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Lecture Abstracts

1 Positron emission tomography for optimizing psychiatric drug treatment: present and future

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Imaging techniques, particularly molecular imaging, have contributed significantly to understanding the relationships between target engagement by psychotropic drugs on the one hand and clinical effects and side effects on the other. Especially for antipsychotics, positron emission tomography (PET) studies of target engagement belong to the standard development program of new drugs.

Examples from the fields of antidepressants and antipsychotics will be discussed that illustrate the relationships between receptor (or transporter) occupancy and plasma levels of prototypic drugs from these classes. These relationships are described for each substance by a compound-specific graph. Once this relationship has been determined experimentally, the measurement of a single blood level is sufficient to determine the occupancy of the molecular target with high accuracy.

By relating the "therapeutic window" determined with the help of PET to the associated plasma levels of the respective drug, the method becomes an excellent tool for establishing therapeutic reference ranges for TDM. This will be illustrated for prototypic antipsychotics (e.g., aripiprazole, olanzapine, risperidone). With examples from the group of antidepressants, it will be shown, however, that for targets such as the serotonin and the noradrenaline transporter the relationships are less clear. New drug classes that do not work on the classic monoaminergic targets represent further future challenges for the field. Likewise, drugs that are not administered on a regular basis, specifically psychedelics, will need new methodological approaches to exploit the potential of the method.

Molecular imaging represents a unique method to study not only the mechanisms of action of psychotropic drugs but also to guide routine therapy.

2 Antipsychotics in pregnancy – do we need Therapeutic Drug Monitoring?

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Treating psychiatric disorders during pregnancy requires balancing of risks between minimal maternal–fetal drug exposure and a maximum maternal efficacy. Physiological changes in pregnancy are known to cause changes in drug disposition and may alter antipsychotic concentrations in serum and plasma. However, evidence regarding changes in antipsychotic disposition seen in pregnancy is scarce.

The English-language literature indexed on PubMed was searched for publications that evaluated pharmacokinetic changes or Therapeutic Drug Monitoring (TDM) of antipsychotic drugs during pregnancy.

CYP3A induction reduces plasma concentrations of antipsychotic drugs. Serum concentrations of quetiapine and aripiprazole decrease by more than 50 % during pregnancy, whereas olanzapine concentrations seem to remain largely unchanged during pregnancy. Olanzapine, haloperidol, clozapine, and risperidone show the highest ratios of antipsychotic excretion into the umbilical cord blood.

The results warrant a reconsideration of the general advice of using the pre-pregnancy "minimum effective dose" of antipsychotics during pregnancy. As drug clearance increases, sub therapeutic drug levels may ensue, potentially exposing the mother and unborn child to both the medication and the illness. Due to the physiological changes of pregnancy and enhanced hepatic metabolism, drug doses may need to be adjusted during pregnancy to sustain efficacy.

3 Update on the Management of Lithium in the Peripartum Period

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Lithium salts are the first-line maintenance treatment for bipolar disorders in most guidelines and also are used in the indication of difficult-to-treat depression and chronic suicidality. With increasing age of childbearing at least in middle and high income countries, a substantial number of bipolar women are treated with mood stabilizers, and amongst those often lithium is used, at the time they wish to get pregnant. As there is no easy alternative for lithium and especially if previous discontinuation attempts have failed, pregnancy and also breastfeeding needs to be considered during ongoing treatment with lithium. In former times, lithium exposure during pregnancy was thought to be a rather strong embryotoxic substance, especially increasing the risk of severe cardiac malformation. However, combined data of several recent studies only point to a low teratogenic risk and there is scarce but rising evidence of the optimal dosing of lithium during pregnancy. Furthermore, mothers often prefer to

breastfeed their children. However, there is indeed evidence that lithium transfers to the breastmilk and can also be detected in the infant's serum. The influence on the infant is still a largely understudied topic, even if no major negative long term effects have been reported. Regular monitoring of the infant's renal clearance, thyroid function, and lithium levels is warranted, when breastfeeding under lithium exposure.

4 Establishing therapeutic drug monitoring to routinely assess pharmacokinetic changes for psychotropic medications prescribed during pregnancy and lactation

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Therapeutic drug monitoring (TDM) has been employed to assess alterations in pharmacokinetics of psychotropic medications due to the physiological changes of pregnancy over the past decades. Here we present an approach to quantify the pregnancy impact on the pharmacokinetics of antidepressants, lithium and antiseizure medications.

We performed systematic literature searches to identify TDM studies comparing levels of antidepressants and antiseizure medications as well as lithium in the same woman in the preconception/postpartum period and during pregnancy. Accordingly, we estimated alteration ratios for dose-adjusted plasma concentrations (C/D ratios) between the 3rd trimester and preconception/postpartum period. The quality of the included studies was assessed using the ClinPK guidelines

A total of 81 studies investigating 15 antiseizure medications, 11 antidepressants and lithium were included. Among antiseizure medications, the largest differences were reported for lamotrigine (n = 188, alteration ratio 0.4, range 0.1-2.4), whereas among antidepressants the largest difference was reported for nortriptyline (n = 7, alteration ratio 0.5, range 0.3-0.7). The quality of studies was invariably acceptable.

Using TDM evidence we reported large changes in pharmacokinetics during pregnancy for several antiseizure medications and antidepressants, which could severely impact treatment outcomes. Thus, TDM should be considered as an essential routine tool of pharmacotherapy for women during pregnancy and lactation.

5 Psychotropic Medication and Breastfeeding – Yes – No – Maybe?

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Yes – no – maybe? The uncertainty in answering the question to what extent breastfeeding under psychopharmacotherapy can be recommended is great and the clinical management of psychopharmacotherapy in lactating women remains a challenge. Due to sparse scientific evidence, the prescription of psychotropic drugs during breastfeeding must be re-evaluated in each individual case separately. However, the risk of decompensation of maternal mental health is an important factor exerting a negative impact on the mother-infant pair, in the worst-case scenario, even with a suicide or infanticide risk. Since neither the US Food and Drug Administration (FDA) nor the European Medicines Agency (EMA) has approved a psychotropic drug for use during the breastfeeding period, treatment is always off-label and should therefore only take place after a careful risk assessment and a comprehensive informed consent with detailed documentation. Each therapeutic decision is a case-by-case decision, considering the overall constellation, consisting of psychiatric history, current diagnosis and risk assessment for the infant, ideally with the involvement of a social support network in the environment of mother and breastfeeding child. Interdisciplinary support by psychiatrists, pediatricians, gynecologists and midwives should accompany the prescription of psychotropic drugs during the breastfeeding period under regular use of therapeutic drug monitoring (TDM).

6 Therapeutic Drug Monitoring of Antipsychotics: Innovations in the 2024 Consensus Guidelines

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Over the past decades, starting in the late 1980s, advancements in molecular imaging (i.e. PET) have dramatically changed the landscape of schizophrenia treatment with antipsychotics. These technologies have shed light on the interplay between drug target engagement and clinical outcomes, leading to the establishment of a receptor occupancy-based therapeutic range for antipsychotics. However, the role and significance of Therapeutic Drug Monitoring (TDM) remain controversial, with many clinicians underestimating their importance. Moreover, TDM has faced challenges such as unclear reporting of drug-specific therapeutic reference ranges in the literature.

In response to these challenges, the current AGNP guidelines are being updated to refine the methodologies for determining therapeutic reference ranges. This presentation will highlight the effective application of these revised methodologies to antipsychotics, including olanzapine and aripiprazole, and how it has led to the update of their therapeutic reference ranges.

The most robust method for establishing therapeutic reference ranges involves a comprehensive systematic review of prospective data. However, such data, especially studies on concentration-response relationships, are rare. For many psychotropic drugs, the correlation between drug concentration and therapeutic response remains unclear. In these instances, valid reference ranges can be determined using retrospective data, ideally incorporating pharmacodynamic informations in combination with molecular imaging data.

The integration of pharmacological insights into clinical practice is essential for rational and effective treatments of mental health disorders. The updated guideline will be an important resource for clinicians, facilitating the application of the latest developments in patient care.

7 Drug safety in special populations: current data from the AMSP Project

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The AMSP program (Arzneimittelsicherheit in der Psychiatrie; Drug Safety in Psychiatry) was established in 1993 with the aim of continuously improvement of drug safety and risk management in psychiatry. It is an ongoing observational drug surveillance program in hospitals that assesses severe adverse drug reactions (ADRs) in psychiatric inpatients in routine clinical treatment. Additionally, pharmacoepidemiological data on psychotropic drug use along with psychiatric diagnoses, age, and sex of surveilled patients is gathered on two index dates per year.

All data are derived from the AMSP database. The drug utilization data with special emphasis on sex differences comprise 44,418 psychiatric inpatients with major depressive disorder (MDD) between 2001 and 2017. The age-dependent utilization data to examine the influence of patient's age on the selection and

dosage of antipsychotic drugs (APDs) used in the treatment of schizophrenia include 32,062 inpatients with schizophrenia between 2000 and 2017.
We identified several sex-related differences in the treatment of MDD with monotherapy being more common among male patients and women found to be more likely to take ≥ 4 psychotropic drugs.
The AMSP data examining APD selection and dosage related to patient's age showed that the selection of APDs changed with age with some APDs (e.g., risperidone, pipamperone) used more frequently than others (e.g., clozapine, olanzapine) in the elderly.

8 The influence of food on the pharmacokinetics of drugs

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The therapeutic success, including effectiveness and tolerability of a drug, can not only be impaired by the simultaneous intake of other drugs. Drug-interactions with food intake or ingredients of food are also possible. Changes in the pharmacokinetics of the drug in all phases from liberation to excretion are possible.
Interactions of meals and food components with drugs are problems that are often underestimated in their importance in everyday life. This applies to both the patient and the prescriber. In addition, the information in the drug instructions is often too imprecise or too complex and therefore requires additional advice from the physician or the pharmacist. The interactions can be of non-specific as well as specific nature. This means that, on the one hand, the time of intake is important, depending on the meal and its composition. On the other hand, there are specific ingredients in food that can pose risks.
Knowledge on the individual mechanisms of the drug-food interaction is essential to ensure drug safety. It is therefore worthwhile to consider the kind of application of the drug. Moreover, the patient's eating habits must be considered when prescribing a medication.

9 Therapeutic drug monitoring in Parkinson's disease

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A patient-tailored therapy of the heterogeneous, neuropsychiatric disorder entity Parkinson's disease (PD) aims to improve dopamine sensitive motor symptoms and associated non-motor features. Subgroups of PD, disease progress and concomitant disorders as well as ageing processes in general, compliance issues, safety and tolerability of the applied drug combinations may influence intake scenarios and dosing regimen and thus the quality of patient care. Therefore, a repeated, individual adaptation of dopamine substituting compounds is required throughout the disease course. Therapeutic drug monitoring (TDM) of dopamine substituting drugs will optimize the quality of drug applications for patients with PD. We suggest plasma determination especially of levodopa, amantadine and dopamine agonists as an essential step. Repeated assessments within standardised protocols in chronic levodopa/dopa decarboxylase inhibitor treated patients will allow monitoring of the levodopa plasma fluctuation index as a potential risk factor for the onset of motor complications in the long term. These measurements may also support the understanding of only partially levodopa responsive PD related syndromes. To date this phenomenon of missing adequate levodopa response has not yet been fully explored in terms of dysfunction of gastrointestinal absorption or blood brain barrier transport of biogenic amines. Measurements of blood levels of dopamine agonists, monoamine oxidase B inhibitors, istradephylline and amantadine are also needed. Outcomes of TDM analyses may serve as disease progression marker complemented by still to be developed future computing procedures on the central need for dopamine supplementation. They will substitute the currently applied calculations of levodopa equivalents as marker of disease progression.

10 Clozapine Monitoring in Serum and Saliva

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For several years, saliva has been investigated as an alternative matrix for therapeutic drug monitoring (TDM). Various studies have been carried out with different drugs. In contrast to previous studies, which took place in an inpatient setting, this study aimed to examine patients taking clozapine in an outpatient setting. The aim of the present study was therefore to identify and name possible influences on the success of this new kind of monitoring in outpatients.
In the period from May 2021 to May 2022, a total of 19 outpatients were included in the study. In addition to repeated blood samples, parallel saliva samples were collected as part of the TDM, up to ten parallel samples. Serum and saliva clozapine and N-desmethylclozapine concentrations were determined by HPLC-MS/MS.
Positive correlations between the serum and saliva concentrations over time of clozapine ($r = 0.663$) and its main metabolite N-desmethylclozapine ($r = 0.222$) were found. Clozapine and N-desmethylclozapine concentration time courses in saliva showed a strong correlation ($r > 0.950$) in 50 % of participants, while in serum, the correlation was significant in 60 % of participants. Clozapine and N-desmethylclozapine showed approximately 20 % and 25 % variation in serum, and 25 % and 15 % in saliva. In comparison, studies in inpatient settings reported higher coefficients of variation – 44 % for clozapine and 29 % for N-desmethylclozapine in saliva.
This study potentially contributes to the establishment of saliva as an alternative matrix for TDM. The notably low variation in saliva is promising, but further research is needed before this method can be widely used.

11 Development of the first consensus guidelines for therapeutic drug monitoring in Neuropsychopharmacology for children and adolescents

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The number of studies on therapeutic drug monitoring (TDM) in children and adolescents treated with psychotropic drugs has steadily increased in recent years. Evidence-based data on dose-concentration ratios as well as concentration-effect relationships are now available for several of the most commonly used antidepressants and antipsychotics in this age group. Despite remaining knowledge gaps, we believe that 20 years after the publication of the first consensus guidelines on TDM of neuropsychiatric drugs by the TDM task force of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP), the conditions are

now in place for the publication of the first expert guidelines on TDM in child and adolescent psychiatry. We report on the consensus meeting of the TDM-KJP expert group – a collaboration between the AGNP working group "Child and Adolescent Psychopharmacology" and members of the "Competence Network TDM in Child and Adolescent Psychiatry" to develop and define (preliminary) therapeutic reference ranges for selected antipsychotics and antidepressants for the use in children and adolescents.

12 Therapeutic drug monitoring of children and adolescents treated with escitalopram in daily clinical practice

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Escitalopram, the (S)-enantiomer of racemic citalopram, is a selective serotonin reuptake inhibitor used off-label in the acute and maintenance treatment of Major Depressive Disorder and anxiety disorders in children and adolescents. Similar to previous analyses within the multi-center 'TDM-VIGIL' project that focused on specific psychotropic medications, this contribution reports the results of therapeutic drug monitoring (TDM) of escitalopram in youth, examining the association between steady-state blood concentrations, dose, and clinical positive and negative effects. The study looked into predictors of response to escitalopram using the Clinical Global Impression scale and the Pediatric Adverse Event Rating Scale as outcome measures. A tentative reference concentration level in this age group will be compared with adult-specific ranges. Additionally, comparisons with other antidepressants will be made in terms of pharmacokinetic profiles. The presentation will conclude by contextualizing the TDM of psychotropic medication in daily clinical practice as decision-making and monitoring tools, particularly in vulnerable populations and complex clinical scenarios.

13 Risperidone plasma concentrations and side effects/effectiveness in children and adolescents with autism spectrum disorder

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Risperidone is one of the most prescribed antipsychotic drug to children and adolescents, however, it is associated with serious side effects, chief among which weight gain. We assessed the relation of risperidone and 9-hydroxyrisperidone PK parameters in children and adolescents with autism spectrum disorder (ASD) with side effects and improvement in behavioural problems in a longitudinal study. Forty-two children and adolescents were included in a 24-week prospective observational trial. Drug plasma concentrations, side effects and effectiveness were measured at several time points during follow-up. Relevant pharmacokinetic covariates, including medication adherence and CYP2D6, CYP3A4, CYP3A5 and P-glycoprotein (ABCB1) genotypes, were measured. Nonlinear mixed-effects modelling (NONMEM) was used for a population pharmacokinetic analysis. A risperidone two-compartment model combined with a 9-hydroxyrisperidone one-compartment model best described the measured concentrations. Higher risperidone sum trough concentrations best predicted higher BMI z-scores during follow-up ($P < .001$). Higher sum trough concentrations also predicted more sedation ($P < .05$), higher prolactin levels ($P < .001$) and more effectiveness measured with Aberrant Behavior Checklist irritability score ($P < .01$). These results indicate a therapeutic window exists, which suggests that therapeutic drug monitoring of risperidone might increase safety and effectiveness in children and adolescents with ASD and behavioural problems.

14 Identifying CYP2C19 and CYP2D6 poor metabolizers from TDM data

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Pharmacogenetic (PGx) analysis and therapeutic drug monitoring (TDM) are tools used for personalized dosing. While PGx enables pre-emptive dose predictions to hit target concentrations of specific drugs based on genetic information, TDM captures all sources of pharmacokinetic variability, but often needs steady-state conditions to provide reliable dose adjustments.Most laboratories perform either TDM or PGx. We used TDM data to predict critical drug-metabolizing phenotype, where poor metabolizers (PMs) of CYP2C19 or CYP2D6 probably represent the most important category.
Leveraged by large-scale data collected in a laboratory performing both TDM of psychotropic medications and PGx analyses, biomarker estimates, such as metabolic ratios (MR) derived from TDM analyses were used to identify CYP2C19 or CYP2D6 PMs. The same approach was applied for other, non-drug agents, using an UPLC-MS analysis that can identify CYP2C19 or CYP2D6 PMs. Escitalopram, sertraline, risperidone and venlafaxine are drugs where MR from TDM analyses were efficiently used to identify CYP2C19 or CYP2D6 metabolism. Among these, escitalopram (CYP2C19) and venlafaxine (CYP2D6) were probably the most promising and reliable ones in detecting PMs. In addition, UPLC-MS analyses could detect solanidine, a CYP2D6 biomarker found in potatoes, which may provide an important, extra value in performing TDM.
MRs of several psychotropic drugs measured by TDM can be used with quite high sensitivity and specificity for the identification of CYP2D6 or CYP2C19 PMs. So far, the dietary biomarker solanidine seems to be the most promising biomarker and might be considered for inclusion in TDM assays to identify CYP2D6 or CYP2C19 PMs.

15 *CYP2D6* genotypes and phenotypes, plasma levels and treatment failure with risperidone or aripiprazole: results from a one-year longitudinal study

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Risperidone and aripiprazole are metabolized by the cytochrome P450 2D6 (CYP2D6). Individuals can be categorized as ultrarapid, normal, intermediate, or poor metabolizers (UM, NM, IM and PM, respectively). Greater odds of switching from risperidone (but not from aripiprazole) were previously reported among PM and UM. Importantly, the duration of treatment up to switching was unknown.

Treatment duration up to switching was analyzed for risperidone (N = 515) and for aripiprazole (N = 467). CYP2D6 *3, *4, *5, *6, *9, *10, *41 and *XN alleles were analyzed. Phenoconversion due to co-medication with CYP2D6 strong inhibitors was also considered.

CYP2D6 genotypes and phenotypes significantly influenced plasma levels of aripiprazole plus dehydroaripiprazole, and of risperidone plus 9-OH-risperidone. Considering PM and (IM + NM + UM), 70 % and 42 % of switching probability from risperidone was found, respectively (p = 0.026). The risk of switching increased over time for PM (interaction term:1.01; p = 0.011), becoming significant after three months (HR:1.79; p = 0.028). Similar results were obtained when considering phenoconversion, although phenoconverted PM risk of switch was constant over time. The incidence of discontinuation from aripiprazole was increased at 3 months (OR:2.57; CI:1.15-5.58) in UM or PM when compared to NM or IM.

Over one year, CYP2D6 PM presented an increasing risk to switch from risperidone over time, the risk becoming significant after three months. PMs or UMs are associated with increased discontinuation rates after 3 months aripiprazole treatment. This supports preemptive genotyping for *CYP2D6* prior to using risperidone and aripiprazole with phenoconversion also being taken into account.

16 Assessment of Genetic and Lifestyle Factors on Clozapine and N-desmethylclozapine Plasma Levels in Schizophrenia Patients

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Plasma concentrations of clozapine (CLZ) vary due to several factors, including age, sex, smoking habits, caffeine consumption, and comedication. Genetic variations might also explain the variations for plasma CLZ (2). Among genetic polymorphisms that may have a role in CLZ metabolism, *CYP1A2 * 1F* is a strong candidate.. Cytochrome P450 oxidoreductase (*POR*) gene *POR * 28* variation is also potentially a considerable target.

Within this context, we have investigated the influence of genetic (*CYP1A2 * 1F* and *POR * 28*) polymorphisms and non-genetic factors (caffeine consumption and cigarette smoking) on CLZ and main metabolite DCLZ concentrations. For this purpose, 112 schizophrenia patients receiving CLZ were included in the current study. Plasma CLZ and N-desmethylclozapine (DCLZ) levels were analysed by using HPLC-UV detector set at 220 nm. Genetic variations were identified using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay.

There was no significant difference between the genotype groups on CLZ, DCLZ levels, and DCLZ/CLZ ratios. In the subgroups created according to the patient's *CYP1A2* genotype, and smoking and caffeine consumption status, significant differences have been observed between *POR * 28* wild-type and variant genotype groups. Regression model analyses revealed that the *POR * 28* polymorphism correlates significantly with both CLZ and DLCZ (ng/ml/mg/kg) levels.

The outcome of our investigation findings suggests that, considering both genetic and non-genetic factors may have the potential to increase efficacy and decrease adverse drug reactions in the treatment of schizophrenia with CLZ.

17 Pharmacogenetics and TDM in patients with long-acting injectable antipsychotics: First clinical experience

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Geno- and phenotyping currently represent the main biological pillars for personalized medicine, particularly with regard to the prescription of psychotropic medications.. Nonetheless we are missing data regarding the usefulness of combining TDM with pharmacogenetics in patients treated with long-acting injectable antipsychotics (LAIs).

In a pilot projects we investigated the prevalence of individual variants of genes/polymorphisms involved in drug metabolism in LAI-treated patients. The catchment area of the Autonomous Province of Bolzano/Bozen counts 520.000 inhabitants For pharmacogenetic testing (PGx) the following methods were used: qPCR, digital PCR and DNA sequencing to determine >3360 SNPs in 24 genes. 138 SNPs from 12 phase I enzymes (CYP2C19, CYP2D6, CYP2C9, CYP3A4, CYP3A5, CYP2A6, CYP2B6, CYP2C8, CYP2E1, CYP1A2, DPYD and G6PD), 20 SNPs from 4 phase II enzymes (UGT1A1, UGT2B 15, NAT2 and TPMT), 7 SNPs from 1 transporter(s) (SLCO1B1), 5 SNPs from 1 transporter(s) (ABCB1(MDR1)) and 9 SNPs from 6 proteins (GSTP1, HLA-B * 58:01, HLA-B * 15:02, HLA-A * 31:01, HLA-B * 57:01 and POLG) that are involved in drug metabolism and transport or associated with drug action. Phenotype prediction was based on in-depth knowledge of knowledge bases and Pharmgenetix internal laboratory research (published and available online: www.Pharmgenetix.com). Furthermore as a secondary objective we aimed to evaluate the association between the identified individual variants of genes/polymorphisms and TDM in these subjects.

Additionally to the study design the talk will provide further analysis regarding epidemiological distributions in the Autonomous Province of Bolzano/Bozen mainly in LAI-treated patients as well as first experiences in a case series' manner adopting a combination for TDM and genotyping for LAIs.

18 The value of therapeutic drug monitoring in the development of and treatment with long-acting injectable antipsychotics

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The development and therapeutic application of long-acting injectable antipsychotics (LAIs) represent a significant advancement in the management of psychiatric disorders. In the developmental context, TDM emerges as an indispensable tool, guiding researchers in optimizing pharmacokinetics and ensuring the efficacy and safety of these novel formulations.

Narrative review of the value and limitations of TDM for the development of and treatment with LAIs using recent examples of the successful use of pharmacokinetic data modeling, population pharmacokinetics and bridging for LAIs of different injection intervals that gained regulatory approval.

Throughout the developmental phase of LAIs, TDM enables the precise measurement of drug concentrations, facilitating the establishment of optimal dosing regimens for sustained therapeutic effects. By integrating TDM data into pharmacokinetic modeling, researchers gain insights into the complex interplay of drug metabolism, absorption, and distribution, thereby refining LAIs to achieve consistent and prolonged therapeutic levels. In the realm of ongoing treatment, TDM continues to play a pivotal role in personalized patient care. Regular monitoring of drug concentrations aids clinicians in tailoring dosages to individual needs, optimizing therapeutic outcomes, and preventing under- or over-dosing. The significance of TDM in real-world scenarios is supported by data indicating that several factors translate into different blood level and clinical results, including patient and illness variability, concomitant medications, and lifestyle that can impact drug metabolism, necessitating an adaptive and personalized treatment approach.
By bridging the gap between research and patient care, TDM emerges as a key facilitator in advancing the precision and efficacy of LAI treatments, ultimately contributing to improved outcomes and quality of life for individuals living with psychiatric disorders

19 Therapeutic Drug Monitoring (TDM) in addiction medicine from the laboratory perspective

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The request of "standard TDM" to aid in dosing of substitution drugs in maintenance therapy is rare. Mostly adherence assessment especially in patients with take-home privilege is needed. The laboratory is asked for support if the clinician suspects that the patient: 1. pauses from substitution, 2. spikes substitute into a drug-free "friend-sample", 3. reduces dose, 4. increases dose with illegal substitute, 5. is not in steady state or underdosed or 6. is injecting substitute. These points show different significance for the different substitution drugs:
A) Methadone or Polamidone: dose reduction or increase (3., 4.) or enantioselective metabolism (5.) can be disclosed with chiral LC-MS/MS analysis of D- and L-Methadone in plasma. Injection of Methadone can be spotted by the detection of lactose or sucrose in urine (6.). Drug of abuse negative urine must contain 2-ethylene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) (2).
B) Buprenorphine: patients on Buprenorphine sometimes discontinue the intake of their dose (1., 5.) to prepare for a Heroin relapse. This can be assumed if the metabolic ratio of Buprenorphine/Norbuprenorphine in urine is falling below the reference range. A higher ratio is indicating a new intake or dose increase of the substitute (4, 5.). Urine must contain Buprenorphine, Norbuprenorphine and the corresponding glucuronides (2). TDM (3., 4.) of Buvidal patients can be challenging due to low concentrations.
C) Morphine: contamination of Substitol with Codeine and formation of the minor Morphine metabolite Hydromorphone makes the interpretation of drug test results difficult.

20 Degree of clinically quantified tolerance to the desired effects of and adverse drug reactions to the full mu opiod receptor agonist morphine, methadone and fentanyl and to the partial agonist buprenorphine during opioid maintenance and analgesic treatment

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Mu opioid analgesics like the full mu opioid receptor agonists morphine, methadone and fentanyl or the partial agonist buprenorphine have remained the mainstay in the treatment of moderate to severe pain. During chronic treatment, the development of tolerance to their antinociceptive effects presents a considerable therapeutic challenge, especially in opioid maintenance patients who, to complicate matters, may or may not abuse opioids on the side. In opioid-based maintenance patients, it is desirable to assess the actual degree of tolerance to effectively treat withdrawal symptoms while avoiding illegal diversion of surplus quantities of the prescribed mu opioid agonist. As a further complication, the degree of tolerance may vary considerably among different opioid effects.
We are currently conducting a systematic review (PROSPERO CRD42023408416) of the quantitative evidence for these varying degrees of tolerance in either patient population (patients with primary opioid dependence, PODs vs 'regular' patients, REGs) for the various desired effects of and adverse drug reactions to morphine, methadone, fentanyl, and buprenorphine.
A preliminary analysis indicates that tolerance to antinociceptive opioid effects in PODs is more than 6-fold (buprenorphine maintenance) to more than 7-fold (methadone maintenance). Of special consideration, no tolerance to the respiratory depressant effect in PODs seems to occur under these controlled conditions.

21 Therapeutic Drug Monitoring as part of the Opioid Withdrawal Therapy

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Therapeutic drug monitoring (TDM) is recommended for opioid maintenance therapy with levomethadone. However, there are not much data available regarding use of TDM to monitor opioid withdrawal therapy clinically although optimization tools are required.
In this observational cohort study, regular TDM with levomethadone was performed according to a prospective opioid withdrawal protocol. Objective and subjective opioid withdrawal symptoms were measured using validated rating scales and correlations to levomethadone serum concentrations were assessed. Plasma levels were measured using high-pressure liquid chromatography with column switching and spectroscopic detection of methadone and its major metabolite.
This study included 31 patients with opioid-dependence. The serum levels of levomethadone were found to be highly variable and below the recommended therapeutic reference range of 250 ng/mL for maintenance therapy. These serum levels were positively correlated with dosage ($r = 0.632$; $P , 0.001$) and inversely correlated with subjective ($r = 20.29$; $P = 0.011$) and objective ($r = 20.28$; $P = 0.014$) withdrawal symptoms.
The evidence provided sheds light on how to improve levomethadone withdrawal therapy in patients with opioid dependence. It seems that higher initial doses at the beginning and lower dose reductions would have been advantageous. TDM can enhance the safety of opioid withdrawal therapies, minimize withdrawal symptoms, and reduce dropout rates.

22 Therapeutic drug monitoring in the opioid substitution treatment

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Opioid substitution treatment (OST) is an evidence-based intervention and different substances are available nowadays as a treatment option. Methadone, a long-acting synthetic opioid, is available e.g. for more than 40 years and was the first widely used opioid for the treatment of heroin dependence, e.g. in

Switzerland since 1975. The Swiss Federal Office of Public Health does not provide any information on the therapeutic reference range in its summary of medical recommendations "Substitution-assisted treatment of opioid dependence". The German S3 guidelines "Medication-related disorders" mentions Therapeutic Drug Monitoring (TDM) and refers to the current "Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017" in which the recommendation levels for the use of TDM are listed. The level of recommendation in the OST differs from substance to substance and is e.g. for methadone (level 2: recommended) the same as for the atypical antipsychotics aripiprazole or risperidone. In fact, TDM for OST still is insufficiently integrated into clinical routine. The new S3 guideline "Opioid-related Disorders" is expected this year and is registered by the Association of the Scientific Medical Societies in Germany (AWMF).

Our pharmacotherapeutic approaches tend to be schematic, which means that individual patient differences (e.g. regarding gender, body weight, liver and kidney function etc.) are not considered in treatment processes. TDM is a precision medicine tool that can enable clinicians to optimize and individualize ongoing treatment with psychotropic medications, including pharmacotherapy for substance use disorders.

23 Pharmacogenetics in Psychiatry: Precision medicine or 'mystic, magic, and mysterious'?

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Prescribers and patients are frequently facing the challenge that treatment standards established at a population level might not be beneficial at the individual level. As a result, lengthy trials are often required before the optimum psychiatric medication treatment, single or in combination, is found. The underlying reasons for this large inter-individual variability treatment outcomes are not fully understood. Important factors that influence drug dose, response and side effects include age, gender, patient compliance, clinical symptoms, co-morbidities, lifestyle, ancestry and genetic factors. In this context, first strategies using pharmacogenetic (PGx) information bear the promise to optimize medication treatment in clinical practice. State-of-the-art summaries of key concepts and strategies of psychiatric PGx need to consider: 1) Reviews of the evidence, clinical utility and studies including randomized clinical trials of distinct gene-drug pairs; 2) Discussion of current expert recommendations (e.g., Clinical Pharmacogenomics Implementation Consortium); 3) How PGx information can be best used in clinical practice, in particular to avoid pseudo-resistance for antidepressants 3) Highlighting ongoing implementation efforts and 5) providing practical support for psychiatrists and pharmacologists.

24 International Guidelines of pharmacogenetic testing focusing on pharmacokinetically relevant genes and there relevance in neuropsychopharmacology

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In 2020, the European Medicines Agency (EMA) recommended that patients have to be tested for the absence of the enzyme dihydropyrimidine dehydrogenase (DPD) before starting systemic cancer therapy with fluorouracil or related drugs. The international guidelines clearly refer to genotype-based dose adjustment or strict avoidance of these drugs if the genotype predicts a non-functioning DPD phenotype. This is one of the most recent examples of the use of pharmacogenetic (PGx) testing for a pharmacokinetically relevant gene in clinical medicine. Fortunately, there is no neuropsychopharmacological substance with a comparable toxicity potential, but we can learn from this application. International guidelines recommend genetic testing of pharmacogenetically relevant genes for several neuropsychopharmacological drugs, e.g. tricyclic antidepressants. The guidelines not only recommend genetic testing for specific drugs, but also include recommendations for genotype-related dose adjustment.

There is no doubt that phenotype-related, i.e. TDM-guided dose adjustment is the ideal way to optimize individual drug doses. However, in patients who show unexpected dose-dependent concentrations or unusual metabolic ratios without pharmacokinetic interactions, genotyping is strongly recommended. Apart from these cases, recent data show that genotyping-guided selection of a neuropsychopharmacological drug leads to a better therapeutic outcome. Thus, genotyping in neuropsychopharmacology appears to be an efficient tool for individualizing drug therapy that complements TDM.

25 Pharmacogenetic testing for selection of antidepressant treatment

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Major depressive disorder (MDD) is one of the most prevalent mental health disorders worldwide, implicating a huge burden for patients and society. Antidepressants represent an essential treatment option. However, more than 50 % of the patients do not respond to the first prescribed antidepressant. Therefore several treatment trials are necessary to find the right antidepressant for a specific patient in the clinical context. In addition, adverse effects may occur in more than 25 % of antidepressant-treated patients. In this context pharmacogenomic testing may represent a tool to match the individual patient with the right antidepressant and to enhance response-rate and tolerability. Pharmacogenomic decision support tools may help clinicians to select a medication based on clinically actionable variants in pharmacokinetic and pharmacodynamic genes. Guidelines exist for the use of pharmacogenomic testing to support antidepressant selection to enhance safety and tolerability, with robust evidence for genetic variants of the CYP450 enzymes such as CYP2D6 and CYP2C19. Meanwhile, three large controlled studies with more than 3,200 patients with MDD investigated the benefit of pharmacogenetically guided selection of antidepressants. While a significant benefit could not be observed, there was some evidence favoring the pharmacogenetic testing in the analysis of secondary outcome measures. Thus large-scale pharmacogenomic trials are needed to strengthen precision medicine approaches for the management of MDD.

26 PGx and/or TDM? How could they interact in daily practice?

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Functional differences for the metabolising enzymes can have a direct influence on the pharmacokinetics of the psychotropic drugs and thus affect the plasma levels.

Under the standard dose, it is possible that a slow metabolic rate may result in overdosing effects with the corresponding tolerability problems or pharmacokinetically induced loss of effect if the metabolic rate is too high.

An additional complication arises from the fact that psychotropic drugs act as a mixture of parent substance and various metabolites. If individual components have their own spectrum of effects and side-effects, patient-specific differences regarding metabolism may lead to different tolerability and efficacy/effectiveness outcomes related to themedication.

These metabolic differences can be related to interactions with other drugs, food, smoking, etc., or can be pharmacogenetically determined as "innate interactions" in patients (phenoconversion).
Pharmacogenetic differences in treatment with psychotropic drugs can now be assessed and therefore drug therapy be better adapted in individual patients. Dose guidelines from international specialist groups are available for this purpose. Therapeutic drug monitoring allows level deviations potentially underlying unsatisfactory treatment outcomes to be directly detected.
Since the effects of pharmacogenetic variants and other interactions have an essential impact on drug metabolism, assessing for pharmacogenetic abnormalities is just as useful as the assessment of other interactions and patient adherence.

Poster Abstracts

27 Sertraline concentration in serum unaffected by hemodialysis: a case report

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About 20 % of patients receiving hemodialysis (HD) show clinical signs of major depressive disorder (MDD). However, end-stage renal disease (ESRD) or HD are often exclusion criteria for clinical studies. Due to that, publications regarding treatment efficacy and pharmacokinetics are rare for this population.
We report the case of a female inpatient with MDD and ESRD (GFR <10ml/min/1,73qm) receiving HD three times a week. We started sertraline and monitored response to therapy using Hamilton Depression Rating Scale (HAMD-21, 21-item-version) and Beck Depression Inventory (BDI). Additionally, we conducted therapeutic drug monitoring (TDM) before and after HD. We then genotyped CYP2C19 as the main metabolizing enzyme of sertraline.
Sertraline serum concentrations were within or slightly above the established range for patients without HD. Intermediate metabolizer genotype (IM-GT) was determined. Our patient responded well to the antidepressive therapy (HAMD 33 at admission HAMD 5 at discharge). Additionally, both blood pressure and need for further pain medication decreased.
Our case report suggests that HD has none or only limited effect on sertraline serum concentration. IM-GT status is likely to be the explanation for the slight elevation measured in serum concentration. Sertraline seems to be an effective treatment option in MDD patients undergoing HD. Additionally blood pressure and need for analgetics improved. Studies with higher numbers of patients are needed to prove effectiveness and acceptability of sertraline in MDD patients during HD.

28 Systematic review on blood concentrations of ADHD medications in children and adolescents

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We present the current results of a systematic review of studies about the use of therapeutic drug monitoring (TDM) for methylphenidate, amphetamine, atomoxetine and guanfacine in the treatment of ADHD and the calculation of the respective preliminary therapeutic reference ranges in children and adolescents.
The study analyzed all TDM studies published until April 2023 (Medline) using the following inclusion criteria: Age under 18 years, assessment of responder status and measurement of maximum blood concentrations (Cmax). Cmax was used to determine potential therapeutic reference ranges by calculating the mean and SD and the median and 25th/75th percentiles.
The results on these four ADHD medications provide preliminary recommendations for therapeutic reference ranges that can be used as a reference for TDM in children and adolescents with ADHD.

29 Therapeutic drug monitoring in children and adolescents using quetiapine for the treatment of schizophrenia and other psychotic disorders – results of a pharmacovigilance study

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Despite quetiapine is increasingly used 'off-label' in children and adolescents, knowledge on its efficacy and safety is rare and no age-specific therapeutic reference ranges (TRR) have yet been established. The aim of this study was to elucidate whether the TRR described for adults is applicable in minors. Furthermore, the relationship between daily dose, serum concentration and clinical outcome of quetiapine in children and adolescents were investigated.
Data from 77 patients, recruited within the multicentre TDM-VIGIL study *, aged between 12 and 17 years were evaluated. Patient characteristics, medication data, doses, serum concentrations and therapeutic outcomes were assessed using standardised measures.
A positive correlation was observed between weight-adjusted daily dose and serum concentration (r_s = 0.580, p < 0.001), with dose variation explaining 34 % (r_s^2 = 0.34) of the variability in quetiapine concentrations. Generally, good clinical effectiveness, comparable to results described in adults, was observed and most patients (88.9 %) experienced no or mild adverse drug reactions. A positive relationship between serum concentration and therapeutic effect was found (r_s = 0.238, p = 0.006). 38.5 % of all serum concentrations were within the recommended TRR described for adults (100-500 ng/ml). A rough calculation method hinted on a considerably lower TRR for minors (14– 290 ng/ml) compared to adults.
This study may contribute to the definition of a TRR for quetiapine in minors, yet further controlled studies with larger sample sizes are needed to verify and strengthen preliminary results.

30 Therapeutic reference range for duloxetine in the treatment of depression revised: a systematic review and meta-analysis

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For duloxetine, a therapeutic reference range (TRR) of 30–120 ng/ml is recommended to attain an optimal antidepressant effect [1]. However, the concentration-effect relationship, which forms the basis of the TRR, lacks systematic investigation. Therefore, the current range is considered preliminary. This review investigates the optimal target concentration for duloxetine's antidepressant effects and identifies factors moderating its blood concentrations.

A systematic literature review and meta-analysis was performed. Four databases were systematically searched for relevant articles reporting duloxetine concentrations in relation to clinical effects/side effects, pharmacokinetics, or receptor occupancy.

11 studies were eligible for qualitative analyses. Evidence for a positive relationship between blood concentrations and antidepressant effect was found in three studies; a concentration-dependent occurrence for the side effect irritability/anxiety was found in one study. Across four studies (N = 223), the population-based concentration ranges were 22–67 ng/ml. A threshold of 58 ng/ml was identified for clinical response. 75 percent of responders had blood concentrations below 123 ng/ml. PET studies reported 80 % serotonin transporter occupancy at blood concentrations above 10–15 ng/ml, whereas 50 % norepinephrine transporter occupancy were reported above 58 ng/ml. Smoking and specific medications led to significantly lower duloxetine blood concentrations.

We suggest a TRR of 20–120 ng/ml for the antidepressant effect of duloxetine. Treatment effectiveness is likely influenced by smoking and specific comedications. This warrants a special indication for therapeutic drug monitoring of duloxetine, particularly when newly prescribed.

31 Therapeutic reference range for clozapine plasma levels when prescribed in patients with Parkinson's disease or dementia: a three-center cohort study and meta-analysis

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Clozapine is a common drug in the treatment of psychotic symptoms in patients with Parkinson's disease (PD) and dementia. However, the therapeutic reference range for clozapine levels in plasma or serum for PD and dementia has not been established so far.

The study was performed in three university hospitals in Germany and Switzerland; each study site was analyzed separately. Patients with PD or dementia treated with clozapine were included. The primary outcome was safety based on reports of adverse drug reactions (ADRs), changes in laboratory test or electrocardiogram, or clozapine discontinuation. We meta-analyzed differences regarding demographic and pharmacokinetic parameters in patients tolerating clozapine well vs. not. A meta-analytic summary receiver operating characteristic (SROC) to establish the clozapine blood level cut-off associated with safety issues was estimated.

Safety problems were reported in 26 (26.3 %) patients from a total of 99 included. Comparing patients with vs without safety problems, we found no difference regarding age (p = 0.3), body mass index (p = 0.5), sex (p = 0.9), smoking status (p = 0.9), or clozapine daily dose (p = 0.3). We found a medium-effect trend of increased clozapine blood concentration in patients with safety problems (Standardized mean difference 0.46, 95 % confidence interval -0.04 – 0.96, p = 0.07). Clozapine blood levels above 193 ng/mL were associated with safety problems (SROC 0.6, sensitivity 39.7 %, specificity 79.9 %).

One out of four patients with PD or dementia treated with clozapine did not tolerate clozapine well. Therapeutic drug monitoring may be used to predict tolerance problems in these patients.

32 Venlafaxine serum concentrations in children and adolescents – preliminary results of a multicenter Therapeutic Drug Monitoring trial

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Venlafaxine is approved in adults to treat depression, anxiety or panic disorders, while its use in children and adolescents is off-label. Our study aimed to examine the relationship between dose and serum levels of venlafaxine and its active metabolite O-desmethylvenlafaxine (active moiety, AM) to explore a potential age- and indication- specific therapeutic reference range (TRR) in pediatric patients.

Steady state serum concentrations of AM venlafaxine were measured in 104 patients (76 % female, mean age 15.9 years) as part of a Therapeutic Drug Monitoring service and within the TDM-VIGIL pharmacovigilance trial. Clinical outcome was assessed by the Clinical Global Impression Scale; side effects by the Udvalg for Kliniske Undersogelser-Side Effect Rating Scale.

The study showed a positive correlation between dose and serum concentrations of AM venlafaxine (rho = 0.515, p < 0.001). 63.5 % of the serum levels lied within the proposed TRR for adults (100 –400 ng/ml). Parameters like age, sex, and comedication did not significantly influence serum levels. 21.5 % of the patients were rated as responders (3.9 % very much improved, 17.6 % much improved), 78.4 % were reported as minimally improved. More than half of the patients experienced no adverse effects (54.9 %). The determined age-specific TRR for venlafaxine in children and adolescents ranged between 100-381 ng/ml (mean serum level +/- SD) or between 145-294 ng/ml (25th-75th percentile) and thus within the recommended range for adults.

In summary, the TRR established for adults, especially the upper limit, should be used with caution in children and adolescents. Further studies with larger samples and under controlled conditions are needed to confirm our results.

33 Equal contribution of pharmacogenetic phenotype and phenoconversion to functional CYP2D6 metabolizer status

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Pharmacogenetics (PGx) of CYP2D6 is gaining more importance in routine clinical settings. CYP2D6 is susceptible to inhibition. Thus, including phenoconversion effects (PC) in result interpretation may maximize precision benefits of PGx. However, studies including the functional enzyme status (PC-informed PGx) are lacking.

We aimed to investigate how the CYP2D6 functional enzyme status affects serum concentrations of psychotropic drugs. Using clinical routine data allows an evaluation of the relevance of this information for patient care.

Two patient cohorts (total n = 316) were investigated for the CYP2D6 functional enzyme status and the associations with serum concentrations of venlafaxine, amitriptyline, mirtazapine, sertraline, escitalopram, risperidone and quetiapine.

When including PC, we found an increase in rates of CYP2D6 intermediate and poor metabolizers, as well as a decrease in normal metabolizers. Moreover, we found associations between amitriptyline serum concentration with the PC-corrected activity score of CYP2D6, and risperidone concentration with CYP2D6 functional enzyme status, as well as between metabolite-to-parent ratio of venlafaxine and risperidone with CYP2D6 functional enzyme status.

The data show the relevance of PC-informed PGx in psychopharmacological treatment. PC should be included in PGx result interpretation, to start with a dose adequate to the respective CYP2D6 functional enzyme status, especially before initiating amitriptyline- or risperidone-treatment. Moreover, PGx and therapeutic drug monitoring should be used complementary but not alternatively.

34 Drug-drug interaction between hydroxybupropion and venlafaxine – a pharmacokinetic study on CYP2D6

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Recently, a study showed a dose-dependent inhibition of CYP2D6-mediated metabolism of venlafaxine by bupropion without reporting associations with serum concentrations.

We aimed to investigate the inhibitory effects of bupropion on the pharmacokinetics of venlafaxine, considering not the dose, but the serum concentration of bupropion. Moreover, we aimed to define a threshold in the serum concentration of hydroxybupropion to predict the CYP2D6 poor metabolizer status.

Inpatients with available therapeutic drug monitoring results for venlafaxine and hydroxybupropion were included in the analysis. One sided Spearman correlation was used to test for associations between the hydroxybupropion concentration and the active moiety concentration of venlafaxine, and between the hydroxybupropion concentration and the metabolite-to-parent ratio (MPR) of venlafaxine. Receiver operating characteristic analysis was used to define a threshold in the concentration of hydroxybupropion to predict the CYP2D6 PM status.

A total of 91 patients were included in the analysis. Serum concentration of hydroxybupropion were positively associated with active moiety serum concentrations of venlafaxine ($p = 0.001$), and negatively with the MPR ($p = 0.02$). A switch from CYP2D6 non-PM to PM could be expected for a minimum concentration of hydroxybupropion of 328.5 ng/mL.

We found an increase of the serum concentration of the active moiety of venlafaxine and a decrease of the MPR with increasing hydroxybupropion concentrations. However, as the threshold for phenoconversion to CYP2D6 PM was lower than the mean concentration for the minimum effective dosage of bupropion (150 mg), phenoconversion must be expected in any patient taking bupropion together with venlafaxine, or another CYP2D6 substrate.

35 PET-derived modelling of D2-receptor occupancy of antipsychotic polypharmacy in patients with schizophrenia

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Treatment with combinations of antipsychotics is common clinical practice. Approximately 20 – 30 % of all patients treated with antipsychotics take two or more antipsychotic substances simultaneously. The evidence supporting the benefit of antipsychotic combination treatment is limited.

There are almost no positron emission tomography (PET)-imaging studies that explored the effect of antipsychotic combination treatment on striatal D_2-dopamine receptor occupancy. However, D_2-receptor occupancy for most antipsychotics can be predicted from a single antipsychotic plasma level.

We present a new developed model for calculating receptor occupancy during antipsychotic polypharmacy (APP).

The receptor occupancy of a single psychopharmacological agent can be derived from the serum concentration C based on the law of mass action:

With this study, we outline a modelling approach that derives the striatal D_2-dopamine receptor occupancy of antipsychotic combination treatment from experimental PET data. Under the premise of this modelling approach, we show that most antipsychotic combinations might exceed the 65 – 80 % window of D_2-dopamine receptor occupancy in the clinical practice.

Our model reveals that treatment with antipsychotic combination has to be clinically evaluated. Consequently, when using antipsychotic polypharmacy, reference ranges should be adjusted and lower dosages used.

36 Elevation of alpha-1 acid glycoprotein during acute infection increases clozapine levels without signs of intoxication

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The monitoring of plasma levels of clozapine – one of the most effective antipsychotics – is highly recommended. Acute inflammatory processes can increase clozapine levels. Alpha-1 acid glycoprotein (AGP), an acute phase protein that significantly increases during inflammation, could also play a role in explaining the link between inflammation and clozapine concentration. This is the first case report that directly compares clozapine levels with AGP levels during an acute infection in a patient under continuous clozapine treatment.

A 58-year old male patient was treated with clozapine because of paranoid schizophrenia. The control laboratory examination detected a rise in clozapine levels up from 405 ng/ml to 1538 ng/ml under continuous treatment with 200 mg of clozapine per day. An influenza-A virus infection was detected by a smear test. AGP, Alpha-antitrypsin-1 (AAT) and C-reactive protein (CRP) were measured over the course of 14 days. An ANOVA was applied using CRP, AGP, and AAT as independent variables and clozapine concentration as dependent variables.

AAT, CRP, and AGP revealed a significant effect only for AGP upon clozapine levels, whereas CRP and AAT did not reach significance ($p > 0.05$). Post hoc regression demonstrated a significant association between AGP and clozapine concentration at $p < 0.0001$.

Clozapine has been reported to be predominantly bound to AGP, suggesting a causal relationship between elevated AGP and clozapine levels in our case. This could explain the absence of clozapine intoxication symptoms despite the total clozapine levels being as high as 1538 ng/mL.

37 Fluvoxamine serum concentrations in children and adolescents – preliminary results of a multicenter Therapeutic Drug Monitoring (TDM) trial

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The selective serotonin reuptake inhibitor fluvoxamine is used on- and off-label in the treatment of children and adolescents with psychiatric disorders. To investigate the relationship between fluvoxamine dose, serum concentration and clinical outcomes in daily clinical practice, and to validate a therapeutic reference range (TRR) in pediatric patients, multicenter prospective and observational study data were analyzed.

Steady state through serum concentrations of fluvoxamine were measured in pediatric patients as part of a therapeutic drug monitoring service (n = 60) and within the TDM-VIGIL pharmacovigilance trial[2] (n = 10). Patient characteristics, doses, serum concentrations, and therapeutic outcomes were assessed by standardized measures.

Seventy children and adolescents (54.3 % female, mean age 14.8 years), 55.2 % diagnosed with obsessive compulsive disorder (OCD) were included. A positive correlation between daily dose and fluvoxamine concentrations was found ($r_s = 0.34$, $p = 0.004$). Gender, age, and concomitant medications had no significant effect on fluvoxamine concentrations. Using a rough estimation-method considering only responders to fluvoxamine, we estimated a transdiagnostic TRR for minors of 40-240 ng/ml (comparable to the TRR of adults 60-230ng/ml), which might be higher for patients with OCD (55-300ng/ml).

Our preliminary results may contribute to a TRR of fluvoxamine in children and adolescents and further establish TDM in child and adolescent psychiatry.

38 Serum Levels of Methylphenidate and Efficacy Measures in Children With Attention-Deficit/Hyperactivity Disorder After Crossover Intake of Ritalin LA and Medikinet retard in a Classroom Setting.

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Aim of this study was to determine the serum levels of methylphenidate and efficacy measures after intake of Ritalin LA and Medikinet retard. Patients with attention-deficit/hyperactivity disorder (ADHD) were assigned in a laboratory classroom-setting.

24 boys, aged 8 to 14 years took part in this single blind, randomized, two-period crossover study. All patients were diagnosed with ADHD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Ritalin LA 20 mg and Medikinet retard 20 mg were given for 7 days each, the classroom setting was on day 7. The Swanson, Kotlin, Agler, M-Flynn, and Pelham (SKAMP) scale and math tests were used to determine the drug's efficacy. Liquid chromatography-mass spectrometry (LC-MS/MS) was performed to measure serum levels of MPH. Blood samples were taken at ten different times on each classroom day. Efficacy parameters were assessed at seven times each classroom day.

The complete determination of the pharmacokinetic parameters could be performed for 20 patients. The mean Cmax serum MPH concentration for Ritalin LA was 18.3 ± 8.7 ng/ml compared to Medikinet retard 22.6 ± 9.3 ng/ml. The mean AUC (0 – 8 h) serum MPH value for Ritalin LA was 93.1 ± 57.2 ng/ml/h compared to Medikinet retard 111.4 ± 45.8 ng/ml/h. MPH concentrations have formed two distinctive peak levels. In a cross-over analysis, the SKAMP Scales showed no significant treatment effects. For both medications, no serious adverse events could be observed.

An analogue classroom setting provides a reliable parallel assessment of behavioral and pharmacokinetic data. Pharmacokinetic data showed remarkable inter-individual variations. In both medication groups, the pharmacokinetic profiles have revealed two distinctive peak levels in some patients.

39 Medical and economic benefits of routinely requested therapeutic drug monitoring of antidepressants

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In psychiatry, therapeutic drug monitoring (TDM) is highly-recommended for a group of psychotropic drugs. Information about the cost-effectiveness of TDM is mainly lacking. We aimed to investigate if routinely requested TDM at admission to hospital offers an advantage with regard to the duration of hospitalization compared to patients where TDM was requested during their stay in hospital.

Patients with TDM for antidepressant drugs during the years 2015-2021 were assessed for analyses, retrospectively. The first TDM request of patients with depressive symptoms (F32/F33), and a duration of hospitalization of at least 7 days were included. Mann-Whitney-*U* test was used to test for differences between the duration of hospitalization attributed to the time of TDM.

When TDM was requested at admission, patients (N = 417) had a significantly shorter stay in hospital compared to patients for whom TDM was requested during their hospitalization (N = 673; p = 5.04 * 10^{-4}).
Due shorter hospitalization duration by in average 5 days, requesting TDM for antidepressants routinely at admission has not only medical, but also economic benefits. In conclusion, in patients with depressive symptoms treated with antidepressants, we suggest routine TDM at admission to individualize antidepressant therapy.

40 Update on dose-related reference ranges for psychotropic drugs

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Dose-related reference ranges (DRRs) are substance and dosage form specific blood concentration ranges predicted for a given dosage. Comparing measured blood concentrations with these calculated ranges enables the detection of pharmacokinetic peculiarities or compliance issues. Previously, a validated methodology to calculate DRRs was published. This presentation will illustrate what pitfalls should be considered when using the validated method to calculate DRRs for the update of the AGNP TDM guidelines.
Pharmacokinetic parameters and product informations were extracted from literature. For calculation of new DRRs, an updated methodology was used.
The validity of a DRR is determined by the methodology used and the statistical dispersion around the pharmacokinetic parameters that define its limits. Indeed, these limits must be defined to precisely reflect the pharmacokinetic data of so-called normal patients. The most robust approach to derive valid pharmacokinetic parameters is a well-conducted systematic literature review including a meta-analysis of extracted data. In cases where a systematic literature review is not feasible or when pharmacokinetic data are limited, less sophisticated methods can be used to approximate the DRR.
Methodological shortcomings in the calculations of DRRs pose the risk of systematic misinterpretation of Therapeutic Drug Monitoring data. Recalculations of current DRRs have been performed and findings are presented in this work. Ranges calculated in the future should account for subgroups with distinct pharmacokinetic properties (i.e. elderly or comorbid patients).

41 Haloperidole serum concentrations in daily child and adolescent psychiatric practice

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The highly potent antipsychotic haloperidole is used as third-line treatment for childhood schizophrenia, Tourette's syndrome as well as severe behavioral symptoms in children and adolescents with autism spectrum disorders or mental retardation. Aim of the study was to investigate the relationship between haloperidole dose and serum concentration as well as to generate information about a possible age-specific therapeutic reference range (TRR) in pediatric patients.
Steady state through serum concentrations of haloperidole were measured in pediatric patients in daily clinical practice as part of a routine drug monitoring service. Patient characteristics, doses, and therapeutic outcomes were assessed by standardized measures.
39 patients (64 % male, mean age 15.6 years), mainly diagnosed with paranoid schizophrenia were included. A positive correlation between haloperidole daily dose and concentration was found (r_s = 0.37, p = 0.02). Using a rough estimation-method considering only responders to drug therapy a transdiagnostic TRR for minors of 1.9 – 6 ng/ml was calculated (comparable to the current suggested TRR of adults 1–5 ng/ml).
Our preliminary results may contribute to define a TRR of haloperidole in adolescents and support to further establish TDM in child and adolescent psychiatry.

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