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Abstracts of the ESDPPP Conference, Prague, Czech Republic, 28–30 June 2023

In June 2023, the 20th conference of the 35th anniversary of the European Society for Developmental, Perinatal and Paediatric Pharmacology (ESDPPP) entitled "Use of clinical pharmacology to improve safe and effective use of drugs in neonates, infants, children, and adolescents worldwide" was held in Prague with a high-level scientific program attended by 111 participants. ESDPPP is a relatively small European, but highly specialized, multidisciplinary professional society focusing on pharmacotherapy in neonatology and paediatrics (research, education, meeting platforms, etc). The scientific guarantor of the congress was Prof. MD Tomáš Zima, DrSc, MBA (Institute of Medical Biochemistry and Laboratory Diagnostics General Faculty Hospital and 1st Faculty of Medicine Charles University in Prague). The patronage of the congress was taken over by the dean of the 1st Faculty of Medicine in Prague, Prof. MD Martin Vokurka, CSc, Ministry of Health of the Czech Republic; Prof. MD Vlastimil Válek, CSc, MBA, for the Health Committee of the Senate of the Parliament of the Czech Republic; MUDr Lumir Kantor, PhD, mayor of the capital city of Prague; Doc. MD Bohuslav Svoboda, CSc; as well as the Embassy of the Czech Republic in Stockholm (Czech Ambassador Anita Grmelová), the Swedish Embassy in Prague (Swedish Ambassador Fredrik Jörgensen).

The congress was preceded by a pre-congress workshop on Principles of Neonatal and Pediatric Clinical Pharmacology led by Professors Gregory Kearns and John van den Anker. This was followed by a 2.5-day conference of lectures and oral presentations of selected abstracts, including a session dedicated to Prof. Dr. Jean-Pierre Guignard, founder of ESDPPP. The congress was conducted as a "pas de deux" of science and music performed by the Wihan Quartet during the welcome ceremony in the Senate of the Czech Republic. The conclusion of the congress was a classy piano recital by Ivo Kahánek in the Rudolfinum.

The congress was held in Prague for the first time in the history of ESDPPP and it is gratifying that it was thanks to the scientific committee (led by Prof. John van den Anker) and the team of organizers (led by Jan Krušina and Klára Bumbálková), marked as a successful congress of our society, ESDPPP, also under the leadership of all members of the Council (academics Mark Turner, Saskia de Wildt, Florian Lagler, Pieter de Cock, Christiane Garnermark , Stephanie Leroux, Robert Flint, Anne Smits and Anna-Maria Wiesinger).

MD Pavla Pokorná PhD
Chairman of ESDPPP 2022/2023
Prague, May 30, 2024

A) Session 3: Clinical Trials in Neonatal and Paediatric Clinical Pharmacology

1 TOWARDS MORE ROBUST EVALUATION OF THE PREDICTIVE PERFORMANCE OF PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELS

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Introduction With the rise in use of physiologically-based pharmacokinetic (PBPK) modeling over the past decade, the use of PBPK modeling to underpin drug dosing in special patient populations (e.g. pediatrics and pregnant women) has become an attractive option. In order to use PBPK models for high-impact decisions, thorough qualification and validation of the model is essential to gain enough confidence in model performance. Currently, there is no consensus on the appropriate validation steps while clinicians demand a clear measure of model performance before considering implementing PBPK model-informed dosing. We aimed to bridge this gap and propose a novel more stringent validation method.

Methodology We chose to use a confidence interval for the predicted-to-observed geometric mean ratio. This approach is more in line with currently accepted bioequivalence testing procedures and can therefore aid in improved model credibility and acceptance. Two different constructions for a confidence interval are outlined, depending on whether individual observations in the clinical comparator data sets are available or not. In addition, an easy-to-use implementation tool is provided to make our proposed method more accessible.

Results The two testing procedures are demonstrated for both clinical and hypothetical data for an example midazolam PBPK model. The example PBPK model validation demonstrates that creating a confidence interval yields a more robust evaluation of the model than a point estimate, such as the commonly used 2-fold acceptance criterion. Additionally, the use of individual predictions can reduce the amount of required test subjects.

Conclusion With this easy-to-implement method, we hope to increase confidence in PBPK model performance to facilitate its use for directly informing drug dosing in clinical care. Especially, in the field of pediatric pharmacology, more thorough validated PBPK models could increase the evidence base of dosing recommendations.

2 PEDIATRIC CLINICAL TRIALS NEED PEDIATRIC CLINICAL TRIAL BUDGETS

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There is a well-known knowledge gap regarding the efficacy and safety of medicines in children of all ages, and clinical trials and the need for new treatments were recently listed among the most important factors for child health. Pediatric clinical trials are faced with several challenges compared with trials in adults. These challenges include the fact that pediatric populations are small and heterogenous, and that there is generally less experience with pediatric clinical trials,, compared to trials in adults both on the sponsor side and at the hospitals. One specific challenge that has received little attention is the importance of adequate representation of costs in pediatric trial budgets. The aim with the present study was to describe some important aspects to consider when a pediatric clinical trial budget is reviewed and identify budget items that often need adjustments in pediatric clinical trials.

We went through the budgets negotiations of the last ten trials sponsored by the pharmaceutical industry where agreements between our site, the Pediatric Clinical Research Center, and the sponsor, had been finalized. The therapy areas represented among these trials were pediatric oncology (2), neurology (4), gastroenterology, neuropsychiatry, cardiology, and nephrology. We reviewed the trial budgets and identified areas where discrepancies between the sponsor´s initial budget, and the final budget, negotiated and agreed between sponsor and site, may arise. The difference in total budget amount between the initial budget and the final budget was +60% (mean 59%, range 31 to 139%). The costs for preparation of the clinical trial, time spent for study activities, and costs for examinations were identified as key budget items for these differences.

Our findings indicate that a substantial part of the trial-related costs would not be covered by the sponsor had the initial budget been accepted. A thorough review at the site and budget negotiation with the sponsor, and to have within the site team a person with specific competence for the budget review and negotiation, are therefore essential to ensure equitable responsibility for the study-related costs and avoid discontinuation of the trials. High-quality pediatric trials are essential to ensure that children have the benefit of treatments based on the same quality of evidence that guides treatment in adults.

3 PAEDIATRIC INVESTIGATION PLANS IN SYSTEMIC LUPUS ERYTHEMATOSUS: REVIEW OF THE PDCO'S EXPERIENCE

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Introduction Recently, the identification of new treatment pathways has led to the initiation of several new medicine developments in Systemic lLupus Erythematosus (SLE). However, compared to adult disease, juvenile-onset SLE (jSLE) exhibits increased disease activity, earlier tissue damage requiring more aggressive treatments. Therefore, appropriate paediatric development is needed.

Methodology The European Medicines Agency (EMA) reviewed aspects of the Paediatric Investigation Plans (PIPs)

agreed by the Paediatric Committee (PDCO) at the EMA in SLE in the period since the Paediatric Regulation came into force until today (2007–2022) to identify current challenges.

Results So far, the PDCO has evaluated 30 submissions for PIPs for (j)SLE. All PIP related products are also being developed for adult-onset SLE. So far 22 have led to an agreed plan correspond to 21 different active substances, each with a different mechanism of action. 4 of them are being specifically developed to target lupus nephritis.

The agreed PIPs focus on patients from 5 years of age, and on average each PIP includes only a single clinical trial (14 of them vs 7 with 2 and one with 4 trials). Of the 32 planned clinical trials included in the PIPs, 14 are RCTs versus placebo, as add-on to standard of care.

On average, a sample size of at least 83 patients was required in the main trial and 17 PIPs contained an agreed modelling and simulation analysis to support appropriateness of paediatric dosing and/or analyse pharmacokinetics/pharmacodynamics (PK/PD).

Belimumab was the first biologic treatment that obtained a paediatric indication for (j)SLE above 5 years of age in the EU. Extrapolation of efficacy data from adults and older paediatric patients eventually allowed regulators to grant an indication in the younger age groups.

Results from other PIPs are awaited.

The number of PIPs for the treatment of (j)SLE evaluated by the PDCO highlights a very competitive area where agreed developments are relatively consistent, but recruitment of paediatric patients seems to be challenging.

Conclusions Stand-alone developments might not deliver results and answer the most pressing research questions in the required timeframe. Therefore, innovative designs considering different mechanisms of actions, potential synergistic effects, potential prioritisation should be explored. Furthermore, research should also focus on bridging biomarkers, to make better use of extrapolation of efficacy from adults.

B) Session 4: New Activities Within ESDPPP: What We Have Reached after Liverpool 2022

5 CZECHPHARMPED: STARTING THE OPTIMIZATION OF PHARMACOTHERAPY IN CHILDREN IN DAILY CLINICAL PRACTICE IN THE CZECH REPUBLIC AND SLOVAKIA (INITIATIVE OF A NETWORKING GROUP OF YOUNG RESEARCHERS)

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Introduction Evidence-based (EB) data on drug dosage optimization in children are already available across Europe. However, their systematic translation was lacking in the Czech Republic and Slovakia. The purpose of our project is to create a Czech drug database (CzechPharmPed) based on evidence of already existing international databases and national specifics, that will have a positive impact on the daily clinical practice. The objectification of this impact is crucial, moreover, provides valuable feedback.

Methodology After the development of the content framework respecting drugs according to the State Institute for Drug Control (SÚKL) and technical development (a system based on PHP, MySQL and CSS, JavaScript technologies provided via a secure HTTPS connection, using HTTP 2.0 technology), the pharmacoepidemiology of paracetamol was evaluated using a cross-sectional study to map baseline values in a single centre.

Results In the pre-implementation analysis, of all paracetamol prescriptions, 8% of errors were found in the indication, 15% in the routes of administration and in 20% inaccuracy of the pharmaceutical form according to the manufacturer. The single and daily cumulative dose were correct for 59% and 70% of prescriptions, respectively. The SÚKL recommendation for prescribing paracetamol was used by 80% of caregivers, but 62% of these were found to be inaccurate for use in children. Therefore, the domains (www.pharmped.cz, www.pharmped.sk.) and the calculator in cooperation with the database iplprecept.cz (individually prepared medicines) were approved for implementation.

Conclusion CzechPharmPed is designed as a web-based, user-friendly, reflecting the need to update the user interface standards required in the Czech Republic and Slovakia while using the pre-implemantation analysis, its impact can be evaluated properly.

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6 REDUCTION OF RISKS IN THE MEDICATION PROCESS AFTER ADAPTING THE EMR-SYSTEM TO CHILDREN AND INTRODUCTION OF THE NATIONAL SWEDISH MEDICATION DATABASE FOR CHILDREN

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Introduction Drug treatment in children is complex with a high risk of medication errors. One of the most frequent medication errors identified are dosing errors, occurring in all parts of the medication process (prescription, preparation, and administration). The aim of this study was to evaluate interventions directed at reducing medication errors at Queen Silvia Children´s Hospital in Gothenburg, delivered through the electronic medical record (EMR). Between the two years in focus 2013 and 2020, the following changes were made:

- The introduction of a Clinical Decision Support System (CDSS) with weight-based dose calculation and Dose Range Check into the EMR.
- The integration of the national Swedish medication database for children ePed into the EMR, delivering experience- and evidence-based pediatric drug information with diagnosis-specific dose recommendations and standardised dilutions as well as relevant information for administration.

Methodology Drug related incidents for children 0–18 years were extracted from the incident reporting system MedControl PRO for the years 2013 and 2020, i.e. before and after the changes were introduced. We classified and compared medication errors reported through this system to evaluate the impact of the introduced changes on the quality of medication process (prescription, preparation, and administration) and the potential consequences regarding medication errors.

Results The total number of drug related incidents in the medication process was unchanged; 309 medication errors were reported in both 2013 and 2020. Instead, we found a change in the quality of errors. The biggest reduction was found for dosing errors during prescription (-27), preparation (-13) and administration (-11). We categorized primary errors which were discovered and stopped as well as primary errors who continued and led to secondary errors. The number of primary errors with a subsequent secondary error was reduced; in 2013 there were 77 errors resulting in 90 secondary medication errors, whereas in 2020 there were 31 primary errors that led to 37 subsequent errors.

Conclusion We conclude that the integration of the experience- and evidence-based pediatric drug information ePed together with weight-based dose calculation and Dose Range Check prevented medications errors, especially dosing errors, in prescription, preparation and administration of medicines to children at Queen Silvia Children´s Hospital.

7 HARMONISATION, OPTIMISATION AND INDIVIDUALISATION OF DOSING RECOMMENDATIONS FOR CHILDREN IN SWITZERLAND: A THREE-STEP APPROACH

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Introduction 45% of all medicines available in Switzerland are not authorised for use in children, and consequently off-label prescribing is common practice in paediatric care.[2] In the absence of official dosing recommendations in drug labels, other strategies are needed to help professionals selecting the optimal dose for their paediatric patients. We present a three-step approach to provide safe off-label dosing recommendations for children on a national level.

Methodology Step 1: Along with the introduction of the paediatric regulation in Switzerland, an initiative was developed to harmonise dosing recommendations for off-label use, based on evidence from scientific literature combined with national expert knowledge from clinical practice.[2] Step 2: When few data were available to harmonise dosing recommendations, real-world demographic data were consulted and/or data from daily clinical routine were gathered. An online platform was built to access and use these data for pharmacokinetic (PK) modelling and simulation. Step 3: In cases where standardised dosing was expected insufficient, a personalised approach was adopted, incorporating therapeutic monitoring (TDM) and pharmacogenetic (PGx) testing to individualise drug therapy.

Results A standardised harmonisation process was established and almost 600 off-label dosing recommendations for 170 active substances were published in the SwissPedDose database. For anti-infective drugs, where the harmonisation was challenging, dosing recommendations were optimised applying in silico simulation for amikacin based on real-world demographic data and PK modelling for gentamicin based on health-related personal data and TDM results from clinical practice using the recently built and secure online platform SwissPKcdw.[3–5] This platform also allowed a PGx analysis to individualise voriconazole treatment in children suffering from invasive fungal infections.[6]

Conclusions Since Swiss drug labels are lacking paediatric dosing recommendations, more emphasis should be placed on improving the safety of off-label prescribing for children. Three steps, first harmonising the dosing recommendations, second applying modelling and simulation to provide a scientific rationale for optimising the recommendations, and third incorporating results of TDM and PGx tests for individualising drug therapy, allow to approach optimal drug dosing in children.

REFERENCES

1. Tilen R, *et al.* Information in drug labels about use in children is limited and needs standardisation: a systematic analysis in Switzerland. Manuscript in preparation (submission to ArchDisChild planned in March).
2. Tilen R, *et al.* Development of the Swiss Database for dosing medicinal products in pediatrics. *Eur J Pediatr* 2022.
3. Gotta V, *et al.* Leveraging pharmacometric approaches to facilitate a national dose harmonization process in neonatology. Manuscript submitted. 2023.
4. Paioni P, *et al.* Gentamicin population pharmacokinetics in pediatric patients-A prospective study with data analysis using the Saemix package in R. *Pharmaceutics* 2021.
5. Goers R, *et al.* SwissPKcdw - A clinical data warehouse for the optimization of pediatric dosing regimens. *CPT Pharmacometrics Syst Pharmacol* 2021.
6. Tilen R, *et al.* Pharmacogenetic analysis of voriconazole treatment in children. *Pharmaceutics*. 2022.

C) Session 5: Drugs in Special Populations and Settings I: Pharmacology of therapeutic hypothermia and other settings

8 CAFFEINE THERAPY FOR APNEA OF PREMATURITY: REAL WORLD DATA ON EFFECTIVITY

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Introduction Apnea of prematurity (AOP) is a clinical manifestation of an immature control of breathing in preterm infants. Caffeine therapy is the cornerstone of pharmacologic treatment for AOP, and is among the most frequently used medications in preterm infants. Although caffeine has been well studied in trials as well as in popPK studies, the daily clinical application may be different. The aim of this study is to describe current clinical use and dosing of caffeine and to evaluate effectiveness of this therapy.

Methods We performed a retrospective cohort study in preterm infants born before 30 weeks of gestation, admitted to the NICU of the Erasmus MC Rotterdam in the period of January 2018 to December 2021. Patients were included if they received treatment with caffeine base during their admission. The primary outcome of our study was treatment failure, defined as the need for an additional caffeine loading dose or co-treatment with doxapram.

Results A total of 554 patients with a median gestational age (GA) of 27 (IQR 26 to 28) weeks and a median birthweight of 980 (IQR 781 to 1200) grams were included in this study. The median caffeine maintenance dose per patient was 5.30 mg/kg/day, range 4.14 to 7.45. Caffeine treatment failed in 278 patients (50%), leading to one or more additional loading doses in 277 patients and co-treatment with doxapram in 99 patients. The median postnatal age at time of treatment failure was 18 days (IQR 7 to 33 days). In patients with a GA of <=27 weeks, treatment failed in the majority of patients. No correlation was found between postnatal age or birthweight and the caffeine maintenance dose at the time of treatment failure as would have been expected based on pharmacokinetic maturation.

Conclusion A high amount of caffeine is used in clinical practice to treat AOP, with relatively low effectivity, especially in the most extreme preterm infants. This in contrast to what would be expected based on pharmacological maturation and related kinetics. This suggests either an inversed age-related caffeine PK/PD relationship, with higher exposures needed in the smaller infants, or overexposure because of treatment resistant apnea. This might result in an unnecessarily high amount of caffeine given to this vulnerable group of extremely premature infants.

9 TISSUE PENETRATION OF PIPERACILLIN-TAZOBACTAM IN CRITICALLY ILL CHILDREN – A MICRODIALYSIS STUDY

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Introduction Critical illness may affect many pharmacokinetic (PK) processes. Research in adults suggests an impaired tissue penetration of beta-lactam antibiotics in critically ill patients compared to healthy individuals. Currently, data in critically ill children are lacking. This study aimed (1) to investigate the tissue penetration of piperacillin-tazobactam, a frequently used broad-spectrum beta-lactam/beta-lactamase inhibitor combination and (2) to assess the safety of microdialysis experiments in critically ill children.

Methodology This pilot study included seven mechanically ventilated children (age range: 1 month - 13 years) receiving piperacillin-tazobactam (75 mg per kg bodyweight, based on the piperacillin component, every 6 h as a 30 min infusion). A microdialysis catheter (10 mm membrane) was inserted in the thigh muscle. Benzylpenicillin was used as internal standard for microdialysis calibration. During one or two dosing intervals, plasma and microdialysis samples were collected (max. stay of microdialysis catheter: 35 h). PK data were analyzed with non-compartmental PK analysis (Phoenix®, Certara). The tissue penetration was calculated by taking the ratio of the AUC(0-inf) in tissue and in plasma.

Results In total, 12 dosing intervals were sampled. Median tissue penetration was 0.68 (IQR 0.55 – 0.84) for piperacillin and 1.10 (0.92 – 1.38) for tazobactam. The extrapolated part of the AUC(0-inf) accounted for less than 20% of the total AUC(0-inf). No adverse events occurred during microdialysis catheter insertion, microdialysis sampling, and catheter removal.

Conclusion To the best of our knowledge, this study is the first to report on tissue penetration of piperacillin-tazobactam in critically ill children. Similarly to what was found in critically ill adult patients (septic shock cohort (Joukhadar 2001): mean 0.19 ± SE 0.03/post cardiac surgery cohort (Brunner 2000): mean 0.27 ± SE 0.04), the tissue penetration of piperacillin is impaired in critically ill children, albeit to a lesser extent than what has been reported in critically ill adults. These findings underscore the limitations of plasma as a surrogate for tissue exposure in critical illness. Contrary to general belief, this study shows that piperacillin and tazobactam have a different PK behavior, with a good tissue penetration of the beta-lactamase inhibitor. Microdialysis is a safe and feasible method for tissue pharmacokinetic research in critically ill children.

10 THE QTC INTERVAL IN FORMER VERY PRETERM INFANTS IS NOT DIFFERENT FROM TERM-BORN CONTROLS

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Introduction There are conflicting data on whether former preterm birth is associated with QTc-Bazett prolongation in later life.

Methods To explore QTc-Bazett interval differences between former preterm and/or extreme low birth weight (ELBW) cases and term-born controls in adolescence and young adulthood, we analyzed pooled individual data after a structured search on published cohorts. To test the absence of a QTc-Bazett difference, a non-inferiority approach was applied (one-sided, upper limit of the 95% CI mean QTc-Bazett difference, 5 and 10 ms). We also investigated the impact of characteristics on QTc-Bazett .

Results The pooled dataset contained 164 preterms and/or ELBW (cases) and 140 controls from 3 studies. The median QTc-Bazett intervals were 409 (335–490) and 410 (318–480) ms in cases and controls. The mean QTc-Bazett difference was 1 ms, upper CI 95% of 6 ms ($p=0.1015$ and 0.0019 for 5 and 10 ms respectively). In the full dataset, females had a significantly longer QTc-Bazett than males (415 vs. 401 ms, $p<0.0001$), and there was a significant, but weak correlation

(Spearman's 0.151, p=0.0377) between QTc-Bazett and plasma phosphate.

Conclusions QTc-Bazett intervals are not significantly different between former preterm and/or ELBW cases and term-born controls, and we rejected a potential prolongation >10 ms in cases. When prescribing QTc prolonging drugs, pharmacovigilance practices in this subpopulation should be similar to the general public.

D) Session 6: Drugs in Special Populations and Settings II: Pharmacology of ECMO and other Extracorporeal Devices

11 MICRODOSED YOHIMBINE AS CYP2D6 PROBE DRUG IN PEDIATRIC HEART PATIENTS AGED 6 MONTHS TO 6 YEARS

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Introduction A safe and effective drug therapy for children requires a fundamental understanding of the role of ontogeny in the pharmacokinetics (PK) and pharmacodynamics of drugs. Age-associated developmental changes in body composition and organ function are dynamic and profoundly affect the response to medications, requiring age-dependent dose adjustments. CYP2D6 is involved in the metabolism of psychotropic drugs as well as beta blockers. The maturation of CYP2D6 during early infancy has been described by being present at 1 week of age, increasing to 20% of adult activity by the age of 1 month, and reaching adult capacity by 3–5 years of age. In addition, genetic polymorphisms can contribute to variations in the expression of CYP2D6 activity, thus suitable probe drugs are evaluated for phenotyping. Yohimbine is a plant-derived indole alkaloid and alpha-2 receptor antagonist. It is metabolized to 11-OH-yohimbine by CYP2D6. The objective of this analysis was to characterise CYP2D6 activity by means of a yohimbine microdose in young children.

Methodology A single-center, open label, fixed-sequence clinical trial primarily evaluating a microdosed anticoagulant cocktail (EudraCT 2019-001759-38) was conducted in children aged 6 months-6 years (body weight >7 kg) after congenital heart surgery. Yohimbine (25 µg p.o.) was used as probe drug to determine CYP2D6 activity. Plasma concentrations over 12 h were quantified by UHPLC-MS/MS. The PK of 14 patients were compared with data of 10 healthy adult volunteers who had received 50 µg Yohimbine p.o. in a previous study.

Results The mean age of the 14 children (6m/8f) was 1.9 (0.5–4.9) years and mean body weight was 10.9 (7.2 –18.2) kg. All patients received concomitant treatment per standard of care. Oral clearance was 167 (95% CI 147–326) mL/min, Volume of distribution was 16.8 (95% CI 13.4–31.9) L. T1/2 was 1.2 (95%-CI 1.0–1.4) h. Cmax was 2757 (95% CI 2028–5249) pg/mL. AUC0-inf was 2500 (95% CI 53–10100) h*pg/mL. PK profiles were similar to those in adults.

Conclusion This small cohort delivers first, preliminary information on the PK of Yohimbine in young children up to 6 years of age. The application of a 25 µg microdose together with highly sensitive analytical methods is a safe and effective methodology to assess CYP2D6 activity in vulnerable pediatric populations. Yohimbine seems to be a suitable candidate as probe drug for CYP2D6 phenotyping in children, which should be evaluated in a larger cohort.

12 MEDICAL CANNABIS FOR CHILDREN WITH AUTISTIC SPECTRUM DISORDER: IS THERE A DIFFERENCE BETWEEN THOSE TREATED WITH CANNABIS AS MONOTHERAPY VS THOSE TREATED WITH CANNABIS AND CONCOMITANT CONVENTIONAL MEDICATIONS?

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Background Use of medical cannabis in pediatrics is increasing. A number of trials have investigated the efficacy and safety of medical cannabis for the treatment of co-morbid symptoms in children with ASD (Autistic Spectrum Disorder). Many of these children are treated with conventional medications.

Objective To compare the efficacy of cannabis monotherapy vs cannabis with concomitant conventional medications in children with ASD.

Methods Children with ASD were treated with cannabis oil at Shamir Medical Center. They underwent evaluation with trained speech therapist (ADOS) and psychologist (WPPSI). Parents and teachers filled questionnaires (Vineland, Conners, sleep, eating) at baseline and after 6 months of treatment.

During biweekly telephone follow-up, dosage was adjusted as per parents' report, which included physical and behavior parameters- appetite, anxiety, aggression, sleep and compulsive behavior.

Laboratory values, efficacy and dosage of medical cannabis were compared between both groups of children.

Results Out of 81 patients, 30 received concomitant medications. Cannabis dose did not differ significantly between both groups. There were no significant differences in the laboratory values for both groups. Parents of children with cannabis monotherapy reported a significant improvement in aggressive behavior (p=0.027), anxiety (p=0.023) and coping with changes (p=0.036). In the group of patients with concomitant treatment, there was a significant improvement in sleep quality (p=0.029).

Conclusions Medical cannabis is probably effective in reducing co-morbid symptoms in children with ASD. However, whether treatment with cannabis as monotherapy is superior to treatment with conventional drugs for co-morbidities warrants further investigation.

13 INDIVIDUALIZED USE OF 6-MERCAPTOPURINE IN THE MAINTENANCE TREATMENT OF CHINESE CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA: A MULTICENTER RANDOMIZED CONTROLLED TRIAL

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Introduction Continuous 6-mercaptopurine (6-MP) dose titration is necessary because of its narrow therapeutic index and frequently encountered dose-limiting leukopenia. An increasing number of studies confirm the significance of TPMT- and NUDT15-guided dosing with regard to thiopurines, however, data from randomized trials that directly compare standard and gene-based doses in Chinese children with ALL are currently lacking.

Methodology This multicenter, randomized, open-label, active-controlled clinical trial was designed to determine whether the initial 6-MP maintenance dose according to TPMT and NUDT15 genotypes is superior to the standard-dose regimen in Chinese children with ALL. This trial randomly assigned Chinese children with low- or intermediate-risk ALL in a 1:1 ratio to receive 6-MP at TPMT- and NUDT15-based dose (n = 44, 10 to 40 mg/m2/day) or standard dose (n = 44, 50 mg/m2/day) before proceeding to maintenance therapy.

Results At the primary endpoint, which was 6-MP-related leukopenia, a 2.1-fold decrease of thiopurine-related leukopenia was observed in the gene-based-dose group with an approximately 50% decrease in the standard initial 6-MP dose (odds ratio, 0.30, 95% confidence interval, 0.83 to 1.06; p = 0.009), with no significant differences in efficacy. Difference was observed for Grade 3 of the primary endpoint between the gene-based-dose and standard-dose groups (22.7% and 43.2%, respectively; OR, 0.39, 95% CI, 0.15 to 0.98; p = 0.04). Severe leukopenia (Grade 4) did not differ significantly between the gene-based-dose and standard-dose groups (2.3% and 9.1%, respectively; OR, 0.23, 95% CI, 0.025 to 2.17; p = 0.85). No significant differences were observed in the secondary endpoints of the incidence of hepatotoxicity and steady-state concentrations of active metabolites in erythrocytes between gene-based dosing and standard dosing.

Conclusion Preemptive TPMT- and NUDT15-based 6-MP dose adjustment will significantly contribute toward further reducing the incidence of potentially lethal adverse drug reactions in Chinese children with ALL. This trial was registered at www.clinicaltrial.gov as #NCT04228393.

E) Session 7: Pharmacology and Pharmacotherapy of Rare Diseases in Neonates and Children

14 A PRECISION MEDICINE TOOL FOR HIGH UTILIZATION AND QUALITY OF INDIVIDUAL TREATMENT TRIALS WITH IMMUNOMODULATORY DRUGS IN MUCOPOLYSACCHARIDOSIS

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The growing understanding of the innate immune response in Mucopolysaccharidosis (MPS) revealed potential targets for intervening, including the repurposing of immunomodulatory drugs. Individual treatment trials (ITT) could efficiently translate this knowledge into clinical use. However, despite the limited efficacy of approved drugs and the high level of suffering this has so far hardly been used - at least these are not reported or published. We analysed the subjective need for, utilisation of and barriers to ITT by an international MPS-expert survey. Based on that and by adapting a validated decision analysis framework (DAF) we developed an innovative, quantitative, personalizable benefit-risk assessment model to overcome barriers to ITT in MPS. Our strategy is based on the following steps i) MPS-expert survey on ITT in MPS, (ii) systematic literature review regarding relevant targets and clinical pharmacology of immunomodulatory drugs, (iii) quantitative DAF data acquisition with the creation of a framed decision context and assigning weights to relevant outcomes, (iv) enabling personali-zability by phenotypic profiling and assessing specific probabilities of expected beneficial out-comes, (v) an assessment standard for ITT with immunomodulatory drugs in MPS. These steps are in accordance with an international, interdisciplinary board of experts as well as patient representatives. Our survey (n=27) demonstrated that the majority of MPS-experts is familiar with the concept of ITT (73%), however only few ever conducted (35%) or published those (6%) reported those. A free service for data-driven treatment choices is expected to in-crease the utilization and quality of ITT by 85%. We identified Anakinra, Adalimumab, Abatacept and Cladribine as top candidates and defined first and second choices for different phenotypes.

Our developed evidence-based, personalizable, quantitative DAF model for ITT characterizes the first step towards precision medicine with immunomodulatory drugs in MPS.

F) Session 8: Pharmacology in Neonatal and Paediatric Critical Care and Legal, Operational and Regulatory Aspects

15 AVAILABILITY OF NEONATAL SPECIFIC DATA IN LABELLING OF COMMONLY USED ANTI-INFECTIVE DRUGS: COMPARISON AMONG THREE REGULATORY AGENCIES

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Introduction Neonatal-specific drug information is critical for optimal pharmacotherapeutic management of neonates in the Neonatal Intensive Care Unit (NICU). To date, the extent of the availability of neonatal-specific drug information for even the most commonly used drugs in the NICU has not been established. Our objective was to examine and compare the quantity and quality of the available neonatal-specific data in the most updated prescription labelling of anti-infective drugs used in the NICU among the United States Food and Drug Administration (FDA), United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) and Health Canada (HC).

Methodology We identified updated Standard Product Labels (FDA), Product Monographs (HC) and Summaries of Product Characteristics (MHRA) of 31 anti-infective drugs listed among the most common 100 prescriptions in the NICU. We reviewed data regarding approval in neonates, availability and type of neonatal-specific studies, and the presence of neonatal-specific adverse events and warnings. We defined approval as having either a specific indication or dosing information for the specified population.

Results We excluded eight drugs due to a lack of access to their most updated labelling. Of the 23 drugs included in the analysis, the FDA approved 13 (57%) and 10 (43%) drugs for term and preterm neonates, respectively, compared to 14 (61%) and seven (30%) by the MHRA and nine (39%) and four (17%) by Health Canada. Term-neonatal specific information was presented for 15 (65%), 18 (78%), and 10 (43%) drugs in FDA, MHRA, and HC labelling, while preterm-neonatal specific information was available for 11 (48%), 10 (43%), and four (17%) drugs, respectively. Six drugs had no neonatal-specific information; nine drugs had no preterm-specific information.

Conclusion The global lack of neonatal-specific information for the most frequently used drugs in the NICU poses critical challenges for neonatal care. Health Canada presents the most challenging drug approval agency lagging behind the other jurisdictions in the provision of important neonatal data. There is an emergent need for regulatory mechanisms to ensure the inclusion of existing pediatric data in Canadian drug monographs.

G) Session 9: Innovative Tools in Clinical Pharmacology I: Artificial Intelligence in Clinical Pharmacology

16 DRUG-DRUG INTERACTIONS AND ADVERSE DRUG REACTIONS IN NEONATES

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Introduction Due to off-label medications, PK/PD variability, and organ dysfunction/immaturity, the incidence of drug-related problems was higher in neonatal intensive care units (NICUs) compared with other paediatric wards. The aim of this study was to determine the probability (causality) and severity of each adverse drug reaction (ADR) and clinically significant drug-drug interaction (cDDI) with newer agents in neonates during NICU hospitalisation.

Methods In this prospective cohort study, each ADR and DDI was assessed using neonatal-specific probability and severity scales. Whether ADRs and DDIs were actually drug-related or not was assessed using the Du's tool for ADRs in neonates and the drug interaction probability scale. The severity of ADRs and DDIs was also determined using the neonatal adverse event severity scale (NAESS) developed by the International Neonatal Consortium and the Lexicomp® drug interaction database.

Results During the study period, a total of 109 neonates were screened and 100 neonates fulfilled the inclusion criteria. All ADRs fell into the "definite" category on the Du's tool. According to the NAESS, 34 (41.5%) of all ADRs (n=82) were considered mild, 27 (32.9%) moderate, 17 (20.7%) severe and 4 (4.9%) life-threatening. All cDDIs fell into the "highly probable" category on the drug interaction probability scale. According to the Lexicomp® drug interaction database, 33 (94.4%) of all cDDIs (n=35) were C (monitor therapy is needed), 1 (2.8%) D (consider therapy modification) and 1 (2.8%) B (no action needed).

Conclusions The use of specific and up-to-date tools to predict the probability and severity of ADRs and cDDIs with the most accurate methods from admission to discharge in neonates, a highly vulnerable population, greatly contributes to clinician decision-making throughout personalised pharmacotherapy. Well-designed randomised controlled trials with larger populations are needed to determine the probability and severity of ADRs and cDDIs.

H) Session 10: Innovative Tools in Clinical Pharmacology II: The FAIR Principle in Clinical Pharmacology

17 ARTIFICIAL INTELLIGENCE FOR THE SAFE USE OF MEDICATIONS DURING BREASTFEEDING

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Introduction Artificial intelligence is becoming a useful tool in clinical practice. We have previously published an explainable machine-learning algorithm for drug use in pregnancy based on multimodal data and suggest an orthogonal ensemble for modeling multimodal data. The model was trained with a set of labeled drugs and processed over 100,000 textual responses collected by our drug consultation service. Structured textual information is incorporated into the model by applying clustering analysis to textual features.

Many medications that are not allowed during pregnancy are also not compatible with breastfeeding. Nevertheless, there are differences and there are medications that are not compatible with breastfeeding that are allowed during pregnancy, and vice versa.

Objective The aim of the current study was to train the algorithm on lactation-related questions and to develop an algorithm for medication use during breastfeeding.

Methods A multimodal machine learning models were developed for prediction of medication safety during lactation. We focus our efforts on tabular and molecule-related features to train ensemble-based machine learning models. The models were evaluated using a variety of evaluation schemes.

Results The area under the receiver characteristic curve (AUC) of 0.921 for cross-validation applied to a dataset of 270 manually labeled drugs. An AUC of 0.963 was calculated when the algorithm was evaluated on a second, independent dataset, labeled by a second group of experts. On these two datasets, the highest performing model uses pregnancy safety and tabular, handcrafted drug features to predict lactation safety. Later, another dataset, consisting of 14 drugs, whose lactation safety is not aligned with pregnancy safety; an AUC of 0.906 was obtained on this dataset for a model trained with tabular, handcrafted, and molecule-based features only. For the later model, the most contributing features identified through SHAP analysis are antineoplastic agents (increase risk), anti-infective agents (decrease risk), and narrow therapeutic drugs (increase risk). Predictions for liraglutide (AUC=0.048) and rosuvastatin (AUC=0.401) for example, demonstrate the strengths and limitations of the model.

Conclusions The models we developed can be used to make more informed decisions when a patient and her doctor discuss potential treatment options, thus improving the safety of drugs, saving lives, and reducing costs.

18 USE OF MACHINE LEARNING FOR DOSAGE INDIVIDUALIZATION OF VANCOMYCIN IN NEONATES

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Introduction High variability in vancomycin exposure in neonates requires advanced individualized dosing regimens. Achieving steady-state trough concentration (C0) and steady-state area-under-curve (AUC0-24) targets are important to optimize treatment. The objective was to evaluate whether machine learning (ML) can be used in clinical practice to predict these treatment targets to calculate optimal individual dosing regimens.

Methodology C0 values were retrieved from a large neonatal vancomycin dataset. Individual estimates of AUC0-24 were obtained from Bayesian post-hoc estimation. Various ML algorithms were used for model building to C0 and AUC0-24. An external dataset was used for predictive performance evaluation.

Results Before starting treatment, C0 can be predicted a priori using the Catboost-based C0-ML model combined with dosing regimen and 9 covariates. External validation results showed a 42.2% improvement in prediction accuracy by using the ML model compared to the population pharmacokinetic model. The results of the virtual trial showed that using the ML optimised dose, 80.3% of the virtual neonates achieved the pharmacodynamic target (C0 in the range of 10–20 mg/L), much higher than the international standard dose (37.7%-61.5%). Once TDM measurements (C0) in patients have been

obtained, AUC0-24 can be further predicted using the Catboost-based AUC-ML model combined with C0 and 9 covariates. External validation results showed that the AUC-ML model can achieve an prediction accuracy of 80.3%.
Conclusion C0-based and AUC0-24-based ML models were developed accurately and precisely. These can be used for individual dose recommendation of vancomycin in neonates before treatment and dose revision after the first TDM result is obtained, respectively.

19 OPEN-SCIENCE SOLUTIONS ENABLED WITHIN A DIGITAL RESEARCH ENVIRONMENT TO SUPPORT PEDIATRIC DRUG DEVELOPMENT AND PRECISION DOSING

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Model-informed drug development (MIDD) has long been an approach to guide pediatric drug development both from the standpoint of challenging critical assumptions regarding the underlying disease biology and clinical pharmacology as well as de-risking critical decisions related to the progression of the clinical development plan. MIDD performance is often based on multidisciplinary engagement of subject matter experts across several institutions. Digital Research Environments (DRE) provide a secure collaborative research environment for digital analysis of data. Essential companions to the DRE are dynamically-updated and searchable metadata catalogs, in situ analysis tools with code versioning, as well as data provenance, and audit trails. This features facilitate the collaboration but also make it compatible with regulatory requirements. The Aridhia DRE specifically is the backbone of several highly successful pediatric multi-institutional collaborations including the RDCA-DAP and neonatal DAP managed by the Critical Path Institute (CPATH) and the International Neonatal Consortium (INC) respectively. Collaborative efforts to support expanded workspace functionality include the addition of nlmixr2 with the nimixr team and Great Ormand Street Hospital (GOSH) for nonlinear mixed effect modeling and r-based system pharmacology capabilities in collaboration with ESQ Labs. Additional proprietary and open-source tools are being added in collaboration with EMA and other stakeholders. The status and functionality of these solutions for pediatric R&D will be showcased and demonstrated at the meeting.

I) Posters

20 M-HEALTH CLINIC PARTNERSHIP PROJECT BETWEEN HHU DÜSSELDORF AND BOSNIA-HERZEGOVINA: CREATION OF A DIGITAL NETWORK OF DIABETES TYPE 1 CHILDREN AND ADOLESCENTS IN RURAL AND REMOTE AREAS IN BOSNIA AND HERZEGOVINA

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Background Type 1 Diabetes Mellitus (T1DM) is a chronic disease requiring lifelong insulin therapy. Poor management can lead to severe acute and chronic complications. Children from rural and remote areas in Middle-Bosnia Canton have limited access to diabetes pediatric care.
Objectives To improve the care of pediatric and adolescent patients with T1DM in rural and remote areas of Bosnia-Herzegovina by creating a digital diabetes network using modern mobile health technologies. With this, the digital diabetes competencies of healthcare professionals in Bosnia should be expanded and patients should be trained and connected with the mHealth diabetes app to the main pediatric diabetology clinic.
Methods Patients and doctors from rural and remote areas were provided with smartphones and a digital diabetes app, Diabetes M and received training in diabetes management. Diabetologists from the main pediatric clinic in Bosnia were digitally connected to patients and could monitor their everyday diabetes management and provide competent advice digitally. The main indicators and measure instruments of the network were the total number of healthcare professionals trained as well as the number of patients and their satisfaction and diabetes mHealth App usability.
Results A network between diabetologists from the main pediatric clinic in Bosnia, 50 patients (with parents), and 10 healthcare professionals from rural and remote areas was created. Thirteen doctors across Bosnia-Herzegovina received training in digital diabetes care. Fifty T1DM patients from rural and remote areas, usually deprived of regular diabetes care, were connected with the main pediatric diabetologist and the team in Sarajevo by utilizing a diabetes app to improve diabetes management and to receive access to diabetes care.
Conclusion mHealth is a powerful tool that can offer seamless communication between patients and their healthcare professionals. For the first time, 50 young patients were able to receive qualified diabetes care remotely, regardless of their location in Bosnia.

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21 A FIRST-IN-HUMAN PHASE 1 STUDY OF SIM0417, A 3CL-LIKE PROTEASE INHIBITOR FOR TREATMENT OF COVID-19, IN HEALTHY ADULT SUBJECTS

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Introduction Safe and efficacious antiviral therapeutics are in urgent need for treatment of coronavirus disease 2019. SIM0417 is a selective 3C-like protease inhibitor that can effectively inhibit severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Methodology We evaluated the safety, tolerability, and pharmacokinetics of dose escalations of SIM0417 alone or with ritonavir (SIM0417 or SIM0417/ritonavir) in healthy subjects, as well as the food effect.
Results The overall incidence of adverse events (AEs) was 22.2% (17/72) and 6.3% (1/16) in intervention and placebo group, respectively. The SIM0417 apparent clearance was 135–369 L/h with SIM0417 alone, and decreased significantly to 19.5–29.8 L/h with SIM0417/ritonavir. The SIM0417 exposure increased in an approximately dose-proportional manner between 250–750 mg when co-administered with ritonavir. After consecutive twice daily dosing of SIM0417/ritonavir, SIM0417 had a low accumulation index ranging from 1.39 to 1.51. The area under the curve of SIM0417 increased 44.0% and 47.3% respectively, after high fat and normal diet compared with fasted status.
Conclusion SIM0417 has adequate safety and tolerability. Its pharmacokinetics indicated a trough concentration above the level required for 90% inhibition of SARS-CoV-2 in vitro at 750 mg/100 mg SIM0417/ritonavir twice daily under fasted condition, supporting further development using this dosage as the clinically recommended dose regimen.

22 MELATONIN DOSING IN CHILDREN AND ADOLESCENTS IN RELATION TO AGE AND OVERWEIGHT STATUS

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Background The prescription of melatonin to children and adolescents has increased dramatically in Sweden during the last ten years. Melatonin is recommended for sleeping disorders in children and adolescents as a second line of treatment after non-pharmacological alternatives in national guidelines. In the present study we aimed to evaluate the prescription of melatonin in relation to age and overweight status.
Methods The population-based BMI Epidemiology Study cohort has height and weight available from school health care records for school children in the city of Gothenburg, Sweden´s second largest city. Information on melatonin prescription was retrieved through linkage with the National Prescribed Drug Register for individuals in the cohort. We included the first prescription of melatonin for boys which also had a weight measurement not earlier than three months before, or later than six months after the dispensing date (n=1,554). We present data for maximum dose and maximum dose per kg body weight in relation to overweight status (including obesity) and age above or below nine years.
Results The range of the maximum dose of melatonin was 1–20 mg for first prescriptions and 1–25 mg for iterated prescriptions. Similar maximum doses were prescribed to individuals with overweight or obesity as to individuals with normal weight, and to individuals below and above 9 years of age. The range of the maximum prescribed melatonin dose per kg body weight was 0.01–0.85 mg/kg for first prescriptions and 0.02–1.53 mg/kg for iterated prescriptions. Of note, age and weight only explained a marginal part of the variance in maximum dose and displayed an inverse association with the maximum dose per kg. As a result, individuals with overweight or obesity, or age above 9 years, received lower maximum dose per kg body weight, compared with individuals with normal weight or below 9 years of age.
Conclusion Thus, the prescribed melatonin dose to individuals under 18 years of age is not primarily informed by body weight or age, resulting in substantial differences in prescribed dose per kg body weight across BMI and age distribution. There is a general lack of knowledge regarding medicines in children, but for the sub-population of children with obesity, this knowledge gap is even larger. Given the ongoing obesity epidemic, there is a huge need to learn more regarding drug disposition in children and youth with obesity and therefore, high-quality clinical studies add.

22 UP TO ONE THIRD OF RAPID THIOPURINE-S-METHYLTRANSFERASE METABOLIZERS MANIFEST CLINICAL AND/OR LABORATORY AZATHIOPRINE SIDE EFFECTS: A SINGLE CENTRE EXPERIENCE

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Background According to ECCO-ESPGHAN consensus guidelines, Azathioprine (AZA) can be used for maintenance of remission in paediatric inflammatory bowel disease (IBD). AZA side effects are well documented. Haematological toxicity affects 2–14% of patients and idiosyncratic pancreatitis up to 7% of them, requiring modification of AZA dosage or its cessation. Thiopurine-S-methyltransferase (TPMT) activity should be tested prior to AZA commencement. Slow metabolizers should not be started on AZA and intermediate ones should get a dose reduction. This study evaluates the incidence of AZA side effects in TPMT rapid metabolizers.
Methods Retrospective evaluation of prospectively collected data in children tested for TPMT and who received AZA between 3/13 and 10/22. Focusing on the incidence of side effects in rapid metabolizers.
Results Ninety children had TPMT tested.

Only 1 intermediate a 1 slow metabolizer were identified. All rapid metabolizers were diagnosed with IBD, 62 (70,5%) with Crohn's (CD), 16 (18,2%) with ulcerative colitis (UC), 7 with very early onset IBD (VEO-IBD) and 1 with IBD undifferentiated. Forty-seven were male (53,4%) and 41 female. The median age at diagnosis was 13.5±3,9 years. Of the 88 rapid metabolizers, 82 (93%) received AZA. The remaining 6 had different treatment strategies. Clinical and/or laboratory side effects were documented in 27 cases (32,9%). Haematological toxicity was most frequent affecting 19 participants (23.1%). In 13 cases (68,4%) leukopenia resolved spontaneously, in 4 cases (21%) dose reduction was required, and in 3 cases (15,8%) AZA had to be stopped. Pancreatitis was identified in 6 patients (7,3%). Half of the cases were discovered by laboratory findings and the remainder had a clinical

correlate. In 2 cases, laboratory pancreatitis normalized on follow-up examination, in the remaining ones AZA had to be withdrawn. Haematological toxicity manifested on average within 10,9 months since treatment start (0.5–43 months), pancreatitis within 0,54 months with one case manifesting after 79 months of treatment. In this single case, autoimmune pancreatitis is debated. Boys had AZA side effects slightly more frequently (15/27, 55%). CD patients had AZA side effects the most (16/27, 59%).

Conclusion Being a rapid TPMT metabolizer should reduce the risk of AZA side effects. However, these data demonstrate a 32,9% occurrence of them, emphasising the importance of clinical and laboratory follow-up in patients on AZA.

23 THERAPEUTIC DRUG MONITORING OF LACOSAMIDE AMONG CHILDREN WITH REFRACTORY EPILEPSY: IS IT HELPFUL?

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Objective This study aimed to investigate the efficacy and tolerability of Lacosamide (LCM) in a pediatric population with refractory epilepsy in relation to serum concentration, age, and dosage.

Methods Demographic and clinical data were collected from the medical records of children with refractory epilepsy treated with LCM at Shamir Medical Center between February 2019 to September 2021, in whom medication blood levels were measured. Trough serum LCM concentration was measured in the biochemical laboratory using High-Performance Liquid Chromatography (HPLC) and correlated with the administered dose and clinical report.

Results Forty-two children aged 10.43 ± 5.13 (range: 1–18) years old were included in the study. The average daily dose of LCM was 306.62 ± 133.20 mg (range: 100–600). The average number of seizures per day was 3.53±7.25 compared to 0.87±1.40 before and after LCM treatment, respectively. The mean LCM serum concentration was 6.74±3.27 mg/l. No statistically significant association was found between LCM serum levels and the clinical response (p=0.58), as well as the correlation between LCM dosage and the change in seizure rate (p=0.30). Our study did not find a correlation between LCM serum concentration and LCM dosage and the gender of the participants: males (n=17,) females (n=23) (p=0.31 and p=0.94, respectively). A positive trend was found between age and LCM serum concentrations (r=0.26, p=0.09).

Conclusion Determination of serum concentrations is not needed in all children treated with LCM. Serum concentrations may be valuable in patients with refractory epilepsy for compliance evaluation or in patients with satisfactory control of seizures to determine their therapeutic baseline.

24 DEVELOPMENT OF A SUSPICION INDEX TOOL TO AID DIAGNOSIS OF ASMD DISEASE

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The diagnosis of acid sphinogomyelinase deficiency (ASMD, Niemann Pick Type A, A/B, B) is frequently delayed by years, due to the highly heterogeneous and often unspecific clinical features. The involvement of different organs, the musculoskeletal system and the central nervous system (especially in infantile neurovisceral/chronic neurovisceral forms of ASMD) represent a diagnostic challenge. Therefore, we aim to develop an innovative suspicion index tool (SIT) for health care professionals to enable an early and accurate diagnosis of ASMD.

Our developed SIT is based on validated tools with literature research for type specific clinical features and differential diagnosis as well as a multi-center chart review with international ASMD centers in Europe and America. ASMD symptoms were categorized into skeletal, vis-ceral and neurologic domains. The finally developed scoring system results from the predic-tion of single symptoms and symptom combinations, as well as ASMD family history via lo-gistic regression.

So far, 160 ASMD patients, non-cases and controls (M. Gaucher, M.Wolman, NPD-C) from literature and 48 further ASMD patients by expert chart review have been analyzed (ongoing).

Key clinical signs were defined as those observed in >10% of ASMD cases. Symptoms occur-ring in more than one category (skeletal, visceral, neurological) as well as family relationships were strong indicators of ASMD. Visceral symptoms were highly suggestive, including sple-nomegaly, hepatomegaly, and mixed dyslipidemia with reduced HDL-C levels (last solely ASMD type B).

So far, our strategy has been very feasible. After the expert chart review is finished, we will finalize the scoring system and implement it as mobile device app for evidence-based clinical support.

25 ANTIEPILEPTIC DRUG USE IN CHILDREN BEYOND EPILEPSY: A POPULATION-BASED LONGITUDINAL STUDY

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Background Epilepsy is frequently associated with psychiatric disorders and migraine in childhood, suggesting a shared underlying pathological mechanism. Moreover, antiepileptic drugs (AEDs) are also used for treatment of specific psychiatric and pain disorders.
Objective To characterize the use of AEDs in children and adolescents beyond epilepsy and seizure disorders.
Methods Study population: Children and adolescents (age: 0–19 years) in British Columbia (BC), Canada, with at least one dispensing for an AED between 1997 – 2018. Dispensings were picked up from the pharmacy by patient or caregiver. Data source: BC health administrative databases pharmacy, medical visit and hospitalization data. Design and Analysis: The first AED dispensing was set as the index date. The longitudinal nature of the study allowed the search for diagnostic codes from birth to the index date for children with epilepsy and seizures and those without. The total number of dispensings and all ICD diagnostic codes for all patients were determined across four age ranges (0–4, 5–9, 10–14, 15–19 years). Categorical and continuous variables were analyzed by CMH chi-square and ANOVA methods.
Results 6,382 patients (42.6% of all AED users) had at least one dispensing of AEDs in the absence of a diagnosis of epilepsy or seizure disorder.

Lamotrigine, valproate and topiramate show increases in the numbers of patients and dispensings in the 5–9 and 10–14 year age categories, with an increase of 45.7% in the patient number for lamotrigine; 12.2% for valproate and 149.1% increase for topiramate. The 2,067 diagnostic codes three months before the first topiramate dispensing in patients 10 - 14 years of age without any evidence for epilepsy or seizure since birth (72.2% of all patients who started topiramate in this age range) included 26.52% for migraine or other type of headaches; 5.1% for mood and bipolar disorder; 13.23% for ADHD and disturbance of conduct, and 6.32% psychosis.
Discussion The increase in topiramate usage in the absence of epilepsy was surprising, since its adverse effects on memory, learning and intellectual development are well described. There is a lack of evidence for the use of topiramate for the prevention of migraine in children between 8 and 17 years of age. A previously published placebo-controlled RCT of 361 children with migraine found that topiramate was not more effective than placebo in reducing the number of headache days over 24 weeks.

26 SALIVA SAMPLING TO FACILITATE PHARMACOKINETIC STUDIES IN CHILDREN: A CASE STUDY WITH METAMIZOLE

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Introduction Pharmacokinetic (PK) studies in young children and infants are challenging, among others because of the invasiveness of blood samples. Using saliva as matrix could increase their feasibility. A recent PK study of the prodrug metamizole (dipyrone), used as off-label intravenous (i.v.) analgesic in infants < 1 year of age, aimed to assess the PK of its main metabolites after a single i.v. dose of 10 mg/kg. It showed increased plasma exposure to the main active metabolite 4-methylaminoantipyrine (MAA) in four infants of 3–12 months compared to children of 1–6 years. We aimed to evaluate the suitability of saliva PK sampling in this study to facilitate further PK studies in a larger infant population for dose optimization.
Methodology Saliva was sampled at up to 6 pre-defined time points until 24 h post-dose. Concentrations of four metabolites were quantified with a novel liquid chromatography-mass spectrometry method. Combined plasma/saliva population-PK modeling was performed to investigate mechanistic aspects of the two active metabolites' distribution (MAA and 4-aminoantipyrine [AA]) and to quantify inter- and intraindividual variability of the metabolites' distribution among the matrices.
Results Overall, 25 and 16 children provided at least 1 plasma or saliva sample, respectively, and 26 children were included in the analysis (median [interquartile range] age: 57 [22.0–58.8] months, weight 17 [11.3–18.7] kg). No distribution delay of the metabolites between plasma and saliva could be quantified. The fractions of MAA and AA distributing to saliva were estimated to (95% confidence interval [CI]) 0.32 (0.22–0.42) and 0.57 (0.49–0.65), with logit-normally distributed interindividual variability of 0.81 and 0.55, respectively. A strong correlation between the two predicted fractions of 0.89 was observed, but no correlation with age or albumin concentrations. Residual intraindividual variability in saliva was 0.47 and 0.28 versus 0.17 and 0.11 in plasma for MAA and AA, respectively.
Conclusion This analysis indicates instantaneous distribution of active metamizole metabolites from plasma into saliva, approximately to the extent of reported unbound fractions in plasma. Due to high variability in saliva, suitability of saliva as single matrix for PK studies in children is compromised. However, rich saliva sampling in combination with reduced plasma sampling could be evaluated to minimize the burden of PK studies in infants and children.

27 CAN PUPILLOMETRY BE USED FOR CYP2D6 PHENOTYPING IN CHILDREN TREATED WITH TRAMADOL?

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Introduction Following the contraindication of codeine use in children, an increase in the use of tramadol has been observed in pain management protocols. However, tramadol PK/PD are also influenced by CYP2D6 activity. Genotyping and phenotyping are available to assess CYP2D6 activity and guide tramadol dosing. In adults, a correlation between pupillary response and tramadol pharmacokinetics has been demonstrated. Our objective was to evaluate pupillometry as a phenotyping method to determine CYP2D6 activity in children treated with tramadol.

Method We included children receiving their first dose of tramadol (2 mg/kg) in the emergency department (ED) of the Geneva Children's hospital as part of their routine care. Children with concomitant treatment with inhibitors of CYP2D6 and inhibitors/inducers of CYP3A and/or with drug with a known impact on pupillary diameter (PD) were excluded. Standard CYP2D6 phenotyping was performed by measuring blood dextrorphan/dextromethorphan metabolic ratio (DOR/DEM MR) and genotyping. Tramadol and its active metabolite, M1, concentrations were measured by LC-MS/MS. Static and dynamic pupillometry were performed with a hand-held pupillometer at the time of tramadol administration and once to twice per hour, during the ED stay . We studied the correlation between M1 concentration, DOR/DEM MR and difference in static and dynamic pupil measurements between T0 and T150.

Results Of the 41 children included (mean age 11 years), 37 had interpretable pupillometric measurements. An effect of the tramadol administration on the static pupil diameter (PD) as well as the pupillary light reflex were observed with 83.8% of children showing a decrease in PD ($p = 0.002$) and 78.4% showing a decrease in reflex amplitude ($p= 0.011$) at T150 compared to T0, respectively. No other correlation could be identified.

Conclusion As expected, tramadol affects pupillary parameters. However, under the real-life conditions of our study, we could not identify any correlation between pupillometry measurements and CYP2D6 activity due to probable confounding factors such as light intensity, pain intensity and stress. Our study confirmed that the pupillometer is safe and well tolerated by children and easy to use by caregivers. Further studies with a higher level of standardization, especially controlled and stable light conditions, are needed to test its use as a reliable phenotyping method.

28 UTILIZATION OF PHARMACOGENETIC MEDICATIONS AT A GERMAN PEDIATRIC UNIVERSITY HOSPITAL

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Introduction Pharmacogenetic (PGx) guided drug therapy is a promising approach for improving drug response and safety. The implementation of PGx information into clinical routine is currently ongoing in adult medicine, but still limited in pediatrics. Thus, we aimed to analyze the impact of PGx on the prescription of medications used in the real-world setting of a German Children's University hospital.

Methodology A retrospective database analysis was performed using routine medication data from patients on general pediatric wards between 2014 and 2019. The database included 25,339 admissions of 16,289 patients. Of these, we analyzed the 17,543 admissions of 11,611 patients who received medication during hospital stays (i) to elucidate the frequency of PGx relevant drugs and (ii) to identify underlying PGx target genes. For the analyses we considered all currently listed 74 drugs with a pediatric guideline annotation on PharmGKB.org website. An age-stratified ranking list for clinically relevant PGx medications has been established.

Results 37.9% (n = 4,401) of all hospitalized patients with medication (n = 11,611) received at least one PGx drug. Only 35 of the 74 PGx drugs with pediatric recommendations were used, resulting in 5,633 exposures to PGx drugs. The most commonly administered PGx drugs were ibuprofen (3,407/5,633, 60.5%), omeprazole (797/5,633, 14.1%), tobramycin (409/5,633, 7.3%), tramadol (198/5,633, 3.5%) and ondansetron (174/5,633, 3.1%). There were no age dependent differences regarding drug exposure except for aminoglycosides which were more often used in neonates, infants and toddlers. The analysis of PGx recommendations related to pharmacogenes resulted in 17 genes relevant for our study population. Here, CYP2C9, CYP2C19, CYP2D6, MT-RNR1, and HLA-B*15:02 are the top candidates.

Conclusion Similar to adults, a high proportion of children and adolescents are treated with at least one PGx drug at our pediatric center, for which PGx guidelines recommend genetic testing preemptively. Based on our prescription data a total of 17 PGx genes should be considered for testing in clinical routine. In addition to PGx, developmental aspects of pharmacotargets need to be addressed in more detail to refine the implementation of PGx into pediatric medicine.

29 FIVE-YEAR REPORT ON THE ACTIVITIES OF THE CONNECT4CHILDREN (C4C) EUROPEAN PAEDIATRIC CLINICAL TRIALS NETWORK IN BELGIUM

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Background/Aims Currently, over 60% of clinical trials in children are unsuccessful due to insufficient recruitment, administrative burden, inadequate methodology, among other reasons. Sponsors experience difficulties identifying adequate and developed sites to conduct pediatric trials. To optimize and facilitate clinical trials, (inter)national networks have been developed by (academic) investigators such as the I-ACT for Children network (U.S.A.), Innovative Medicines Initiative 2 conect4children (IMI-c4c) grouped network (Europe), and MICRYN (Canada). For Belgium, the Paediatric Clinical Trial Network within BPCRN Belgian Paediatric Clinical Research Network), was developed in 2009 and included in c4c in 2018, managed by the Ghent University (Hospital).

Method This report describes an update on the progress of c4c over the past 5 years. The Belgian Paediatric Clinical Trial Network has 15 hospitals connected. The network has been involved in 2 academic trials, 10 industry trials and over 35 preliminary feasibility requests.

Results The Belgium national network (BPCRN) was selected in 2/4 academic trials, and 5/5 industry trials within c4c. Constructive communication with the sponsor increased the number of sites from 2 to 8 for the academic studies. The added value of the BPCRN in the academic trials was help by the national hub in regulatory submission and budget plan. For the industry studies, the administrative requests have been centrally buffered, with over 66% of the feasibility questionnaires being pre-filled. Moreover, an additional 32% new sites were identified for the industry sponsors.

The network is also involved in i) data standardization, inclusion of real-world data and rare disease data-dictionary development, ii) expert panels and iii) teaching pan-European courses for site and investigator development. Moreover, the Belgian network has been the liaison for the totality of European national networks with the US-based network I-ACT for Children, for clinical trials running outside of the c4c project scope.

Conclusion Over the past 5 years, substantial developments and progress have been made with the Belgium network activity by BPCRN. Central optimalisation of site identification, site development and trial start-up have been prioritized. To achieve a sustainable network after IMI2 funding, a longitudinal commitment of both sites and sponsors is needed.

30 CZECH NATIONAL CENTRE: POTENTIAL FOR IMPROVING PHARMACOTHERAPY IN THE PAEDIATRIC POPULATION IN THE CZECH REPUBLIC AND SLOVAKIA

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Introduction The Czech National Centre represents new activities in the field of pharmacotherapy in paediatrics and neonatology in CR and Slovakia as well as the successful ongoing involvement of the Czech Charles University scientific team in the conect4children (c4c) consortium within the collaborative pan-European network (CzechNatHub). Currently, this project aims to facilitate CzechNatHub's sustainability and business plans within and beyond the c4c-periods.

Methodology The project is within the Europe-wide Innovative Medicines Initiative2 (IMI2)2 with joint funding from the European Federation of Pharmaceutical Industry and Associations (EFPIA) and the European Commission The coordination centre for the Czech Republic is the Department of Pediatrics and Inherited Metabolic Disorders of the 1st Faculty of Medicine of Charles University and the General Hospital in Prague is involved in the WP 2,6,7 (education, infrastructure, and research) and WP4 (expert group) with a focus on the c4c maturity matrix (strategic feasibility advice, network, data standards, education, patient and public involvement) using nationally based logistic analysis.

Results Key c4c points were identified to support the skills (beneficiaries) in the field of clinical studies of the entire study team (CRO), to define the role of the study coordinator and his responsibilities and practical skills (industry through AIFP), to teach young doctors, research nurses (Enpr-EMA) and non-medical experts and the public (YPAGNET) to work together as a team where everyone has a defined role and responsibilities, and to develop links with academic societies (Czech Paediatric Society, ESDPPP), and to find funding. The spring multi-stakeholder meeting will bring all this together.

Conclusion The Czech National Centre has become a coordinating academic centre established for pharmacotherapy in the paediatric population for the Czech Republic and Slovakia.

Acknowledgement Horizon 2020 c4c IMI2, on behalf of Czech consortium.

31 AN UPDATE ON THE CHALLENGES OF CONDUCTING PEDIATRIC CLINICAL TRIALS: 15 YEARS OF PROGRESS SINCE EMA REGULATION IMPLEMENTATION

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Background/Aims Still 60% of drugs used in children are off label. Although the EMA regulation, increased largely the timely submission of Pediatric Investigational plans (PIP) and initiation of clinical trials (CT), the majority of these CT's remained unsuccessful due to insufficient recruitment, administrative burden, inadequate methodology, among others. Historically, the concept was largely developed for blockbuster drugs where the adult indication and design, was translated into the pediatric population.

Method This report describes the core principles of conducting trials in a pediatric setting, gathered through literature and a collected global expertise of over 30 years of clinical trials in children.

Results The main principles include adapting trial study teams for pediatric needs, limiting sampling and optimizing imaging, communication between trial site and sponsor (with or without network aid), as well as placing child and/or parent centrally within the trial design, targeting the pediatric indication of the drug. The increasing number of orphan drugs, with often major only indication in children, demands specific expertise. Alternative solution to sampling, such as sparse sampling and dry blood sampling are recommended. Novel anesthesiology and play therapy are highly encouraged and more widespread available. US-based and European networks have been developed (IMI2 conect4children (c4c), I-Act for Children) with increasing connectivity with rare diseases consortia (ERN, EJPRD, ERICA, EPTRI) and patient/parent organizations- Regarding patient engagement, a special focus on patient-reported outcomes is mandatory. Moreover, a national and continental budgeting plan for a pediatric setting has been developed, to speed up the initiation of the trials

Conclusion In efforts to making the utopian completely on-label prescription of drugs in children a reality, learnings and expertise needs to be grouped and widely distributed. A dedicated expert or course in the conduct of pediatric clinical trials for young investigators could be beneficial.

32 EMPOWERING THE NEXT GENERATION: HOW THE YOUNG ESDPPP COMMUNITY IS NURTURING YOUNG PAEDIATRICIANS AND PHARMACOLOGY EXPERTS

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Research Objectives Informal networking with colleagues, including teachings of vast evolving novel technologies within pharmacometrics, has been identified as essential in all stages of a paediatric and pharmacology career. Young researchers have expressed the need to gain knowledge and information from peers and colleagues through a community platform.

Methods This report describes the formation and growth of the Young ESDPPP community.

Results In response to the identified need by ESDPPP leadership, the Young ESDPPP was established in 2022. A recruitment and formation session was held during the ESDPPP conference. Since its establishment, the association has organized nine sessions, each attended by an average of four participants from different nationalities. The members consist of young researchers pursuing a PhD or at the post-Doc level, with research interests spanning from qualitative research to drug development trials and pharmacomodeling. The sessions are conducted in both formal and informal styles, featuring invited speakers as well as present-your-research sessions. Additionally, an informal platform called Slack is utilized for brainstorming ideas and requesting speakers. The formal sessions cover various topics such as pharmacogenomics, scientific integrity, and the MADAM project on pharmacological data collection for pregnant women. The association aims to address potential educational gaps and promote advocacy efforts for a scientific career.

Conclusion A young ESDPPP in a paediatric pharmacology setting has been shown to improve collaborations, knowledge, and general well-being of its science faculty. Similar establishments and cross-over sessions with other communities are necessary to aim for a sustainable and substantial impactful scientific community within Belgium.

33 WHEN THE CHILD VOMITS AFTER ORAL DRUG INTAKE – DEVELOPMENT AND INTRODUCTION OF A DECISION SUPPORT

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Introduction Vomiting after oral drug administration is common in pediatric care. Uncertainty then often arises regarding absorption of the given dose and whether a new dose should be given. There are local traditions both within Sweden and abroad to deal with vomiting after drug administration, but official guidelines from the Swedish Medicines Agency or the European Medicines Agency EMA are missing.

Methodology At Queen Silvias Childrens Hospital, a decision support has been developed based on published evidence, physiological, pharmacokinetic and pharmacodynamic considerations, and clinical experience. Specialists in pediatric medicine and clinical pharmacology as well as pharmacists have contributed.

Results To be able to make a reasonable decision if the patient should receive a new dose (or not) after vomiting after oral drug intake, we identified three important aspects to consider:

- The time between drug administration and vomiting
- The patient's situation and medical background: Why is the child vomiting? How important is it that the patient receives the current dose? Is there a risk that the child will vomit again?
- The pharmaceutical substance, dosage form (tablet, suspension, or delayed-release formulation) and its pharmacokinetics: How quickly do you see the effect of a medicine? How long does it last? Are there risks with double dosing, too low dosing or missing a dose?

Additionally, we collected a list of clinically frequently used substances and developed general recommendations on whether or not to give a new dose, depending on the time between intake and vomiting (< 15 minutes, 15–30 minutes, > 30 minutes). For substances or preparations with special risks to consider, we added information, for example a warning for a slow-release preparation with risk of sedation or respiratory depression. The decision support has been in use for two years and has recently been updated and more substances have been added.

Conclusion Our decision support document has been in clinical use for two years. The decision support uses time, the patient's situation, and the medications´ pharmacology. It has recently been updated, the number of medications has been expanded and it is going to be made accessible in the whole region of West Sweden.

34 PHARMACOTHERAPY-RELATED PRACTICES AND SKILLS AS REPORTED BY ATTENDEES OF THE NEONATAL ONLINE TRAINING AND EDUCATION (NOTE) COURSE ON NEONATAL CLINICAL PHARMACOLOGY

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Introduction We intended to get a snapshot of pharmacotherapy-related practices at the initiation of the 2022 clinical pharmacology NOTE course.[1] Besides guiding education, this also informs us of contemporary practices, research or additional needs of early career colleagues.

Methods The online questionnaire was developed by the NOTE content coordinator of the pharmacology module (KA), subsequently distributed to the NOTE pharmacology faculty for input. Topics covered were: (1)Who do you contact with drug-related questions? (2)Does a pharmacist visit your unit? (3)Have you ever reported an adverse drug reaction (ADR)? (4)What information sources do you use? (5)Have you ever assisted in a trial as (co)investigator? (6)What are the top 5 prescribed drugs in your unit?

Results Fifty three (77%) responses were received from 69 participants (United Kingdom 15, Qatar 7, India 5, Trinidad/Tobago 5, Ireland 5, Emirates 5, Palestinian Authority 4, Norway 4, Nigeria 3, Denmark 2, Canada 2, Zambia 2, Mauritius 2, and Bahrain, Japan, Kenya, Iceland, Indonesia, Malta, Portugal, United States), mainly doctors (64). On Q1, colleague-neonatologists (39), external sources/formularies (5), or pharmacists (9) were mentioned. Q2: 27 (39%) reported regular/daily visits of a pharmacist, 9 weekly, 17 had no structured visits. Q3: 17 (32%) have reported an ADR on at least one occasion. Q4: Information sources (formulary) used by the respondents were BNFc (22), NeoFax (through Micromedex) (21) Neonatal Formulary (3) or Lexicomp (through UpToDate) (5). Others (25) mentioned local, regional or national formularies. Q5: Six respondents had assisted at least in one drug research trial. Q6: The top 5 drugs prescribed by the respondents were caffeine, gentamicin, benzylpenicillin, ampicillin, amikacin.

Discussion This snapshot reflects large heterogeneity in practices (who to consult for drug-related questions, access to pharmacist, information sources) and experiences (ADR reporting, trial involvement), and provides guidance on needs (pharmacists, ADR reporting, information sources awareness) on pharmacotherapy. The top 5 drugs reflect the common use of antibiotics.

Conclusions The results of this questionnaire reflect needs to improve our practices, by raising awareness of formularies, ADR reporting or a broader involvement in clinical trials. Questionnaires are useful to learn from and interact with NOTE participants.

REFERENCE

1. https://moodle.neonataltraining.eu/

35 PRESCRIBING BEHAVIOR OF ANALGOSEDATIVES FOR EXTREMELY PREMATURE NEONATES: A RETROSPECTIVE ANALYSIS

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Introduction Managing pain in extremely premature (EP) neonates is complex, and protocols at institutions often lack tailored advice for different indications or patient characteristics, increasing the risk of inadequate pain management. This study aims to examine clinician prescribing behavior, identify areas for improvement, and suggest modifications to existing protocols, which enables the improvement of analgosedative therapy for EP neonates.

Methodology In this single center, retrospective study, we analyzed data from all EP neonates admitted to our NICU between 2017 and 2021, comparing baseline characteristics and drug administration data.

Results Of the 2633 neonates admitted to the NICU, 10.2% (n=268) was EP at the time of admission. Of these, 53.4% (n=143) received analgosedative therapy. 'Pain' was the most common therapeutic indication (51.8%). Morphine, fentanyl, and acetaminophen were prescribed to more than half of the patients. Over 90% of patients received their analgosedative drugs exclusively intravenously (IV). Morphine and midazolam were mainly administered via continuous infusion, while fentanyl and acetaminophen were mostly given as bolus. During the initiation of continuous infusion, loading doses were administered for morphine and midazolam in 67.6% and 58.6% of cases, respectively. At dose escalation, these percentages decreased to 39.8% and 33.3% for morphine and midazolam, respectively. Morphine continuous infusion patients who always received a loading dose required a lower median dosage at 24 hours (5.0 mg/kg/hr) than those who didn't (11.0 mg/kg/hr). This trend was not observed for midazolam (see table 1).

Conclusion The observed higher dosages required by EP neonates who did not receive a loading dose highlights the need for a critical evaluation of the use of loading doses during the initiation and dose escalation of continuous infusions, with the aim of reducing pain in this vulnerable population.

36 IMPLEMENTATION PROCESSES IN PAIN ASSESSMENT IN THE NICU: AN INTERACTIVE "MEET THE PAIN" TUTORIAL

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Introduction Adequate pain management is one of the key issues in neonatal intensive care units. However, pain assessment in non-verbal critically ill preterm neonates remains a daily challenge. Therefore, systematic education, implementation, and validation of better practices in pain assessment are essential. The aim of this study was a valid and reproducible pain assessment in the NICU as a step toward optimizing pain management and analgesia.

Methodology Thirty-four NICU nurses were included in the interactive educational program "Meet the pain" running from December 2022 to March 2023 (32/23 S-IV Grant). The program was led by a healthcare team consisting of three neonatologists, two head nurses, and one research nurse. The nurses were tested in COMFORTneo and Numeric rating scale on the representative videos of preterm neonates admitted to the NICU (23 – 34 postmenstrual weeks). Inter-rater variability was validated by Cohen ?. Descriptive statistics were performed to reveal disagreements in individual items of the COMFORTneo scale.

Results Testing of inter-rater variability demonstrated moderate agreement ?=0.44 in pain assessment at this stage of implementation. Based on the results, the COMFORTneo items with high-rate errors (alertness and body movement) were adjusted concerning extreme prematurity. Surprisingly, 8/34 raters made a formal/numerical error while completing the form. The educational re-training of nurses has been performed.

Conclusion Systematic processes in pain assessment, identification of "weak spots" and education of caregivers are the key elements in the optimization of pain management in the NICU.

37 PHARMACOKINETICS OF INTRAVENOUS FENTANYL IN NEONATES, A SYSTEMATIC REVIEW

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Introduction Fentanyl is a frequently used analgesic in the neonatal intensive care unit (NICU). Its minimal effect on hemodynamic stability, and its apparent exemption from the effects of hepatic and renal illness make it an ideal candidate for use in critically ill neonates. Despite its common use, prescribing fentanyl remains off-label for the neonatal population. Our aim was to review the available pharmacokinetic data of fentanyl in neonates.

Methodology In this systematic review we searched Ovid MEDLINE, the Cochrane Central Register of Controlled Trials and PubMed from inception to February 2023 for studies that included pharmacokinetic data on the use of intravenous (IV) fentanyl in neonates. We did not apply language or study design limitations. Animal studies and duplicate records were excluded. Two reviewers screened and extracted data. The ROBINS-I was used to assess the risk of bias of individual studies.

Results Seven prospective observational studies containing pharmacokinetic data regarding the use of IV fentanyl in 208 neonates up to and including a postconceptional age of 44 weeks were included. Studies included 30 (15%) term and 173 (85%) preterm with GA (min, max) of 23–42.3 weeks and postnatal age (min, max) of 1–71 days. Postnatal age and gestational age were identified as covariates of importance contributing to the interindividual pharmacokinetic variability of IV fentanyl. One study applied a population pharmacokinetic model to recommend gestational age and postnatal age-based dosing.

Conclusions Pharmacokinetic data of IV fentanyl in neonates, although limited, is available and can be applied to the use of this drug in neonatal patients. This data needs to be presented in the prescription labelling for enhanced knowledge translation and to achieve optimal safety-efficacy balance in use of this drug. Future research on pharmacokinetics-pharmacodynamic relationship of IV fentanyl in the neonatal population will pave the way toward an individualized approach to therapeutic dosing among these vulnerable neonates.

38 ACCURACY OF ANTIBIOTIC CONCENTRATIONS IN DRUG DISPENSING: A RISK FOR LOW DOSES IN NEONATES

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Introduction Antibacterial therapy plays a crucial role in neonatal infections. Antibacterial efficacy is closely related to the actual dose given to the neonates. Thus, we aimed to evaluate the factors affecting actual dose of intravenous antibiotics in the dispensing process to ensure the precision therapy in neonates.

Methodology Meropenem, cefoperazone/sulbactam and piperacillin/tazobactam with two drug strengths were used as representative drugs to evaluate three different drug dispensing methods. Method A was once dilution method, in which the drug powder was dissolved by a small volume of 5% glucose and then diluted once to a certain concentration. Method B was the same with method A except that the volume of 5% glucose used to dissolve the drug powder was doubled. Method C was double dilution method, in which the drug powder was dissolved by 5% glucose and then diluted twice to a certain concentration. The drug concentration was measured by high performance liquid chromatography. The relative error (RE) of the drug concentration was used to evaluate the accuracy of the preparation.

Results A total of 648 drug concentrations were measured. The average of RE absolute value of the drug concentrations obtained by method B was 1.4% with small drug strength, and 6.7% with large drug strength, respectively. The RE absolute value of drug concentration obtained by method A and C was larger than that by method B. The average of RE absolute value of the drug concentrations obtained by method A was 7.8% with small drug strength, and 15.6% with large drug strength, respectively; and the values obtained by method C was 4.5% with small drug strength, and 6.9% with large drug strength, respectively.

Conclusion The factors affecting actual dose of intravenous antibiotics in the dispensing process were the volume of solvent and the drug strength, as well as the dilution times for drugs with poor stability. Method B was more suitable for neonatal drug dispensing because of its high accuracy and simple operation.

39 POPULATION PHARMACOKINETICS OF MEROPENEM IN NEONATAL AND PEDIATRIC EXTRACORPOREAL MEMBRANE OXYGENATION: A RETROSPECTIVE PILOT STUDY (PRELIMINARY ANALYSIS)

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Introduction Meropenem is a broad-spectrum antibiotic commonly used to treat serious infections in the pediatric population treated with extracorporeal membrane oxygenation (ECMO). It is known that ECMO may affect the drug's pharmacokinetics (PK) by altering the drug's clearance (CL), volume of distribution (Vd), and protein binding. There are limited data on ECMO influence on PK of meropenem in neonates and children undergoing ECMO. Therefore, the aim of this study was to describe PK of meropenem in critically ill neonates and children undergoing ECMO.

Methodology Data from therapeutic drug monitoring (TDM) were available from 25 (14 female, 11 male) critically ill patients (median (interquartile range, IQR), body weight (BW): 5 (3.28–13.50) kg; postnatal age (PNA): 124 (15–1008) days) treated with meropenem (average intermittent dose of 20 mg/kg or continuous infusion), of whom 15 received veno-venous (VV) or veno-arterial (VA) ECMO. Meropenem levels ranged between 0.68 and 67 mg/L. Population PK analysis was performed using NONMEM V7.3.0. The following covariates were tested: maturation variables: BW, PNA; disease status: laboratory values, including serum creatinine, serum urea, serum albumin, total bilirubin, blood pH, aspartate transaminase, and alanine transaminase; concomitant therapy: use of diuretics, inotropes, as well as use of continuous renal replacement therapy; ECMO variables: on/off ECMO, duration of ECMO treatment, ECMO flow rate.

Results According to the model, PNA is a covariate for both CL and Vd, while BW is a covariate of CL. ECMO and CRRT have no significant impacts on the PK parameters. In a one-compartment model, CL and Vd for a typical child of median BW (5 kg) at median PNA (124 days) are 0.459 L/h (RSE = 22.7%)) and 1.76 L (47.3%), respectively. The coefficients of variation for inter-individual variability (IIV) for CL

and Vd are 51.5% (17.6%) and 26.9% (22.3%), respectively. A proportional error with a coefficient of variation of 42.7% (9.8%) provides the best description of the residual variability.
Conclusion ECMO does not affect the PK of meropenem in the cohort. Further larger studies should confirm these results.

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40 NO DIFFERENCE IN THE INCIDENCE OF HEARING LOSS AFTER INTRODUCING A VANCOMYCIN LOADING DOSE IN NEONATES: A SINGLE CENTER ANALYSIS OF A TERTIARY NICU

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Introduction While many studies have reported on the pharmacokinetics (PK) of vancomycin in neonates, data on the pharmacodynamics or safety (PD) are scarce. The recently published NeoVanc study indicated that a vancomycin loading dose might be associated with an increased incidence of hearing loss, as a secondary safety analysis.[1] The aim of the current retrospective study was to examine the difference in the incidence of hearing loss in two cohorts from the same NICU that were treated either with or without a loading dose to evaluate this loading dose safety signal. Furthermore, we aimed to investigate the relationship between vancomycin treatment duration, cumulative dose and cumulative AUC and hearing loss.
Methodology Clinical data, vancomycin routine care therapy data and available BERA (Brainstem Evoked Response Audiometry) hearing tests were retrospectively collected for cohort 1 (June 2011-December 2012, without a loading dose) and cohort 2 (November 2017-June 2019, with a loading dose). Hearing loss was described as a failed BERA test at least unilateral after the first failed screening. The difference in the incidence in hearing loss between both cohorts was compared using an unconditional Z-pooled exact test and a Fisher exact test to determine the differences in treatment duration, cumulative dose and cumulative AUC (both tests p-value < 0.05 significant). AUC was calculated using a validated PK-model.[2]
Results In total, 102 neonates without a vancomycin loading dose and 56 with a loading dose were included. There was no difference in the incidence of hearing loss between both cohorts (cohort 1 11.76% hearing loss vs cohort 2 12.00%, p-value 1). Furthermore, treatment duration (p-value 0.656), cumulative dose (mg/kg) (p-value 0.992) and cumulative AUC (p-value 0.497) did not differ significantly between patients with normal and abnormal hearing when pooling both cohorts.
Conclusion In this single-center study, a vancomycin loading dose was not associated with increased hearing loss. Even a detailed AUC based assessment was not associated with hearing impairment. Due to remaining knowledge gaps, assessment of safety, both on short- and long-term outcome, after drug exposure in the neonatal period remains important.

REFERENCES

1. Hill, *et al. Lanct Child Adolesc Heal* 2022.
2. Janssen, *et al. AAC* 2016.

41 DRUG TREATMENT OF NEONATAL SEIZURES BY NEONATOLOGISTS AND PAEDIATRIC NEUROLOGISTS: A SURVEY OF PRACTICE IN AUSTRALIA AND NEW ZEALAND

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Background Guidelines recommend that recurrent or prolonged seizures in neonates be treated with phenobarbitone being the preferred drug for initial treatment. A 2005 survey of neonatologists and paediatric neurologists in Australia and New Zealand (ANZ) reported that 95% of respondents chose phenobarbitone (PB) as initial therapy?. Newer anti-epileptic drugs have become available which may have better safety profiles, although efficacy is less well-established. This current study aimed to reassess the practice of ANZ neonatologists and paediatric neurologists with regards to choice of drugs for initial and escalation treatment of neonatal seizures and to assess whether seizure management by each specialty has changed since 2005.
Methodology Neonatologists and paediatric neurologists in ANZ were invited to complete an online survey. A scenario suggestive of acute symptomatic seizures in a 12-hour-old, term infant was presented. Participants were asked multiple choice questions about drug treatment choices. Survey questions were modelled on the questions of the 2005 survey with additional questions to detect practice change.
Results Neonatologists (n=70) and paediatric neurologists (n=16) completed the survey. When presented with a scenario of an infant in a referring hospital who had several brief clinical seizures, 22% (18) of respondents chose no drug treatment while awaiting a retrieval team. Of those that did choose treatment, 93% chose PB and 7% levetiracetam (LEV). Neurologists were more likely to use LEV than neonatologists ($p<0.05$). To treat a second episode of seizures 69% of respondents chose another dose of PB compared with 84% of respondents in2005 ($p<0.05$). Others chose LEV (24%), phenytoin (3%), or topiramate (1%). For a third episode of seizures, of the 83% who would treat, 24% chose PB and 51%, LEV, while the remainder chose phenytoin or a benzodiazepine. Half of participants (52%) would not continue treatment after cessation of seizures.
Conclusion PB remains preferred for initial treatment of neonatal seizures among ANZ neonatologists and paediatric neurologists. Phenytoin or benzodiazepines choices decreased but LEV is increasingly chosen for seizures refractory to PB. Considerable practice variability persists in management of neonatal seizures and reduction in this may improve outcomes.

REFERENCE

1. Carmo KB, Barr P. Drug treatment of neonatal seizures by neonatologists and paediatric neurologists. *J Paediatr Child Health* 2005;**41**(7):31.

42 CLINICAL ENDPOINTS FOR PHENOBARBITAL IN NEONATAL TRIALS

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Introduction The disposition of phenobarbital in newborns may be affected by developmental changes in PK, treatment modalities and other factors. Phenobarbital treatment ultimately requires therapeutic monitoring (TDM) to optimize treatment.
Objective The purpose of this literature search was to obtain information on the primary (efficacy) and secondary (safety) parameters of phenobarbital and dosing regimen recommendations in this population.
Methodology Systematic literature search in PubMed, EMBASE, Web of Science, MEDLINE (March 1977– March 2023). Articles were marked as relevant if they included PK and parameters of efficacy and safety.
Results 49 relevant original articles were identified, of which 8 were conducted under hypothermic environment. Study cohorts were stratified into 76 subgroups (according to demographics, modality). PK was studied in 41%, the efficacy (seizure modification) of phenobarbital alone in 52%, and with co-medications in 51%. The safety of the treatment was described in 49% (bradycardia was noted 4 times, hypotension 7 times, oversedation 5 times, and respiratory depression 7 times. Plasma concentrations were measured in 82%. A dosing regimen was recommended in 47%, but dosage regimen validated in only 1%.
Conclusion Most studies focused on both PK parameters, and dose adjustments, while the efficacy and safety parameters still vary among the centers.

43 CORRELATION BETWEEN MATERNAL, FETAL AND NEONATAL DIGOXIN AND FLECAINIDE CONCENTRATIONS AND (SIDE) EFFECTS IN MOTHER AND CHILD, TREATED FOR FETAL SUPRAVENTRICULAR TACHYCARDIA – A CASE SERIES TO IMPROVE DOSING

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Introduction Sustained fetal tachycardia often requires transplacental antiarrhythmic therapy. Little is known about the dose-concentration-effect correlation in the mother, fetus, and newborn. Our aim was to evaluate the relationship between perinatal digoxin and flecainide therapy, measured maternal and umbilical concentrations, and effect.
Methodology We conducted a retrospective case series including all pregnant women with their fetuses treated for fetal tachycardia in the period from January 2017 until February 2023. The main study endpoints were effects, expressed as fetal conversion to sinus rhythm, maternal side effects, and digoxin and flecainide serum concentrations in relation to the applied doses at the time of conversion.
Results Twenty-one fetuses were included at a median gestational age of 30 (IQR 29–32) weeks with a median fetal heart rate of 240 (IQR 231–266) bpm. Digoxin monotherapy (1.5 mg followed by 0.75 mg daily) (n=9) converted 4 (44%) fetuses to sinus rhythm after a median time of 2.0 (IQR 1.8–2.0) days with digoxin through concentrations of 1.4 (IQR 1.4–1.5) µg/L. Five fetuses did not convert with dioxin monotherapy, despite of median through concentrations of 1.15 (IQR 0.95–1.43) µg/L. One of these fetuses switched to sotalol, without effect. In the other 4 fetuses flecainide was added after 4 days to reach conversion. Flecainide monotherapy (300 mg daily) (n=3) converted 3 (100%) fetuses to sinus rhythm after a median time of 1.0 (IQR 1.0–2.0) day with a median through concentration of 0.97 (IQR 0.33–0.66) mg/L. Combination therapy of flecainide and digoxin converted 4 of the 8 (50%) hydropic fetuses after 2.0 (IQR 1.8–2.5) days with through concentrations digoxin of 1.4 (IQR 1.1–1.6) µg/L and flecainide 0.40 (IQR 0.32–0.46) mg/L. Conversion was not reached in 4 fetuses despite of median through concentrations of digoxin 1.2 (IQR 1.0–1.4) µg/L and flecainide 0.47 (IQR 0.34–0.58) mg/L. Two of these fetuses eventually converted by adding a beta blocker. Cardiac complications and mild side effects occurred in 90% of the mothers. Fetal to maternal umbilical cord ratios were available for two cases, 0.57 and 0.63 for digoxin and 0.85 and 1.23 for flecainide.
Conclusion Transplacental antiarrhythmic resulted in successful conversion in 16(76%) of the fetuses and mild maternal side effects. Maternal plasma concentrations and umbilical cord ratios were high which may indicate that lower doses may also be effective.

44 PRENATAL CANNABIS EXPOSURE AND THE RISK FOR NEUROPSYCHIATRIC ANOMALIES IN THE OFFSPRING: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background As cannabis use becomes more common worldwide, an increase in its use is also observed among women of reproductive age, including during pregnancy. Several studies examined the possible impact of prenatal cannabis exposure on children's psychiatric and neurobehavioral development. However, the variability and inconsistency in the associations observed make it difficult to fully evaluate the risks and potential harm of in-utero cannabis exposure. Therefore, our objective is to evaluate the existing data and assess the association between cannabis exposure during pregnancy and the risk for neuropsychiatric outcomes in the offspring.
Methods We followed the PRISMA 2020 guidelines for systematic review and meta-analysis. MEDLINE, EMBASE, and Cochrane databases were searched up to August 2022. Data were independently screened for eligibility and extracted by two reviewers. Studies were eligible for inclusion if they reported quantitative data on long-term neuropsychiatric outcomes in the offspring prenatally exposed to cannabis versus control. Data were pooled using random-effects models.

Results Fourteen eligible observational studies were included in the review, and twelve were included in the final quantitative analysis. The pooled odds ratio (OR(for ADHD was 1.12 (95% confidence interval (CI): 1.00–1.27); for ASD, the pooled risk ratio (RR) was 1.18 (95% CI 0.7–1.97); for psychotic symptoms, the pooled RR was 1.18 (95% CI 0.95–1.45); for anxiety, the pooled OR was 1.63 (95% CI 0.78–3.40); and for offspring's marijuana use the pooled OR was 1.2 (1.01–1.42).

Conclusions There was no association between exposure to cannabis during pregnancy and ADHD, ASD, psychotic symptoms anxiety in the offspring. The association between prenatal cannabis exposure and the mildly increased risk for ADHD might be due to residual confounding and not because of the exposure. These results should be interpreted with caution, given the observational nature of the studies and the potential for residual confounding.

45 DON'T CRY OVER SPILT MILK: WOMEN TREATED WITH MEDICATIONS CAN (IN MANY CASES) DONATE MILK TO A HUMAN MILK BANK

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Introduction Human breast milk is the recommended nutrition for newborns and premature neonates according to the World Health Organization. Breastmilk is of utmost physiological importance for neonates and is crucial for the survival of premature newborns, preventing necrotizing enterocolitis and other medical conditions. Recently, the National Israeli Human Milk Bank was established by the emergency medical service-Magen David Adom (MDA). Around 10% of women willing to donate milk to the milk bank are taking medications. The Drug Consultation Center at Shamir Medical Center provides guidance regarding dilemmas related to these milk donations. Our aim is to set criteria for milk donations designated for premature newborns, from women treated with medications.

Methods In order to maximize the potential of milk donations, we assess the safety of the donation by evaluating the Relative Infant Dose (RID) and other pharmacokinetics (PK) parameters: molecular weight, protein binding and oral bioavailability of the medication. Possible undesirable effects on the premature newborn are also being taken into consideration. The attitude toward medication compatibility with breastfeeding differs between a mother breastfeeding her own child versus milk donation intended for premature newborns. Upon the safety assessment, recommendation regarding the milk donation are provided: decline, accept donation, or accept the donation-but, with dilution. In the latter case, the milk amount will not exceed 10% of the total batch. Other donations from the same batch should not contain other medications from the same pharmacological group.

Results Around 65 consultations were performed. 30% of the queries were regarding anti-depressant and anti-anxiety medications, 14% regrading anti-thrombotic and anti-platelet therapy and 10% - treatment for allergic conditions. 5% of donations were declined due to potentially hazardous medications (e.g. doxorubicin). 21% of donations were accepted (e.g. loratadine). In 74% of the queries, the recommendation was to accept the milk donation with dilution (e.g. fluoxetine).

Conclusions The human milk bank is a lifesaving service. In the near future, milk donations' samples will be transferred to our unit in order to measure the concentration of the medications. This collaboration enables to use donated human breastmilk "up to the last drop".

46 I AM A LAW STUDENT TREATED WITH AMPHETAMINES FOR ATTENTION DEFICIT HYPERACTIVE DISORDER (ADHD): CAN I BREASTFEED MY CHILD? A PILOT STUDY

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Introduction In recent years, there has been a steady increase in ADHD medication use by young adults, including women of childbearing age and during pregnancy. Most data on the safety of these medications is from recreational abuse of meth-amphetamine. Little is known on the safety of amphetamine stimulants for ADHD treatment during breastfeeding. Amphetamines are excreted into human milk and may be found in the urine of nursing infants. Poor sleeping and irritability have been reported in some nursing infants, but long-term developmental effects were not described.

Methods A prospective pilot study of women who approached the TIS Zerifin between the years 2017–2022 for information on the safety of the use of amphetamine stimulants – lisdexamphetamine or mixed racemic amphetamine salts (Adderall®) during breastfeeding. A telephone follow-up interview was conducted to assess the outcome and the neurodevelopment of the children by using Pediatric Quality of Life (PedsQL), and Denver Developmental Scale.

Results Thirteen women were included in the analysis, 6 (46%) exposed to lisdexamphetamine, and 7 (54%) to mix racemic amphetamine salts. Mean maternal age at the time of the first contact was 32±5.8 years. Most of the women had a high academic education (11/13, 85%). Seven women used amphetamines during pregnancy, and 4/13 (31%) were exposed throughout pregnancy. Three (23%) women used concomitant psychotropic medications. Median (IQR) age of the child at the follow-up was 18 (5.25–34) months. Nine (69%) children were fully breastfed. Adverse effects were reported among five (38%) children: somnolence (1, 8%), crying/restlessness (3, 23%), GI effects (colic/constipation) – 4, 31%.

All children were reported to have normal gross motor development, based on Denver developmental scale. Neurodevelopment, as measured by PEDsQL, were also normal with PEDsQL score (median, IQR): total 97.16 (91.48–100), Psychosocial Health 99.33 (94.83–100), Physical Health 98.75 (87.8–100).

Conclusions Exposure to amphetamine stimulants during breastfeeding was not associated with negative neurodevelopment of the offspring. However, due to the small sample size, further studies are needed in order to conclude on the effect of prolonged exposure to amphetamine stimulants during breastfeeding.

47 DETERMINING THE CONCENTRATION OF MATERNAL MEDICINES IN HUMAN MILK: THE UMBRELLACT STUDY PROTOCOL

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Introduction An extensive information gap regarding safety of medicines during lactation still exists today. At least 50% of women need pharmacotherapy in the postpartum period and the proportion of breastfeeding women needing medication is rising, due to higher maternal age at pregnancy and increased prevalence of chronic maternal diseases, among others. Considering the lack of information, informed and shared decisions on the use of a medicine during breastfeeding are often challenging. This may result in unnecessary cessation of breastfeeding or avoidance of pharmacological treatment. The objective of UmbrelLACT, this prospective observational study, is to collect data on the human milk transfer of maternal medicines, child exposure and general health outcome of the child. In addition, we aim to evaluate the predictive performance of lactation and pediatric physiologically-based pharmacokinetic (PBPK) models. These models are an accepted approach to predict medicine exposure in special populations.

Methods Breastfeeding women taking medication will be recruited via UZ Leuven, the BELpREG website and other external facilities. Each compound for which samples might be collected, will be evaluated by the team in terms of feasibility and relevance, such as societal need of data, available evidence in literature and access to an analytical assay. Participants will be asked to report clinical maternal and child variables, to collect milk samples over 24h and, optionally, to donate two blood samples (at peak and trough levels). A blood sample of the child may be collected if the parents consent. Approval of the internal Ethics Committee has been obtained (S67204; 20/01/2023).

Results We expect to enroll 5–15 breastfeeding mothers using medication per year. We will determine the concentration of maternal medicines in human milk and estimate the intake of medicines by the nursing infant through parameters such as daily infant dose (DID) and relative infant dose (RID). We will investigate if medicines with limited available data result in low concentrations in human milk and, subsequently, in minimal exposure in breastfed children.

Conclusion The systematic approach of the UmbrelLACT initiative in Belgium to study the concentration of medication in human milk will generate essential data, substantiating evidence-based risk assessments on the use of medicines during lactation. Furthermore, the UmbrelLACT data will contribute to the evaluation of PBPK models.