5, ABCB1, and ABCG2 gene polymorphisms were not associated with the bleeding risk of rivaroxaban.

### Model-informed evidence approach for paediatric and neonate dosing of tramadol

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RFMO-03 - Rapid Fire Session Monday, M1-M2, September 25, 2023, 2:30 PM - 4:00 PM

Tramadol is a useful medication to treat postoperative pain in children, including neonates and infants. Tramadol has complex pharmacokinetics, which makes identifying the ideal dosage for these populations challenging. Specifically, these challenges include age-based physiological changes, enzyme expression variability, and active metabolites. The approved indication of tramadol in these populations varies greatly by country, yet off-label use for postoperative pain in these patient populations is common. Therefore, this project focused on bridging the knowledge gap of neonate and infant tramadol pain management care through mechanistic modelling methods which incorporated age-based physiological changes to compare tramadol exposure across age groups (neonates, infants, children, and adults) for dose optimization. In lieu of dedicated clinical trials in these vulnerable populations, we developed a physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) model, which incorporated both intrinsic and extrinsic population properties to accurately predict tramadol exposure after oral or IV administration. Specifically, the final model incorporated enzyme (CYP2D6, UGT2B7) and transporter (OCT1) expression data, active metabolite generation/exposure, developmental age-based changes in physiology, and tramadol physiochemical properties. Model simulation results indicated a significant age-based exposure trend for tramadol and its active metabolite. The effect of these exposure changes was evaluated using an Emax pharmacodynamic model, under the assumption that the exposure-response relationship of tramadol and its active metabolite remains the same amongst all age groups. The results of these PBPK/PD analyses suggested the dose-exposure-response relationship was not equivalent among these populations, but this nonequivalence could be

alleviated via dose decreases based on age, e.g. 2 mg/kg in children (2-7 years), 1 mg/kg in infants (1 month-2 years), and 0.60 mg/kg in neonates (< 1 month). Overall, by utilizing a physiologically based modeling approach we were able to quantify differences in tramadol and active metabolite exposure-response amongst varying age groups, including neonates and infants. This suggests that dosing can be optimized based on these differences. Future work will focus on further validating these dose optimization findings in the context of clinical practice.

### Development of the physician-pharmacist partnership intervention to deprescribe medications (PPPi-DM) and its feasibility in primary care

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**Background:** Deprescribing is a systematic process of withdrawing potentially inappropriate medications (PIMs) to minimise polypharmacy and improve patient outcomes. Previous studies in developed countries found that deprescribing interventions which involved pharmacists have been effective in reducing PIMs. To date, there is limited data on deprescribing interventions for older persons in upper- and middle-income countries like Malaysia.

**Purpose:** To develop and evaluate the feasibility of the Physician-Pharmacist Partnership Intervention to Deprescribe Medications (PPPi-DM) among ambulatory older persons in a primary care clinic in Malaysia.

**Methods:** The PPPi-DM was developed based on findings from a qualitative study, which reported that doctors preferred a step-by-step deprescribing intervention that included pharmacists to review patients' medications. This led to the development of the PPI-DM. We modified the physician-pharmacist-partnership for patient safety (PPP-PS) intervention, which was initially developed in our setting to identify drug-related problems in patients. This intervention consists of five steps: 1)obtaining a comprehensive medication history, 2)identifying any PIMs, 3)determining whether medication can be ceased and prioritised, 4)planning and initiating medication withdrawal and 5)monitoring, support and documentation. The feasibility of PPI-DM was then conducted in March 2022. Older patients (≥65 years) with multiple chronic diseases, prescribed ≥5 medications and having ≥1 PIMs (according to Beer's Criteria 2019) were recruited. Primary care trainees (defined as doctors who were undergoing their 4-year specialist training in family medicine) who were treating these patients were also recruited. Outcomes measured were the proportion of PIMs identified and deprescribed, doctors' acceptance rate

regarding pharmacist's recommendations and the process of delivering the intervention in a feasibility study.

**Results:** 20/35 (response rate=57.1%) patients and 14/14 doctors (response rate=100%) were recruited. A total of 36/167 (22%) PIMs were identified from 20 patients; 34/36 (94%) PIMs were identified by the pharmacist and 2/36 (6%) were identified by doctors. Deprescribing was performed on 14/20 (70%) older patients. The number of PIMs accepted for deprescribing was 19/36 (52.7%). A total of 17/34 (50%) PIMs proposed by the pharmacist and 2/2 (100%) by doctors were deprescribed. Minimal issues were encountered during the process of delivering this intervention. The eligibility criteria used for recruitment and the current workflow used for deprescribing medications were suitable. Both patients and doctors were able to understand and complete all procedures. The total time taken for one patient to complete the entire process ranged from 45-60 minutes. The pharmacist was able to perform medication reviews in a designated room in the clinic and experienced no problems with documentation using predesigned forms. Patients and doctors were receptive to the idea of deprescribing. All patients agreed to deprescribe their medication when suggested by their doctor. Some doctors did not deprescribe medication(s) as it was still indicated 15/17 (88.2%), did not want to interfere with medications prescribed by another specialist 1/15 (6.7%), and insufficient time during the patient-doctor consultation 1/15 (6.7%).

**Conclusion:** The PPPi-DM was successfully developed and was found to be feasible in our setting. A randomised controlled trial should be conducted to assess the effectiveness of PPPi-DM in improving clinical outcomes.

### Association between SLCO1B1 gene marker and simvastatin-induced myopathy: A systematic review and meta-analysis

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RFMO-03 - Rapid Fire Session Monday, M1-M2, September 25, 2023, 2:30 PM - 4:00 PM

#### Background:

Statin is used for the treatment of hyperlipidemia to prevent and treat myocardial infarction and stroke and reducing cardiovascular morbidity and mortality in certain patients. Statin use is commonly associated with muscle-related adverse effects, ranging from myalgia, to life-threatening rhabdomyolysis leads to non-adherence, discontinuation or reduction of statin dose by the patients. The variability of myotoxicity is caused not only by traditional clinical factors, such as female sex and diabetes, but also by genetic variations. Genetic associations with statin-induced myopathy also have been reported, but with the large numbers of candidate genes and single-nucleotide polymorphisms (SNPs) involved, a statistically convincing pooled analyses is still lacking. This study aimed to investigate the association between SLCO1B1 gene marker

and the incidence of simvastatin-induced myopathy through a comprehensive meta-analysis.

#### Methods:

The electronic databases of PubMed, Scopus, Web of Sciences and SpringerLink were searched for publications from 2005 until 2022. The combination of the following keywords was used: (simvastatin or statin or hypercholesterol\* drug or Hydroxymethylglutaryl-CoA Reductase Inhibitors) AND (myotoxicity or myalgia or muscle symptoms or creatinine kinase elevate\* or muscle weakness) AND (SLCO1B1 or genetic polymorphism or hepatocytes protein or biomarker or rs4149056). The Downs and Black tool was used for assessing the quality of included studies. Nine studies were included and assessed. Cochrane Review Manager (RevMan) V.5.4 software was used for meta-analysis. The software was utilized to produce Forest Plot which illustrates heterogeneity and pooled results. The software also generated Funnel plot for assessing publication bias.

#### Results:

A total of 1368 articles were originally identified. After removing 347 duplicate articles, 1021 articles were left for abstract screening and full-text assessment. After abstract screening, 993 records were excluded following reading the title and abstract. 19 studies then were left for full-text assessment. After evaluating the full-text according to inclusion and exclusion criteria, 9 studies were eligible for further meta-analysis. Nine observational studies were included in the meta-analysis. The pooled analysis showed that statin-induced myopathy was significantly associated with the SLCO1B1 gene marker. The results did not have statistical significance since the combined results (the diamond) crossed the vertical "line of no effect", with OR 0.67 and 95% CI 0.40 to 1.12. It means that the overall outcome rate in the cases group is much the same as in the control group. On the other hand, p-value of the chi-squared test is <0.00001, indicating significant heterogeneity. Moreover, the I<sup>2</sup> value is 89% suggesting considerable or high heterogeneity. A random effect model can be used in the meta-analysis since the heterogeneity is high. This shows that there is variability among the nine studies.

#### Conclusion:

Simvastatin and other statins are dose-dependent that can cause statin-induced myopathy. Other than that, variant C allele may be a high-risk factor also for statin-related myopathy. Anyway, in this meta-analysis, the overall outcome rate in the intervention group is similar as in the control group. Therefore, the results show that SLCO1B1 gene is not associated with risk of statin-related myopathy in individuals getting simvastatin treatment.

## Using co-design to develop an anti-microbial clinical dosing decision support tool

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RFMO-03 - Rapid Fire Session Monday, M1-M2, September 25, 2023, 2:30 PM - 4:00 PM

**Background:** Numerous pharmacokinetic-based clinical dosing decision support tools have been developed to support healthcare professionals with individualised drug dosing and therapeutic drug monitoring (TDM). However, poor usability and integration into workflow have partly limited their uptake in practice. This likely represents the limited involvement of healthcare professionals in the development of dosing decision support tools. This study applied co-design principles using the experiences and expertise of healthcare professionals to inform the design of an anti-microbial dosing decision support tool to address barriers in drug dosing, using vancomycin as an example.

**Purpose:** To identify pharmacist and prescriber barriers in vancomycin drug dosing and explore how clinical dosing decision support tools can address these barriers.

**Method:** A co-design process was conducted as a series of three workshops with pharmacists and prescribers. User journey storyboards, personas and prototyping tools were used to gather participants' opinions on existing barriers to practice and opportunities to address these through the design of a dosing decision support tool. A prototype of the tool's user interface was presented to participants for feedback.

**Results:** 11 hospital pharmacists and 6 prescribers with  $\geq 2$  years of clinical experience were recruited. Participants identified a lack of confidence in vancomycin dosing and pharmacokinetic understanding, as well as difficulty in accessing practice guidelines as key barriers which could be addressed through tool implementation and design. Accessibility to information (e.g. guidelines and pharmacokinetic resources), the types of information required, and ways to visualise and communicate data depended on the needs and experience of the user.

**Conclusion:** Clinical dosing decision support tools need to be designed with and for the end-user to promote successful translation into practice. Their design needs to be adaptable to the needs and workflow of clinical users. The whole clinical context of the patient also needs to be considered, not just the drug itself. The involvement of healthcare professionals in the development of dosing decision support tools, as well as training and education, is needed to

promote tool utilisation in practice and improve individualised drug dosing and TDM.

## Translation of advanced therapeutics to clinical practice

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RFMO-03 - Rapid Fire Session Monday, M1-M2, September 25, 2023, 2:30 PM - 4:00 PM

### Background

The world is experiencing a tsunami of advanced therapeutics through clinical trials and in clinical practice. This is leading to a substantial increase in the number and complexity of pharmaceutical and advanced therapeutic medicinal products required to be compounded or prepared for administration by pharmacists in public health facilities. One such complex product is bacteriophage therapy. The state of New South Wales, Australia, were the first in the world to intravenously administer a good manufacturing practice quality bacteriophage therapy and is running the world's first national open label clinical trial. Pharmacists working in the public health service need to be prepared to support the translation of advanced therapeutic clinical research into clinical practice.

### Purpose

To promote how pharmacists and the state Government Health Department can work together in supporting public health service readiness to provide advanced therapeutics to patients. Case studies of advanced therapeutics identified gaps in the supply chain. Pharmacist expertise was required to address these gaps, including preparing a policy for the handling and preparation of advanced therapeutics and consultation with regulatory bodies.

### Method

A state-wide working group of key stakeholders from research, nursing, medical and specialist aseptic compounding pharmacists was established to advise on the policy. The working group considered legislation, infrastructure, workforce, and training needs to standardise the compounding and preparation of pharmaceutical and advanced therapeutic products, by either the centralised pharmacy service or nursing and medical clinicians in the patient care area. A specialist pharmacist was included in the Bacteriophage Therapy Regulation Working Group which was formed to consult with key research clinicians and regulatory bodies to consider the options for regulation of bacteriophage therapy.

### Results

The state Government Health Department developed a policy for the preparation of pharmaceutical and advanced therapeutic products. The policy details the importation, preparation, infrastructure and regulatory requirements to improve supply chain for advanced therapeutics and clinical trials. Specialist pharmacist involvement in the Bacteriophage Therapy Regulation Working Group guided and supported the translation between researcher ideals

and public health service legislation and capabilities. Bacteriophage regulation remains under consultation, not meeting the current classifications of either a pharmaceutical or a biological. Pharmacist involvement has identified that workforce development and regulatory decisions are major limiting factors for the translation of advanced therapeutics and precision medicine into clinical practice. The specialised skills and knowledge required by pharmacists demands accredited education and training.

**Conclusion**

Public health service preparedness is essential for the translation of advanced therapeutics into clinical practice and improve Australian health outcomes. Specialist aseptic compounding pharmacists skills and knowledge are key to developing the necessary workforce in good manufacturing practice, compounding and preparation of clinical trials and advanced therapeutics. It is essential for pharmacists to work with the Government Health Department to improve the translation of advanced therapeutics. We need more specialised pharmacists to inform on the regulatory decisions and to drive policy, facilitating the safe provision of these therapies to our patients.