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1 Case report: Major depression and Therapeutic Drug Monitoring in patient with CYP2C19 genetic polymorphism

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Introduction Several CYP2C19 genetic polymorphisms are described to be associated with ultrarapid (UM) or poor drug metabolism (PM), inducing treatment resistance and/or adverse drug events, and might therefore be related to pharmacoresistant severe mental health disease.

This case report presents a female 61-year old, in-patient, suffered from drug resistant severe major depression (ICD-10, F33.2). Antidepressant drugs like mirtazapine, duloxetine were changed before. Low serum levels of sertraline in steady-state were monitored during psychiatric care.

Methods Clinical course documentation, therapeutic drug monitoring with low-serum level concentration of sertraline in steady-state and dose related, medical imaging (cMRT, EEG).

Results Low-serum level sertraline were < 4,88 µg/ml (10–150 therapeutic range), desmethylsertraline 22,8 µg/l, ratio N.N (1,7–3,4) after four weeks, and two weeks later sertraline were 5,4 µg/l, desmethylsertraline 26,8, ratio 4,96 (1,7–3,4). In the clinical documentation the patient suffered from resistant-symptoms of major depression like anhedonia and apathy.

Gene duplication associated with UM has been found at CYP2C19 (duplet of alleles CYP2C19 * 17/ * 17).

Conclusion In this case report we demonstrate consequent therapeutic drug monitoring as an option to identify high-risk patients with genetic polymorphisms.

Nevertheless, knowledge of individual metabolism and in particular CYP2C19 genotyping should be considered for clinical workup and therapy adjustment in resistant patients in adolescent psychiatry and might permit better treatment outcome, increased treatment adherence and diminished adverse drug events.

2 Drug interactions in patients undergoing opioid maintenance therapy

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Introduction Patients undergoing opioid maintenance therapy (OMT) have a high rate of additional consumption of cannabis and of somatic (especially hepatitis virus infections) and psychiatric comorbidities. Cannabis interferes with Cytochrome P 450 (CYP) isoenzymes and seems to be a potential inhibitor of CYP3A4 and by this may lead to drug-drug interactions. Buprenorphine (BUP), a partial µ-opioid agonist widely used for opioid maintenance therapy (OMT) is mainly metabolized to pharmacologically active norbuprenorphine by CYP3A4. We present OMT patient data of cannabis use on BUP plasma levels with and without psychiatric comedication duloxetine, trazodone. Further an OMT woman before and after successful hepatitis c treatment.

Methods 1. Retrospective analysis of clinical symptoms and of BUP and nor-BUP plasma levels in liver healthy OMT patients substituted with BUP, either with (n = 15) or without (n = 17) concomitant use of cannabis. 2. Analysis of BUPs and antidepressant drug plasma levels of a female OMT patient in various stages of hepatitis virus disease and with and without cannabis use.

Results 1. Cannabis users and non-users received similar doses, but users had 2.7-fold higher concentrations of BUP (p < 0.01) and 1.4-fold for nor-BUP (1.4-fold, p = 0.07). The metabolite-to-parent drug ratio was 0.98 in non-users and 0.38 in users (p = 0.02) with no significant effect of gender. 2. During cannabis abstinence a higher plasma level of duloxetine and trazodone could be found.

Conclusion Cannabis use decreases the formation of nor-BUP and elevates BUP and nor-BUP concentrations and lowers blood plasma levels of duloxetine and trazodone most probably by inhibition of CYP3A4. TDM can detect interaction effects by comedication and/or coconsumption of drugs.

3 Therapeutic drug monitoring in relapse prevention of alcohol dependent patients

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Introduction Despite the high prevalence of alcohol dependence (AD), only a few medications are approved for AD treatment, such as naltrexone, acamprosate and disulfiram. These treatments suffer from modest effect sizes, limited patient compliance and low impact on clinical practice [1, 2]. Hence, there is an urgent need for improvement of AD pharmacotherapy. Such improvements could arise from the optimization using therapeutic drug monitoring (TDM).

Methods Naltrexone and 6 β -naltrexol levels were analyzed at weeks 4, 8 and 12 using liquid chromatography in 43 patients with AD who were treated with 50 mg naltrexone daily in the framework of a randomized-controlled clinical trial. In addition, alcohol craving intensity was assessed using the Obsessive-Compulsive Drinking Scale (OCDS). In addition, we conducted a literature review of TDM studies in AD.

Results Plasma levels of naltrexone and its metabolite showed a high inter-individual variability and correlated negatively with OCDS craving scores ($\beta = -0.341$, $p = 0.014$). Group comparisons indicated that patients, which experienced a significant reduction in alcohol craving by 70% had higher naltrexone and 6 β -naltrexol plasma levels ($p = 0.045$). Receiver operating characteristics analyses found that alcohol drinking reduction was significantly higher when plasma concentrations of naltrexone plus 6 β -naltrexol were above 16.6 ng/ml. Results of the literature review highlight the potential of TDM for naltrexone and disulfiram in AD.

Conclusion Results show that plasma levels of relapse-preventing pharmacological agents, such as naltrexone, can predict treatment response in AD patients and thus highlight the potential utility of TDM to optimize AD treatment.

Conflict of Interest None.

References

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4 Mood stabilizers during pregnancy – significance of therapeutic drug monitoring

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Introduction Using a mood stabilizer can be essential for pregnant women suffering from bipolar disorder to protect them from relapse. However, every prescription for psychotropic drugs during pregnancy must be subjected to a critical assessment of the benefits and risks for the mother and the embryo and/or fetus. Depending on the substance, intrauterine exposure to mood stabilizers is associated with different teratogenic risks, whereby the serum concentration of the substance can be decisive. As physiological changes during pregnancy can lead to changes in drug concentrations, therapeutic drug monitoring (TDM) may be indicated to minimize risk.

Methods The literature indexed on PubMed was searched for original observational studies, case reports, and case series that evaluated or described TDM of mood stabilizers during pregnancy.

Results Pregnancy-related changes in absorption, distribution, metabolism, and elimination are associated with significant and clinically relevant changes in plasma concentrations of mood stabilizers. This applies to varying degrees to lithium, lamotrigine, carbamazepine, and valproate, but also to the atypical antipsychotics used as mood stabilizers. While plasma concentrations of lithium and valproate decrease, they increase significantly for lamotrigine during pregnancy; the plasma concentrations of carbamazepine remain largely unchanged. Moreover, levels of most atypical antipsychotics used as mood stabilizers decrease during pregnancy.

Conclusion Since pregnancy-related physiological changes may result in significant and clinically relevant changes in plasma concentrations of mood stabilizers, optimal dose management during pregnancy is essential to reduce the risk of relapse. Therefore, therapy with mood stabilizers during pregnancy should be guided by TDM.

Conflict of Interest The author has no conflict of interest to declare.

5 Escitalopram: Drug monitoring for dose titration? Systematic literature review on the therapeutic and the dose-related reference range

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Introduction For the antidepressant drug escitalopram, current guidelines recommend Therapeutic Drug Monitoring for dose titration within a blood concentration range of 15-80 ng/ml [1]. This systematic review discusses the evidence for the validity of escitalopram's reference range and evaluates the association between blood levels, clinical effects and serotonin transporter (SERT) occupancy.

Methods Four databases were searched (Update March 2022) for relevant articles following our previously published protocol [2]. Evidence for a certain

concentration/effect relationship was graded into a level. Mean concentrations were extracted from studies and 25-75% interquartile ranges computed.

Results Of 1032 abstracts screened, a total of 31 studies met the eligibility criteria; 10 of these reported clinical effects, 12 reported escitalopram blood concentrations, and 9 studies used SPECT or PET neuroimaging. A positive relationship between escitalopram blood concentration and response was described in one study (Level C; low). ROC analysis suggests a threshold of 20 ng/ml for antidepressant response. Three PET studies report EC₅₀ values around 17 ng/ml. No concentration-dependent side effects were found. None of the reviewed studies examined a TRR for escitalopram. The interquartile range across seven studies was 15-39 ng/mL.

Conclusion The evidence for a concentration/ effect relationship for ESC is low. However, from current evidence we suggest a target range of 15-40 ng/mL for optimal antidepressant efficacy.

[1] Hiemke C., Bergemann N., Clement H.W. et al. Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017. *Pharmacopsychiatry*, (2018); 51(1-02), 9-62

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6 Discussion: Genotyping in real life setting

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The drug metabolism of individual people sometimes differs greatly. In the past, pharmacogenetic characteristics of patients increasingly came into focus as triggers for deviations in efficacy and side effect rates in drug therapy.

The availability of a growing number of concrete dose guidelines, as a sign of an ever increasing accumulation of evidence, makes it possible that today pharmacogenetic diagnostics can be applied more and more easily in daily clinical routine.

The greatest challenge is no longer the costs or the analytics itself, which can provide results within a very short time for an three-digit amount of Euros, but rather the transfer of the complex results into a format that makes it possible to obtain the most concrete information possible, on the basis of which therapy can then be adjusted.

This raises the question of what the ideal indication for such diagnostics is, when they should be used in the course of therapy and what kind of patient could benefit most? Should only unexplained plasma levels be clarified by pharmacogenetics or should such diagnostics already be used in the initial phase of therapy? What is the best way to consider 'innate' and facultative interactions (= drug interactions) simultaneously? The question is changing more and more from whether to test to when it is best to test and who benefits most.

In the lecture, these points will be presented and discussed as examples.

7 Serious adverse drug reactions to antipsychotics in children and adolescents with multiple disabilities: Avoidability and potential cost savings by Therapeutic Drug Monitoring

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Introduction Children with multiple disabilities and mental illnesses are frequently treated with antipsychotics because of 'challenging behavior'. However, these patients are particularly susceptible to serious adverse drug reactions (sADRs). This retrospective study examined the frequency of sADRs referring to antipsychotics in minors with multiple disabilities and mental illnesses and the potential avoidability of these sADRs through therapeutic drug monitoring (TDM), as well as the potential socio-economic benefits of TDM.

Methods Patients treated at a special child and adolescent psychiatric clinic for pediatric patients with multiple disabilities between January 2017, and December 2018 were retrospectively examined on the basis of the patient file for the occurrence of sADRs (definition according to European Medicines Agency), their causality with antipsychotic treatment as well as their avoidability (Schumock criteria). Furthermore, the prolongation of the hospital stay due to sADRs was calculated as well as the cost savings estimated if TDM had been applied.

Results 102 children and adolescents who were administered at least one antipsychotic drug during inpatient treatment were identified. In 22 (21.6%) of these patients sADRs were documented with at least a possible causal relationship with the antipsychotic treatment. Eleven sADRs (50%) would have been potentially avoidable through TDM. Mitigating ADRs through TDM would have led to shorter hospitalization and thus considerable savings for health insurance companies.

Conclusion The routine implementation of TDM is urgently recommended for antipsychotic treatment in minors with multiple disabilities and mental disorders to increase drug therapy safety for this vulnerable patients.

8 Is Therapeutic Drug Monitoring Relevant for Antidepressant Drug Therapy? Implications From a Systematic Review and Meta-Analysis With Focus on Moderating Factors

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Introduction Efficacy and safety of antidepressant drug therapy may be limited by inter-individual differences in antidepressant drug concentration. Accounting for this inter-individuality, Therapeutic Drug Monitoring (TDM) enables clinicians to adjust antidepressant dosage based on individual information on antidepressant concentration attained in blood. However, research on the basic assumption of TDM, association between antidepressant concentration and effect, has yielded ambiguous results. It has been argued, that this ambiguity may be caused by methodological shortcomings in studies investigating the relationship between antidepressant concentration and effect.

Methods A systematic review and meta-analysis of randomised controlled trials (RCTs) investigating the association between antidepressant concentration and clinical outcomes (efficacy and side effects) will be presented. Furthermore, the investigation of methodological characteristics of primary studies as potential moderators of the antidepressant concentration-effect relationship will be addressed in the presentation.

Results The association of antidepressant concentration and effect is significantly moderated by methodological characteristics of primary studies. It will be presented, that the use of a flexible dose design as well as the exclusion of concentrations in lower – or subtherapeutic ranges significantly moderate the relationship between antidepressant concentration and effect.

Conclusion The results provide the first statistical evidence for the impact of methodological characteristics of primary studies on the relationship between

antidepressant concentration and efficacy. These findings should be considered in the interpretation of evidence on the association of antidepressant concentration and efficacy as well as in future research, not only in antidepressants, but also in other drug classes.

Conflict of interest GG has served as a consultant for Allergan, Boehringer Ingelheim, Institute for Quality and Efficiency in Health Care (IQWiG), Janssen-Cilag, Lundbeck, Otsuka, Recordati, ROVI, Sage, and Takeda. He has served on the speakers' bureau of Gedeon Richter, Janssen Cilag, Lundbeck, Otsuka, Recordati. He has received grant support from Boehringer Ingelheim, Lundbeck and Saladax. He is co-founder and/or shareholder of Mind and Brain Institute GmbH, Brainfoods GmbH, OVID Health Systems GmbH and MIND Foundation gGmbH. RK reports modest honoraria for consultancy, lectures, and support for research from Bayer Pharma, Berlin-Chemie Menarini, Daiichi Sankyo, Ferrer, Sanofi, and Servier outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

9 How valid are therapeutic reference ranges for psychotropic drugs?

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Introduction A key principle of Therapeutic Drug Monitoring is the comparison of individual drug concentrations in the blood of a patient to a reference system, the drug-specific therapeutic reference range. Inconsistent methodologies concerning the way that reference ranges were determined has led to a high variation of ranges reported in the literature. Reported ranges from previous guidelines are more or less considered as experts' opinions [1].

Methods Therapeutic reference ranges yield pharmacodynamic information from a reference population on increased likelihoods for the occurrence of desired drug effects and adverse drug reactions. The presentation will address methodological difficulties, which arise when following this concept. On the basis of examples from the literature, a methodology for finding a therapeutic reference range will be introduced.

Results The most robust method to find therapeutic reference ranges is a well-conducted systematic literature review including a meta-analysis of prospective data. However, prospective studies, showing concentration/response-relationships, are scarce. It will be presented that for most psychotropic drugs, a relationship between drug concentration and therapeutic response is not well established. For these drugs, a preliminary range for referring individual drug concentrations can be, for instance, computed using population-based concentration ranges. In this context, retrospective data, ideally comprising pharmacodynamic information, can be helpful.

Conclusion The methodology used to estimate the limits of a reference range determines the validity of this range. Valid ranges do not solely base upon single (concentration efficacy) studies. Recommendations should also consider insights from e.g., TDM and neuroimaging studies. Validation studies of ranges that are currently in use are past due.

References

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10 Therapeutic reference range for aripiprazole revised: A systematic review and combined analysis

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Introduction The current reference range for the atypical antipsychotic aripiprazole is 100-350 ng/mL (150-500 ng/mL for the sum of aripiprazole + active metabolite) [1]. The range(s) might be transferable to aripiprazole's long-acting injectable (LAI) formulation [2]. As published previously, valid reference ranges derive from systematic evaluation of up-to-date literature of the relationship between blood levels, clinical outcomes and receptor occupancy, not solely from experts opinions [3].

Methods We performed a systematic literature review followed by a qualitative and quantitative analysis of the literature to identify a target range for aripiprazole. Studies in humans were selected without restriction to diagnosis. Population-based ranges were computed from concentration data.

Results 54 study cohorts met the eligibility criteria. 29 studies report blood level after oral and 16 after injectable formulations. 13 and 10 of them reported clinical or side effect assessments. Conflicting evidence for a relationship between concentration and efficacy or side effects exists resulting in a grading as low or absent, respectively. The mean aripiprazole concentration across 17 studies (N = 3778) was 230.2 ng/mL. When treated under flexible doses, 50 % of patients with schizophrenia and related disorders had drug concentrations within a range of 120-273 ng/ml (N = 3373). PET studies report quite consistent values of 90 % receptor occupancy above 89-110 ng/mL. Several LAI studies have demonstrated concentrations within the current recommended range for oral ARI.

Conclusion Conflicting evidence exists for the concentration/efficacy relationship of aripiprazole. However, including also evidence from TDM and neuroimaging studies, we suggest an optimal target range of 120-270 ng/mL for aripiprazole and 180-370 ng/mL for the sum.

References

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 [3] Hart X.M. et al. Therapeutic Reference Ranges for Psychotropic Drugs: A Protocol for Systematic Reviews. *Frontiers in Psychiatry* 2021; 12: 787043

11 Linking pharmacokinetics of aripiprazole to side effects and effectiveness in children and adolescents

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Introduction Aripiprazole is one of the most frequently prescribed antipsychotics in children and adolescents. However, pharmacokinetic data in this population are sparse, and especially little is known about the correlation between pharmacokinetics and clinical outcomes. This study aims to describe the relationship between dosages, plasma levels and weight gain and clinical effectiveness of aripiprazole in children with autism spectrum disorder (ASD).

Methods We conducted a prospective observational multicentre trial with a 6 month follow-up in children diagnosed with ASD and comorbid behavioral problems using aripiprazole. The primary outcome was BMI normalised for age and sex (BMI z-score). Weight, height and effectiveness (ABC-Irritability scale, ABC-I) were measured at baseline and during follow-up. Sampling of aripiprazole and its active metabolite dehydroaripiprazole was performed by venepuncture and dried blood spots. Population pharmacokinetics were modelled using NONMEM 7.4. Subsequently, simulated pharmacokinetic parameters were correlated to BMI z-scores and effectiveness through mixed model analyses.

Results 21 children were included (71% boys, median age 9.7 years, median bodyweight 39.2 kg), from whom we measured 88 aripiprazole and dehydroaripiprazole plasma levels, and calculated 101 BMI z-scores and 45 ABC-I scores. The pharmacokinetics of aripiprazole and dehydroaripiprazole were best described using a one-compartment model. We found a significant positive correlation between sum (aripiprazole + dehydroaripiprazole) plasma levels and BMI z-score ($\beta = 0.003$, $p = 0.009$), but not ABC-I ($\beta = -0.006$, $p = 0.674$).

Conclusion Higher aripiprazole sum plasma levels are associated with a higher BMI z-score in children and adolescents. Therapeutic drug monitoring may limit weight gain in this population.

12 Antidepressants in pregnancy – focus on therapeutic drug monitoring

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Introduction Even if an increasing number of women is treated with antidepressants during pregnancy, data about the pharmacokinetics is still sparse and no guidelines exist that describe dosing strategies in this vulnerable period [1].

Methods We aimed at investigating serum levels of about 13 different antidepressants during pregnancy at different time points in a naturalistic sample of

patients consisting of about 60 datasets. In addition, the rough developmental milestones of the exposed children were assessed.

Results During pregnancy, in the majority of analysed antidepressants, we found a decrease in serum concentrations from the first to the second and again to the third trimester. The exposed children did not show clinically significant higher numbers of birth complications or developmental abnormalities compared with children who were not exposed in pregnancy.

Conclusion We could find hints that most antidepressants are faster metabolised during pregnancy leading to decreased concentrations. There is no point in automatically decreasing the dosage of an antidepressant as soon as a pregnancy is known which still is common daily practice. Regular therapeutic drug monitoring can help to make optimal individual risk-benefit decisions when treating pregnant women with antidepressant medication.

Conflict of interest The authors have no conflict of interest to declare.

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13 Is it Time to Reevaluate the Therapeutic Reference Range for the Antidepressant Drug Venlafaxine?

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Introduction Current guidelines recommend Therapeutic Drug Monitoring (TDM) of venlafaxine (VEN) for dose titration within 100–400 ng/mL, referring to the active moiety (VEN + O-desmethylvenlafaxine; ODV). A therapeutic reference range bases upon a sound concentration efficacy relationship, which has not been systematically verified for VEN/ODV yet.

Methods Following our previously published protocol [7], four databases were systematically searched for relevant articles reporting VEN/ODV concentrations in relation to dose, clinical effects or receptor occupancy. Available evidence for certain concentration/effect-relationships was graded into levels. Mean active moiety blood levels (BLs) were combined and a population-based range (25–75% interquartile) was computed.

Results 69 studies met the eligibility criteria. Evidence for a positive relationship between BL and antidepressant effect could be found in five studies (Level C1; low). One study reported a correlation between BL and the occurrence of tremor (Level C1; low). Sex, age and BMI were identified as relevant influences on VEN/ODV BLs. For serotonin transporters (SERT), 80% effective concentrations (EC_{80}) of 85 ng/mL (ODV) and of 14 ng/mL (VEN) were reported. For norepinephrine transporters (NET), EC_{50} for was 671 ng/mL (VEN + ODV). The mean VEN + ODV concentration across 10 studies (N = 3248) was 360 ng/mL (interquartile 228–453 ng/mL).

Conclusion Low evidence for the relationship between VEN blood concentration and antidepressant effects exists. A certain threshold has not been proposed. While expecting serotonergic antidepressant effects, we suggest a lower threshold of about 100 ng/mL for VEN + ODV. However, low NET occupancy under common doses might necessitate drug levels above 400 ng/mL.

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14 Using TDM data to study treatment failure

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Introduction Psychotropic drug treatments are associated with frequent 'trial-and-error' events reflecting insufficient clinical responses or serious side effects. The term treatment failure is in this context defined as an unsuccessful outcome of the medical intervention. Accordingly, indirect endpoints of treatment failure comprise drug discontinuation (1), drug switch (2), hospitalization or nonadherence during drug treatment (3), serum concentrations outside the target range (4), and treatment-resistance (5). Use of therapeutic drug monitoring (TDM) data in research projects offers unique possibilities of providing rates of such endpoints and also relate their occurrence to patient factors, including pharmacogenetics.

Methods The talk will in more detail present how endpoints of psychotropic drug treatment failure could be drawn from TDM databases. In addition, examples of research projects at the Center for Psychopharmacology in Oslo, Norway, using this methodology are presented.

Results By using longitudinal TDM data coupled to pharmacogenetic profiles, studies have been able to investigate the relationship between genotypes and switch rates, along with genotypes and serum concentrations, both for antidepressants and antipsychotics. Further, nonadherence rates have been measured by studying the occurrence of undetectable serum concentrations of antipsychotics during prescribing of recommended doses in schizophrenia. Another example is characterization of longitudinal TDM profiles of antipsychotic drugs preceding initiation of clozapine, as an endpoint of treatment-resistant schizophrenia.

Conclusions TDM data have the potential to study different measures of treatment failure. Longitudinal TDM profiles are often necessary, which requires that TDM data from different laboratories are merged at a national level.

15 A compilation of serum concentrations of 12 antipsychotic drugs in a therapeutic drug monitoring setting

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Introduction A comprehensive collection of routine therapeutic drug monitoring (TDM) data for antipsychotic drugs can support the physician when individualizing dosing and determining treatment strategies for the specific patient.

Methods The compilation consists of TDM-data from twelve antipsychotics substances. The drugs included are amisulpride (n = 506), aripiprazole (n = 1610), clozapine (n = 1189), flupentixol (n = 215), haloperidol (n = 390), olanzapine (n = 10268), perphenazine (n = 1065), quetiapine (n = 5853), risperidone (n = 3255), sertindole (n = 111), ziprasidone (n = 1235) and zuclopenthixol (n = 691). As only one sample per patient is included the number of patients equals the number of samples. For each drug median serum concen-

trations as well as 10th and 90th percentiles are given for a range of daily doses. Comparisons are made between males and females, between patients younger and older than 65 years of age and between those treated with a low and a high dose of each drug. The concentration-to-dose (C/D) ratio is the primary variable used in these comparisons. Within and between subject variation (CVs) for the serum concentrations of each drug are presented.

Results In general, the C/D ratios were higher in females than in males, were higher in those older than 65 years of age than in younger subjects and were lower in those treated with higher doses than in those treated with lower doses. CVs between individuals were larger than within subjects, and the CVs were highest for the drugs with short elimination half-lives.

Conclusions For each antipsychotic drug the results presented can serve as a reference tool for pharmacokinetic interpretation of the individual patient's serum drug level.

16 Influences on therapeutic drug monitoring of psychotropic drugs – analyst's perspective

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Introduction Therapeutic drug monitoring (TDM) of psychotropic drugs is an essential tool for therapy management. A lot of different analytical methods are in use. Does the determination method used influence the results? Which other factors are decisive?

Methods An overview of Methods reported in the German External Quality Assessment (EQA) schemes for psychotropic drugs is given and different methods discussed. The general principle of the methods will be presented including significant advantages and disadvantages. In additions, analytical challenges for the determination of enantiomeric pure drugs such as escitalopram are discussed. Various influences and interfering factors for TDM are reflected.

Results The spectrum of methods used range from atomic absorption to chromatography-based methods (HPLC-UV or LC/MS-MS), and immunoassays. Variances of the individual methods in EQA are similar. Discrepancies are seen for Lithium. However, humans exert significant influences, whether during blood collection, sample processing, or by the patient themselves through individual metabolism or compliance.

Conclusion Most analytical procedures work very well. TDM of psychotropic drugs is substantially influenced by correct blood collection and processing as well as the patient.

Conflict of Interest No conflict of interest exists

17 The relevance of TDM for long-acting injectable antipsychotics

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Introduction Pharmacoepidemiological data suggest an emerging prescription trend for second generation antipsychotics including long-acting injectable (LAI) formulations. Further, the use of therapeutic drug monitoring (TDM) as part of clinical routine of treatment with LAI antipsychotics receives increasing attention. We systematically reviewed available TDM evidence during the switch from the oral formulation to the LAI counterpart as well as in the LAI maintenance treatment.

Methods Available TDM studies for LAI antipsychotics can be classified as follows: 1) positron emission tomography (PET) findings regarding dopamine (D₂/D₃) receptor occupancy related to LAI antipsychotic blood levels, 2) TDM studies on the transition from oral to LAI antipsychotics and 3) TDM data from patients receiving maintenance treatment with LAI formulations.

Results Demographic characteristics, such as age and sex, genetic peculiarities affecting metabolizer status and clinical variables including co-medications and co-morbidities may crucially impact LAI antipsychotic blood levels. A trend towards lower concentrations under LAI compared to oral antipsychotics was observed implying the need to adapt therapeutic reference ranges for some LAI antipsychotics adopted from their oral counterparts.

Conclusion Available TDM evidence suggest varying bioavailability patterns for newer LAI antipsychotics, essentially captured with the use of regular TDM. Thus, we recommend using TDM when switching an antipsychotic from oral to its LAI formulation as well as during dose selection.

Conflict of Interest GS has served as a consultant for HLS Therapeutics and Thermo Fischer.

18 Liquid Chromatography/Tandem Mass Spectrometry (LC-MSMS) Analysis of neuropsychiatric drugs: Challenges from the perspective of the laboratory physician

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Introduction Due to a broad spectrum of neuropsychiatric drugs available and the numerous indications for a therapeutic drug monitoring (TDM) guided therapy, the proportion of quantitative analyses of these drugs within TDM services is large as well as steadily increasing. Whereas there are a few drugs for which automated analyses on general clinical chemistry platforms are available, the carrying force for the analytics are chromatographic procedures, particularly those based on the LC-MS/MS technique. Although LC-MS/MS has faced enormous technical development in the last decades providing important advantages for the implementation of routine TDM services, analysis by LC-MS/MS does not automatically mean the results are more reliable and that the methods are superior to other assays.

Methods Based on the literature published and on personal expertise of the speaker the presentation will point out challenges concerning the single phases of the analytical procedure life cycle (e.g. method design; method validation/performance verification; method life cycle management) and their impact on laboratory results.

Results The content of the presentation is intended to support proper interpretation of laboratory results under consideration of their analytical quality and to highlight measures needed to improve method consistency within- and between laboratories.

Conclusions To exploit the diverse advantages of LC-MS/MS, efforts to cope with its challenges and to align analytical performance with clinical requirements are essential.

19 Therapeutic drug monitoring of mirtazapine in children and adolescents: Analysis of dose, steady-state concentration and responsiveness in a naturalistic clinical setting

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Introduction Mirtazapine is a tetracyclic piperazino-azepine antidepressant with a unique mechanism of action through modulating serotonergic and noradrenergic neurotransmission. Being the second-choice medication in child-

hood depression, it is also used alone or as an add-on to treat insomnia, eating or other internalizing disorders. Despite its therapeutic benefits, no systematic therapeutic drug monitoring (TDM) examination of mirtazapine in children and adolescent exists.

Methods Within the prospective multicenter “TDM-VIGIL” study, valid datasets from 55 participants (48 females; mean age 15.75 ± 1.16; range 13–17 years) treated with mirtazapine for various psychiatric indications were analyzed. Patient blood samples were collected at a steady-state and drug serum concentrations were determined using the isocratic reversed-phase high-performance liquid chromatography. Medication-specific treatment effects were quantified using an adapted version of the Clinical Global Impression (CGI) scale.

Results A strong dose–concentration effect was found ($\beta = 0.83$, $p < 0.001$, $R^2 = 0.683$). The model with covariates, including sex, age, body weight, psychiatric co-medication and nicotine consumption, showed significant effects of age and co-medication. No effects with dose or serum concentration were observed with therapeutic and side effects, neither transdiagnostically nor separately for the two main diagnostic groups (depression, eating disorder). The 25th–75th interquartile range in good responders was 15–37 ng/ml.

Conclusions The effects of age and co-medication in this flexible-dose-TDM study are of relevance for pharmacovigilance and dose calibration in young patients treated with mirtazapine. The lack of associations with clinical improvement may potentially be explained by the heterogenous diagnostic and treatment picture, real-time scenario with uncontrollable variables and low signal-to-noise ratio.

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20 Ketamine Metabolite Plasma Levels as Potential Blood Markers of Ketamine Efficacy in Treatment Resistant Depression

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Introduction Accumulating evidence has revealed robust fast-acting antidepressant effects of ketamine, an *N*-methyl-D-aspartate receptor (NMDAR) antagonist, in patients with treatment-resistant depression (TRD). However, considering that clinical responses can only be observed in 50% of TRD patients [1], treatment decisions lack predictors on patients’ individual benefit. Even though ketamine and norketamine plasma concentrations did not correlate with the acute effects or the immediate antidepressant effects of ketamine [2], there seem to be more and more indications that the metabolites (f.e. hydroxyketamine) could be essential for the prediction of its long-term antidepressant effects [3].

In this study, (R,S)-ketamine metabolite plasma concentrations will be examined as a potential blood biomarker for treatment response in the course of the NeuroMarket (Neuroimaging and Blood Markers as Indicators of Ketamine Efficacy in Treatment Resistant Depression) study.

Methods NeuroMarket aims to acquire data from 1) a large multimodal patient sample and 2) a parallel animal study with harmonized observation time points. Centralized analyses of specimen will include combined blood biomarkers of peripheral proteomics, BDNF levels, acetylated alpha-tubulin, and ketamine metabolites with non-invasive functional MRI markers and electrophysiology. TRD patients will receive six ketamine injections. Blood, as well as brain biomarkers, will be assessed 24 hours later and compared to a baseline measurement before the injection.

Plasma levels of ketamine, its enantiomers and its metabolites will be measured at baseline, one hour after injection, 24 hours later and directly before the next injection at all six injection time points.

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21 Therapeutic drug monitoring of sertraline in pediatric population: A naturalistic study with insights into the clinical response of obsessive-compulsive disorder

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Introduction Sertraline is the first-line medication for treatment of pediatric anxiety, depression and early-onset obsessive-compulsive disorder (OCD). Owing to complex etiologies underlying psychiatric disorders and differing metabolisms, relationship between pharmacokinetics, pharmacodynamics, efficacy, and tolerability of sertraline across indications and in individual cases, particularly in non-adult patients, is not fully understood.

Methods This therapeutic drug monitoring (TDM) study was implemented in a transdiagnostic sample of children and adolescents ($n = 78$; mean age, 14.22 ± 2.39 ; range, 7–18 years) treated with sertraline, as part of the international “TDM-VIGIL” project. Associations between dose, serum concentration, medication-specific therapeutic and side effects measured by an adapted Clinical Global Impression scale were investigated. The 56-item Pediatric Adverse Event Rating Scale served to assess drug tolerability.

Results The analysis showed a linear positive association between dose and serum concentration, with dose explaining 45% of the variance in concentration, as well as significant effects of weight and co-medication. Neither dose nor serum concentration were associated with side effects transdiagnostically, and overall a mild-to-moderate tolerability profile was reported. Notably, when split into depression (MDD) and OCD diagnoses, the probability of clinical improvement significantly increased with both higher doses and higher resulting concentrations, unlike for MDD.

Conclusions This study revealed a significant diagnosis-specific effect between sertraline serum concentration and clinical efficacy for pediatric OCD. Possibly, sertraline-related improvements in OCD are not dependent on the short-term availability of serotonin, but rather on long-term postsynaptic changes. TDM may be a valuable discovery tool in psychiatry and may facilitate a personalized medicine approach.

Conflict of Interest KE, RT, MR, MG and PP received grant research support from BfArM. MR currently receives a research grant from Kids-Safe, Innovation Committee of the German Federal Joint Committee (G-BA grant number 01NVF16021). PP receives grant research support from the German Federal Ministry of Education and Research (BMBF) and was involved in clinical trials from Servier and Lundbeck; he received an advisor honorarium from Boehringer Ingelheim and speaker's honoraria from Shire, Infectopharm and Gerot Lannach. CC has been a consultant and/or advisor to or has received honoraria from: AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Axsome, Damitsa, Gedeon Richter, Hikma, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Medscape, Merck, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Servier, SK Life Science, Sumitomo Dainippon, Sunovion, Supernus, Takeda, Teva, and Viatrix. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, Rovi, Supernus, and Teva. He has received grant support from Janssen and Takeda. He received royalties from UpToDate and is also a stock option holder of LB Pharma. TB received personal fees from Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Takeda, Infectopharm, and Eli Lilly; serving as an advisor or consultant to Bristol Myers Squibb, Desitin Arzneimittel, Eli Lilly, Medice, Novartis, Pfizer, Shire, UCB, and Vifor Pharma; receiving conference attendance support, conference support, or speaking fees from Eli Lilly, Janssen McNeil, Medice, Novartis, Shire, and UCB; being involved in clinical trials conducted by Eli Lilly, Novartis, and Shire; and receiving royalties from Hogrefe, Kohlhammer, CIP-Medien, and Oxford University Press. SW has received in the last 5 years royalties from Thieme, Hogrefe, Kohlhammer, E. Tini et al. Comprehensive Psychiatry 115 (2022) 152301 9 Springer, Beltz. Her work was supported in the last 5 years by the Swiss National Science Foundation, diff. EU FP7s programs, Hochspezialisierte Medizin of the Kanton Zurich, Switzerland, BfArM, ZInEP, Hartmann Müller Stiftung, Olga Mayenfisch, Gertrud Thalman, Vontobel, Unicentia, Erika Schwarz Fonds, Gesundheitsförderung Schweiz. The other authors (ET, LS, CW, AK, KR, UM, SU, MS, HR, GA, WB, CF, TH, HI, MKae, MKo, TR, SR, CR, GS, FT, and SF) declare no conflict of interest.

22 Current data from the AMSP Project on the risk of treatment with antidepressants and antipsychotics within the clinical setting

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Introduction The monitoring of adverse drug reactions (ADRs) has become increasingly important within modern psychopharmacology. AMSP (“Arzneimittelsicherheit in der Psychiatrie”; Drug Safety in Psychiatry) was founded in 1993 and is a drug safety monitoring program with special emphasis on severe and unusual ADRs during treatment with psychotropic drugs.

Methods Data derives from the AMSP database. > 100 psychiatric hospitals in Germany, Switzerland and Austria have participated from 1993 up to now. Data on psychotropic drug use was gathered on two reference days per year along with mean duration of treatment. ADRs were determined using ASMP definitions and rating questionnaire. Causal relationship between observed symptoms and drugs given at that time were carefully assessed.

Results A total of 462,661 psychiatric inpatients were monitored from 1993 to 2016. Antipsychotics and antidepressants were the most commonly prescribed drug classes. Polypsychopharmacology increased over the years: The average number of prescribed psychotropic drugs increased from 2.2 per patient in 1994 to 2.6 psychotropic drugs in 2017. The mean number of all drugs prescribed also increased from 3.0 in 1993 to 4.4 drugs per patient in 2017. A total of 7293 severe ADRs were registered from 1993 to 2016, 50.2% of which were caused by a combination of drugs. ADRs most commonly observed under combination treatment were urinary retention, hyponatremia, seizures, and delirium.

Conclusion Observation of naturalistic prescription and safety data of psychotropic drugs, especially in combination with other (non-)psychotropic drugs, is a useful tool in estimating the risk/benefit ratio of drug therapy within clinical settings.

23 Case series: Higher antipsychotic drug levels in patients with schizophrenia after COVID-19 vaccination

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Introduction Safety studies have shown that COVID-19 vaccinations can provoke inflammatory processes in patients. The subsequent release of cytokines is accompanied by an increased inflammatory marker, *C-reactive protein* (CRP) [1]. For some antipsychotic drugs, inflammatory processes have been associated with increased drug levels, even above therapeutically approved ranges [2, 3]. It is not clear, whether this holds also true for COVID-19 vaccinations.

Methods We present a case series comprising of 10 inpatients at the CIMH treated with an antipsychotic drug. Patients received a first, second or third dose of the COVID-vaccination *Comirnaty* in the morning. Blood samples were taken directly before the injection and were followed on day 1 and 4 while constant dosing. Blood testing included drug levels, safety laboratory, and CRP.

Results CRP levels were elevated in nine patients; four of those also presented an increase in antipsychotic drug levels within a few days after COVID-19 vaccination. Blood level changes were i) + 0%, + 24%, + 125%, + 116% in quetiapine-, ii) + 0%, + 0%, + 100% in olanzapine-, iii) + 0, + 42% in clozapine-treated

patients, and iv) + 205% in one risperidone-treated patient. As a result, three patients had drug levels above the therapeutically recommended range.

Conclusion We present a series of patients with increased antipsychotic drug levels after COVID-19 vaccinations mediated via inflammatory processes. The intensity of inflammatory reactions strongly varies across patients. Hence, COVID-19 vaccinations may constitute an unpredictable risk factor for increased drug levels. Therapeutic drug monitoring can help to prevent safety risks in those patients with supra-therapeutic drug levels.

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24 The therapeutic reference range for olanzapine revised – how to combine old and new findings

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Introduction Therapeutic Drug Monitoring (TDM) for olanzapine (OLZ) is highly recommended in current guidelines for dose titration within a blood concentration range of 20 to 80 ng/mL [1]. A range between 10 and 40 ng/mL has been recently discussed for long-acting injectable OLZ [2]. A relationship between OLZ concentration and clinical response is the basis for a valid reference range. A clear relationship however could not yet be demonstrated in the current literature [3].

The present systematic review discusses literature on the relationship between OLZ blood levels (OLZ BL), clinical outcomes and dopamine receptor occupancy in terms of the therapeutic reference range for OLZ.

Methods For study selection and quality assessment, we followed our review protocol published previously [4]. Four electronic databases were systematically searched for relevant articles. The mean OLZ concentration was computed from eligible studies. 65% and 80% effective concentrations (EC₆₅; EC₈₀) were extracted from neuroimaging studies.

Results 34 studies met the eligibility criteria. The mean OLZ BL was 31 ng/mL (CI 95: 27–36 ng/mL). Four studies found a positive relationship between OLZ

BL and response after oral intake (Level C1; low). Five studies consistently report higher clinical efficacy with OLZ BL > 20 ng/mL. No correlation between OLZ BL and occurrence of extrapyramidal or other side effects was found. EC₆₅₋₈₀ ranged between 24-43 ng/mL.

Conclusion Our work strongly suggests an optimal target range of 20-40 ng/mL for oral OLZ with increasing efficacy above the lower threshold.

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