XIV[th] Symposium of the Task Force Therapeutic Drug Monitoring of the AGNP

Date/Venue:
May 13[th]–15[th], 2020, Mannheim, Germany

Due to safety considerations in connection with the spread of SARS-CoV-2, this meeting was cancelled. It may be held at a later date, please check the AGNP website for updates.

Organizing committee:
Gerhard Gründer, Xenia Hart
Program committee:
Gerhard Gründer / Chairman
Niels Bergemann, Karin Egberts,
Ekkehard Haen,
Ursula Havemann-Reinecke,
Gudrun Hefner, Christoph Hiemke,
Andreas Menke, Rainald Mössner,
Florian Ridders, Georgios Schoretsanitis

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

Authors Adamovic I[1], Michaelis S[1], Streit F[2], Binder L[2], Degner D[1]
Institutes 1 Clinic of Psychiatry and Psychotherapy, University of Göttingen Medical Center, Germany; 2 Institute for Clinical Chemistry, University of Göttingen Medical Center, Göttingen, Germany
DOI 10.1055/s-0040-1710109

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

Results Sertraline level was low, < 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 was 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 allels 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

Authors Adamovic I[1], Vierke C[1], Boettcher M[3], Hiemke C[4], Havemann-Reinecke U[1,2]
Institutes 1 Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, University of Göttingen, Germany; 2 DFG Research Center of Nanoscale Microscopy and Molecular Physiology of the Brain (CNMPB), Göttingen, Germany; 3 MVZ Dessau Laboratory GmbH, Dessau, Germany; 4 Department of Psychiatry and Psychotherapy, University Medical Center Mainz, Mainz, Germany
DOI 10.1055/s-0040-1710110

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 (BUB), 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.

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 antidepressive 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 of antiepileptics and mood stabilizers in pregnancy and lactation

Author Augustin M[1]
Institute 1 Protestant University of Applied Sciences, Bochum, Germany
DOI 10.1055/s-0040-1710111

Introduction Therapeutic Drug Monitoring (TDM) is an essential tool to monitor psychopharmacological treatment and detect causes for adverse events and clinical non-response. The specific value of TDM of antiepileptics and mood stabilizers during the period of pregnancy and lactation is a matter of debate. Data on pharmacokinetic changes in the metabolism of psychopharmatropic drugs in special patient groups is limited.

Methods A literature review was performed to collect peer-reviewed studies and clinical reports on the clinical relevance of TDM of antiepileptics and mood stabilizers in pregnancy and lactation. Results for these two different clinical situations were separately reported.

Results Pregnancy-related changes affect all pharmacokinetic aspects such as absorption, distribution, metabolism and elimination. During pregnancy, these changes warrant therapeutic drug monitoring in substances such as lithium,

lamotrigine and valproic acid, if the latter is used at all due to severe teratogenic risks.

For breastfeeding most mood stabilizers appear to be safe with little fetal exposition of the substances. Exceptions are lithium and lamotrigine which are considerably excreted into breast milk.

Conclusion The available data suggest an individual decision on therapeutic drug monitoring depending on the substance and the clinical situation. Therapeutic drug monitoring has high clinical relevance in certain situations such as prescription of lithium or valproic acid during pregnancy and lactation.

4 Slow-drop infusion versus oral administration of citalopram: Comparison of plasma concentrations of the enantiomers of citalopram and its metabolites

Authors Baumann P[1], Nil R[2]

Institutes **1** Department of Psychiatry (DP-CHUV), University of Lausanne, Prilly-Lausanne, Switzerland; **2** Uerikon, Switzerland

DOI 10.1055/s-0040-1710112

Introduction The pharmacological activity of the chiral antidepressant citalopram (CIT) resides mainly in its enantiomer escitalopram (S-citalopram; S-CIT) rather than in R-citalopram (R-CIT). We reported earlier [1] on plasma concentrations of racemic citalopram measured in patients treated with either slow-drop infusion or oral administration in a double-blind double dummy design. Here, we report on plasma concentrations of the individual enantiomers of citalopram and its metabolites from this study [1].

Methods In the plasma probes collected in this study [1], the steady-state concentrations of citalopram and its metabolites were measured by a stereoselective HPLC procedure. The probes were collected before daily dosing at 7:30 h after a 10-day treatment with 40 mg/day citalopram, administered either p.o. or by slow-drop infusion.

Results In the group with active intravenous infusion (n = 27), the following concentrations were measured: S-CIT: 24 ± 0.2 ng/mL; R-CIT: 45 ± 14.5 ng/mL; S-desmethyl-CIT: 13 ± 4.4 ng/mL; R-desmethyl-CIT: 17 ± 8.2 ng/mL. In the orally treated patients (n = 25), the corresponding figures were: 30 ± 12.7 ng/mL; 51 ± 17.4 ng/mL; 13 ± 4.6 ng/mL; 17 ± 7.9 ng/mL.

Conclusion Due to the high bioavailability of citalopram, the plasma concentrations of the individual enantiomers remained independent from the route of administration. Lower plasma concentrations of S-CIT than R-CIT are a result of their different metabolism.

References [1] Baumann P, Nil R Bertschy G, Jecker A, Brändli H, Morand J, et al. A double-blind double-dummy study of citalopram comparing infusion versus oral administration. J Affect Disord. 1998;49:203–210

5 Course of tranylcypromine enantiomer plasma concentrations in patients with depression

Authors Buspavanich P[1,2,3], Hindinger C[1,2,3], Ricken R[1,2,3], Adli M, Ulrich S[1,2,3]

Institutes **1** Department of Psychiatry, Psychotherapy and Psychosomatics, Brandenburg Medical School Theodor Fontane, Campus Neuruppin; **2** Department of Psychiatry and Psychotherapy, Campus Mitte, Charité University Medicine; **3** Medical-Scientific Department, Aristo Pharma GmbH, Berlin, Germany

DOI 10.1055/s-0040-1710113

Introduction Tranylcypromine (TCP) is an irreversible monoamine oxidase (MAO)-A/B inhibitor prescribed in treatment resistant depression. Plasma concentrations of TCP enantiomers have not been reported for continuous treatment with the racemic antidepressant to date.

Methods Enantiomer TCP plasma concentrations were measured by a validated liquid-liquid extraction method (LC/MS) after a first single dose and during continuous treatment.

Results Lower plasma concentrations of (+)- TCP than (-)- TCP were found after the first dose of 10 mg TCP with an enantiomer AUC-ratio$^{(+/-)}$ = 0.04 to 0.16 (n = 3). The AUC-ratio$^{(+/-)}$ increased to 0.64 for a dose of 20 mg (n = 1), and to 0.88 to 0.94 (n = 4) for 40 mg during continuous treatment of 40 mg/day. Racemic C_{Max} and AUC were disproportionately high for continuous treatment compared to first single dose.

Conclusions TCP is a special antidepressant drug in that MAO is simultaneously the enantiomer selective pharmacological target and drug metabolizing enzyme. With intact MAO for the first single dose, (+)- TCP is more rapidly metabolized because this enantiomer is a better MAO "suicide" inhibitor than (+)- TCP ($\Delta LogIC_{50} > 1$). The difference in metabolization vanishes as MAO activity is decreased during continuous treatment. The TCP enantiomer AUC-ratio$^{(+/-)}$ is therefore a test for peripheral MAO activity and may be a surrogate of central MAO activity. More studies are needed for this interesting pharmacokinetic-pharmacodynamic relationship. For example, recovery of peripheral MAO may be investigated with TCP test doses after discontinuation of TCP, or fluctuations of MAO activity may be detected during long-term treatment.

6 A multicenter pharmacovigilance study on antidepressant and antipsychotic use in children and adolescents in daily clinical practice

Authors Egberts K[1], TDM-VIGIL-Consortium[2], Plener P[3], Fekete S[1], Taurines R[1], Gerlach M[1], Romanos M[1]

Institutes **1** Department of child and adolescent psychiatry, University Hospital Wuerzburg, Germany; **2** Selected members of Competence-Network Therapeutic Drug Monitoring (www.tdm-kjp.com); **3** Department of Child and Adolescent Psychiatry, Medical University Vienna, Austria

DOI 10.1055/s-0040-1710114

Introduction To learn more about the prescription patterns and safety of antidepressants and antipsychotics in children and adolescents in daily clinical practice a multicenter clinical pharmacovigilance trial ('TDM-VIGIL-study'), funded by the Federal Institute of Drugs and Medical Devices (BfArM), was performed.

Methods Children and adolescents treated on- and off-label with antidepressants and antipsychotics for various psychiatric disorders by 18 centers in Germany, Austria and Switzerland were prospectively followed between October 2014 and December 2018. The follow-up included standardized assessments of side effects and serum concentrations (therapeutic drug monitoring/TDM); an internet-based patient registry was used for data collection.

Results 710 children and adolescents, mean age 14.6 years, 66.6 % female, were observed 167 days on average. 25.5.% were suicidal at enrollment. 76.9 % received antidepressants, 47.8 % antipsychotics. About 70 % had at least one medication episode under off-label conditions. Adverse drug reactions (ARDs) occurred in more than 40 % of the patients, but were mostly rated as mild. All serious ADRs (8,7 %) developed favorably and proportions of serious ADRs were not increased due to off-label use.

Conclusion Our results confirm the chosen method of standardized patient and TDM as valuable approach of post-marketing surveillance.

7 The dose-related reference range – a new approach with improved predictive quality

Authors Endres K[1], Haen E[2]

Institutes **1** Clinical Pharmacology, Departement of Psychiatry and Psychotherapy and Departement of Pharmacology and Toxicology at the University of Regensburg; **2** Institut AGATE, Pentling

DOI 10.1055/s-0040-1710115

Introduction Three calculation methods for the dose-related reference range (DRR) in normal patients have been proposed to date: cav (Haen 2008), cmin (AGNP TDM guidelines 2017) and cmin (Haen 2018). All methods have different disadvantages. An evaluation of the methods regarding to the predictive quality has not yet been carried out. The aim was to further develop the methodology and to compare all methods in terms of predictive quality of the

trough levels in steady state of amlodipine, bisoprolol, metoprolol, hydrochlorothiazide and ramipril/ramiprilate.

Methods The developed method, Cmin,R2019, is based on the Bateman function and takes into account the total available and suitable literature of the pharmacokinetics of the mentioned substances. The visualization of the drug concentration curves was realized with SigmaPlot. The predictive quality regarding to published trough levels was determined.

Results Cmin,R2019 enables the visualization of the drug concentration curves with regard to the dosage form, variable dosages, dosage intervals (τ) and specific patient groups. Cmin,R2019 showed an improved precision in the prediction of trough levels in steady state compared to the other three methods (127.5 vs. 12,952.8 (Haen 2008), 4741.3 (AGNP TDM guidelines 2017) and 9196.3 (Haen 2018)).

Conclusion The new procedure offers an improved overall predictive quality compared to the methods presented so far. The visual representation of the drug concentration curves is helpful for the interpretation of the measured values, especially if the blood collection did not take place in the trough level. The new method should be applied to other drugs and the predictive quality of the various methods should be compared.

8 Serum concentrations of venlafaxine and risperidone and their metabolites from childhood to old age

Authors Fekete S[1], Scherf-Clavel M[2], Gerlach M[1], Romanos M[1], Kittel-Schneider S[2], Unterecker S[2], Egberts K[1]

Institutes 1 Department Child and Adolescent Psychiatry, Psychosomatic Medicine and Psychotherapy, Center of Mental Health, University Hospital of Wuerzburg, Germany; **2** Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, Center of Mental Health, University Hospital of Würzburg, Germany

DOI 10.1055/s-0040-1710116

Introduction Pharmacokinetic data about the antidepressant venlafaxine (VEN) and the antipsychotic risperidone (RIS) over the lifespan and especially in children and adolescents is lacking. To fill some of this gap, this study aims to investigate the relationship between age and serum concentrations of VEN and RIS and their metabolites.

Methods Drug serum levels of patients treated with VEN and RIS of the University Hospital of Würzburg, Germany, between 2015 and 2019 were retrospectively investigated.

Results For both substances, no age-dependent difference in metabolite to parent ratios (MPRs) was found. However, minors treated with VEN (N = 26) and RIS (N = 79) showed lower dose corrected concentrations of VEN and RIS than adults (n = 637 / 348) or elder adults (> 60 years) (n = 290 / 140). Moreover, 80 % of MPRs of RIS in minors were below the range of a "normal" CYP2D6 function in adults.

Conclusions We suggest minors' higher renal clearance as an explanation for lower dose corrected concentrations of VEN and RIS. Metabolism of VEN or RIS by CYP2D6, characterized by MPRs, was not associated with age. However, MPRs of RIS are lower in minors, possibly due to a higher clearance of 9-OH-risperidone.

9 Influence of comedication on amitriptyline underscore the necessity of TDM

Authors Geiben A[1], Haen E[1]

Institute 1 Klinische Pharmakologie am Istitut AGATE und an den Lehrstühlen für Psychiatrie und Psychotherapie und für Pharmakologie und Toxikologie, University of Regensburg, Germany

DOI 10.1055/s-0040-1710117

Introduction Amitriptyline is the most prescribed tricyclic antidepressant. It is metabolized by the enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Nortriptyline is its active metabolite. Due to the many degradation pathways, multiple interactions are possible, but so far, their extent is largely unknown. In this study, we investigate the impact of certain interactions in TDM measurements of specimens from clinical routine.

Methods The KONBEST TDM-database compromises 1275 measurements of amitriptyline. 1219 of these were accompanied by comedication. The serum levels of amitriptyline and its active metabolite nortriptyline were investigated in the context of comedications with metamizole, lamotrigine or melperone. The concentration-dose-coefficient (C/D) was calculated to compare the concentration independent of the dose.

Results The median C/D for the active moiety of amitriptyline was 1.3 (IQR 0.97). The interactions of amitriptyline with metamizole (N = 46, C/D 0.87, IQR 0.74), lamotrigine (N = 89, C/D 1.41, IQR 0.99), and melperone (N = 44, C/D 1.78, IQR 1.18) were investigated in detail. Only for melperone a significant difference to the monotherapy was found (P-value 0.008). The median number of taken drugs within the investigated samples was 6.

Conclusion Despite the high variability in the measured concentrations, trends due to induction or inhibition effects can be identified. The extent of the pharmacokinetic interactions cannot be predicted exactly, since in most cases a polymedication was present. An analysis of specific interaction pairs is not possible due to the small number of cases. In order to assess the effect of a polymedication in an individual patient, serum level concentration measurement with pharmacological evaluation is necessary.

10 How valid are therapeutic reference ranges for psychotropic drugs?

Authors Hart XM[1], Gründer G[1], Hiemke C[2]

Institutes 1 Department of Molecular Neuroimaging, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany; **2** Department of Psychiatry and Psychotherapy, University of Mainz, Germany

DOI 10.1055/s-0040-1710118

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 Most robust method to find a therapeutic reference range is a well-conducted systematic literature review of prospective data. However, prospective studies, showing concentration/response-relationships, are scarce. 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 retrospective data, ideally comprising pharmacodynamic information.

Conclusion The methodology used to estimate the limits of a reference range determines the validity of this range. Valid preliminary ranges can be determined by the use of retrospective data.

References [1] Hiemke C. Bergemann N. Clement, et al. (2018). Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017. Pharmacopsychiatry, 51: 9–62

11 Psychopharmacotherapy in geriatric patients

Author Hefner G[1]
Institute 1 Vitos clinic for forensic psychiatry, Eltville
DOI 10.1055/s-0040-1710119

In elderly patients, age-related pharmacokinetic and pharmacodynamic changes and factors such as multimorbidity and polypharmacy determine the different efficacy and safety of drugs compared to younger patients. Poor evidence for the effectiveness of many drugs in old-aged patients and large variability of the pharmacokinetics and pharmacodynamics explain the high need of an individualized pharmacotherapy and of a close monitoring of efficacy and tolerability during drug treatment in elderly patients.

Amongst others, it is important to avoid potentially inappropriate medication (german Priscus list, FORTA list) and excessive polypharmacy and therefore pharmacodynamic and pharmacokinetic drug-drug interactions. But also undertreatment and underdosing should be avoided. Therapeutic drug-monitoring of psychotropic drugs should be used to detect pharmacokinetic peculiarities and to detect the frequent compliance problems of old-aged patients.

12 Therapeutic Drug Monitoring in the relapse prevention treatment of alcohol dependence

Authors Kiefer F[1], Bekier NK[1], Hiemke C[2]
Institutes 1 Dept. of Addictive Behaviors and Addiction Medicine, CIMH Mannheim; **2** Dept. of Psychiatry, University Hospital Mainz
DOI 10.1055/s-0040-1710120

Introduction Therapeutic drug monitoring has not been used to optimize and individualize drug effects in anti-craving treatment in alcohol use disorders (AUD) up to now. One compound of common use, naltrexone, shows high inter-individual variability in both plasma availability and treatment outcome. We present data aiming at the definition of a therapeutic plasma concentrations of naltrexone and its active metabolite 6β-naltrexol that are predictive for treatment response.

Methods In a RCT sample of 43 subjects suffering from AUD who were treated with naltrexone with a dose of 50 mg/day, naltrexone and 6β-naltrexol were analyzed by high performance liquid chromatography with column switching and spectrophotometric detection. Blood was taken for drug analysis 8 h after the last dose of the day at week 4, 8 and 12. Alcohol craving was assessed with the Obsessive-Compulsive Drinking Scale (OCDS).

Results The plasma concentrations of naltrexone and 6β-naltrexol showed high inter-individual variability. They were predictive for treatment response, as they correlated significantly with the reduction of alcohol craving. Defining patients with OCDS reduction of 70 % or higher as responders, the mean ± SD concentration of naltrexone plus naltrexol was 22 ± 13 ng/ml compared to 15 ± 8 ng/ml in patients with score reductions of 1-69 %. Further analyses indicated that concentrations of 17–50 ng/ml at 8 h and 7–20 ng/ml at 24 h after drug intake were required for treatment response.

Conclusions Since plasma concentration of naltrexone plus 6β-naltrexol was found to be predictive for reduction of alcohol craving, it is concluded that therapeutic drug monitoring has the potential to enhance naltrexone's moderate therapeutic efficiency in patients with AUD.

13 Therapeutic drug monitoring in pregnancy and post-partum period – antidepressant substances

Authors Kittel-Schneider S[1,2], Preis K[2], van Braam L[1], Unterecker S[1]
Institutes 1 Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, Center of Mental Health, University Hospital of Würzburg, Germany; **2** Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital of Frankfurt, Goethe University, Frankfurt
DOI 10.1055/s-0040-1710121

Introduction Up to date, there are several studies showing that various antidepressants can be considered safe in early pregnancy regarding the risk of malformation. However, data about the safety of antidepressant medication in breastfeeding is sparse.

Methods We determined therapeutic drug levels of 25 patients in each trimester of prganancy and parallel in serum and breastmilk at different time points (Trough levels after 12 h / 24 h and 4 h / 8 h after intake). Measurements were determine by an isocratic reversed-phase high performance liquid chromatography (HPLC). To roughly determine the potential effect of the medication on the exposed child, data from the routine preventive medical examination were analysed.

Results Antidepressant serum drug levels decreased during pregnancy even if the patients were taking the same dosage. Serum levels at any timepoint and breastmilk concentration were not significantly correlated (Spearman Rho's correlation, $p > 0.05$). Daily dosage was significantly correlated with trough serum levels ($p = 0.001$) but not with breastmilk levels ($p = 0.88$). There was great interindividual variation of the levels of different substances in different time points. The breastfed children did not show any adverse effects from the medication.

Conclusion Antidpressant serum concentration decreases during pregnancy. From our data, it cannot be concluded that there is a general rule when the lowest concentration of medication in the breastmilk can be expected. However, even if we could measure partly very high levels of the medication in breastmilk, none of the babies showed any adverse effects or delayed development.

14 Physiologically based pharmacokinetic modelling of risperidone and 9-hydroxyrisperidone to determine cytochrome P450 2D6 phenotypes in schizophrenia patients

Authors Kneller LA[1], Hempel G[1]
Institute 1 Institute of Pharmaceutical and Medicinal Chemistry, Clinical Pharmacy, Westfälische Wilhelms-Universität Münster, Germany
DOI 10.1055/s-0040-1710122

Introduction Therapeutic drug monitoring (TDM) of risperidone and its active metabolite 9-hydroxyrisperidone is recommended by many experts [1], as a large interindividual variability in plasma concentrations can be observed. One reason for this is the genetic polymorphism of cytochrome P450 (CYP) 2D6. Therefore, different physiologically based pharmacokinetic (PBPK) models were developed on the one hand to determine the phenotypes and on the other hand to use them for dose optimization in future.

Methods Based on available plasma concentrations of risperidone and 9-hydroxyrisperidone, modelling software PK-Sim® was used to develop PBPK models for all types of CYP2D6 metabolizer. In the next step all models were extrapolated to the elderly and clinical data of geriatric inpatients from the literature were integrated. Subsequently, CYP2D6 phenotype was determined using metabolic ratio (risperidone / 9-hydroxyrisperidone) and modelling.

Results PBPK models were able to predict the plasma concentrations for all types of CYP2D6 metabolizers. Mean prediction error of risperidone and 9-hydroxyrisperidone amounts to 52.2 % and −22.2 % (extensive metabolizer), 37.4 % and −10.6 % (intermediate metabolizer), 28.0 % and −7.8 % (poor metabolizer) as well as 45.4 % and −28.3 % (ultra-rapid metabolizer). After model extrapolation, plasma concentrations and phenotypes of all inpatients were predicted. Here, 88.2 % of the plasma concentrations were within the 2-fold error range. Finally, one patient was identified as a poor metabolizer.

Conclusions PBPK modelling in combination with calculated metabolic ratio is a cost-effective and fast new approach to draw conclusions about CYP2D6 phenotyping that can easily be done during TDM to finally adjust the dosage during therapy.

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

15 A HPLC-UV/VIS method for the quantification of valproic acid in human serum

Authors Lipecki Y[1], Haen E[1]
Institute 1 Clinical Pharmacology, Institute AGATE, Pentling/Germany, Department of Psychiatry and Psychotherapy and Department of Pharmacology and Toxicology of the University of Regensburg, Germany
DOI 10.1055/s-0040-1710123

Introduction Valproic acid (VPA) nowadays is not only used for the treatment of epilepsies, but also for schizophrenia, bipolar disorder, and several off-label indications. Except for epilepsies, therapeutic reference ranges (TRR) for useful therapeutic drug monitoring (TDM) are scarce. Most TDM-methods rely on HPLC-MS or immunological methods, because HPLC-analysis via UV/VIS-detection of VPA is challenging. However, occurring VPA concentrations showed to be high enough for reliable UV/VIS-detection. Developing a HPLC-UV/VIS method for the quantificantion of VPA in serum samples would give more laboratories the possibility to offer TDM.

Methods A simple and rapid method for the quantification of VPA in serum samples via HPLC-UV/VIS was developed. Sample preparation consisted of a protein precipitation step followed by centrifugation. Elution was performed under isocratic conditions with a mixture of methanol and phosphate buffer at pH 2.4. Detection wavelength was 210 nm and the total runtime 8 minutes.

Results The method was validated according to the FDA guideline for bioanalytical method validation and showed linearity over a concentration range from 5–300 µg/ml, with a limit of detection of 3 µg/ml. The recovery rate was found to be 96.97 %. 269 drugs and metabolites were tested and showed no interference with the analyte.

Conclusion This novel method will enable the determination of VPA-concentration in human serum in order to assess TRRs suitable for other indications than epilepsy. As the method provides a broad calibration range, measuring samples even far outside the epileptic TRR is ensured. Therefore, it is suitable for routine TDM and a valuable tool for making VPA treatment simpler and safer.

16 Using physiologically based pharmacokinetic (PBPK) modelling and SCHOLZ databank's MDDI calculator (SDB-MDDI) to predict potential drug-drug interactions (DDI) of psychopharmaceuticals

Authors Lücht UR[1], Geiben AK[2], Brune S[3], Scholz WU[3], Hempel G[1]
Institutes 1 Department of Pharmaceutical and Medicinal Chemistry Muenster, Germany; **2** Bezirksklinikum Regensburg, Germany; **3** ePrax GmbH Muenchen, Luedenscheid, Germany
DOI 10.1055/s-0040-1710124

Introduction Bupropion is occasionally added for augmentation to depression treatments with venlafaxine. Its inhibitory potential to CYP2D6, venlafaxine's main metabolic pathway, may provoke a higher risk for toxic or adverse drug effects. Therefore, the question arises if a dose reduction is needed.

Methods PBPK modelling with PK-Sim® and SDB-MDDI calculator predict the possible extent of DDI. Initially, models based on literature were developed. To evaluate the DDI-PBPK model prediction's expressiveness, 30 trough plasma concentration samples of 11 male and 12 female patients (median characteristics: 50 (range 33–73) years; 90 (57–140) kg; 171 (158–185) cm, 30 (20–47) kg/m^2) were extracted from the TDM-databank Konbest. These patients took bupropion and venlafaxine without any relevant comedication.

Results Compared to equally characterized patients, who are not treated with bupropion, TDM data reveals a significant increase of venlafaxine's median concentration-dose-ratio (C/D) about 134 %. The PBPK model calculates a 3.94-fold increase of venlafaxine's AUC. Active metabolite O-desmethylvenlafaxine's C/D decreases significantly about 28.1 % (PBPK-model: AUC – 51.7 %) and active moiety's C/D increases not significantly about 18.3 % (PBPK-model: AUC + 9.31 %). SDB-MDDI calculator does not indicate a significant pharmacokinetic interaction for the combination.

Conclusion Due to the low increase of AUC and trough concentration of the active moiety it is concluded that the DDI is clinically irrelevant and a dose reduction is not needed. This is consistent with findings of venlafaxine kinetics in CYP2D6 poor metabolizers [1].

References [1] Schoretsanitis G et al. (2019), Eur Arch Psychiatry Clin Neurosci 269(7): 851–857.

17 Using TDM data to study treatment failure

Author Molden E[1]
Institute 1 Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway
DOI 10.1055/s-0040-1710125

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.

18 Optimizing Therapeutic Drug Monitoring (TDM) of mirtazapine – Next step to personalized medicine

Authors Nierychlewski K[1], Meinzer S[1], Musil R[2], Schwarz M[1]
Institutes 1 Institute of Laboratory Medicine, University Hospital, LMU Munich, Germany; **2** Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Germany
DOI 10.1055/s-0040-1710126

Introduction TDM is an effective method to optimize and individualize pharmacotherapy through rapid dose-finding, to minimize side effect and to control for a possible non-adherence. In everyday clinical practice, just the therapeutic index (TI) is applied. However, this only includes an assumed standard dosage without referring to the individual daily dose. Moreover, information about possible abnormal drug metabolism or (partial) non-adherence cannot be deduced from TI. Beyond the TI to obtain a range between which a drug is effective or toxic, we tested following: a) Dose-Related Concentration (DRC) to integrate a patient's individual dosage into a theoretically expected drug concentration range. b) Metabolic Ratio (MR) to compare metabolite to parent compound concentrations.

Methods In a naturalistic setting, we included 326 inpatients (186 m, 140f; age: 53 years ± 17) treated at the psychiatric hospital of LMU Munich. Referring to the Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology (Hiemke et al. 2017) we compared the above calculations (TI, DRC, MR). Serum concentrations of mirtazapine and desmethyl-mirtazapine were quantified by LC-MS/MS. Statistical analyses were performed by using SPSS (25.0).

Results 41 % of the samples had concentrations below the TI (< 30 ng/ml) and 8 % had concentrations exceeding the TI area (> 80 ng/ml). Based on our naturalistic data we redefined these factors [DRC_{low} = 0.51 and DRC_{max} = 2.19], covering around 85 % of patients concentrations. 18 samples (5 %) exceeded the MR range (< 0.2; > 1.2).

Conclusion Altogether, only through the interplay of all of these methods (TI, DRC, MR) the therapy can be monitored more precisely, optimized and personalized.

19 Therapeutic Reference Ranges of Cariprazine and Atomoxetine

Authors Oster O[1], Ruppert K[1], Schulz E[1], Fleischhaker C[1], Clement HW[1]
Institute 1 University Medical Center Freiburg, Center of Mental Disorders, Department of Child and Adolescent Psychiatry, Psychotherapy and Psychosomatics
DOI 10.1055/s-0040-1710127

Introduction The effective concentrations of psychotropic drugs should be within the therapeutic reference range. The therapeutic reference range of atomoxetine, has so far only been defined for adult patients between 200–1000 ng/ml. Cariprazine, a second-generation antipsychotic, is indicated for the treatment of schizophrenia. The therapeutic reference range is given as 10–20 ng/ml. The aim in this study is to analyze the pharmacokinetics of atomoxetine and cariprazine more precisely and to re-evaluate recommendations for the therapeutic reference range.

Methods The analytical method for the determination of serum levels of atomoxetine was HPLC/UV. A total of 94 serum atomoxetine levels of 74 children and adolescents were determined and analyzed. Serum levels of cariprazine (CAR) and its pharmacologically active metabolites were quantified using LC-MS/MS.

Results For atomoxetine, maximum serum levels were confirmed in the time window of one to four hours after atomoxetine intake. For the weight normalized dose and the corresponding serum levels a significant correlation according to Pearson was shown (r = 0.807, p = 0.028, n = 7). A preliminary therapeutic reference range for children and adolescents was between 220 and 440 ng/ml. For cariprazine, mean values of 2.7 ng/ml (CAR), 1.6 ng/ml desmethyl-cariprazine and 10.5 ng/ml didesmethyl-cariprazine were measured, maximum values 5.3 ng/ml (CAR), 2.5 ng/ml desmethyl-cariprazine and 18.5 ng/ml didesmethyl-cariprazine.

Conclusion The reference range of atomoxetine for children and adolescents seems to be narrower than for adult patients. In the measurements for cariprazine, the therapeutic reference range established so far was only reached when the sum of the three active compounds was formed.

20 The relevance of TDM in opiate withdrawal

Author Roll SC[1]
Institute 1 Vitos Klinik Eichberg, Eltville, Germany
DOI 10.1055/s-0040-1710128

Introduction Levomethadone has a high interpatient variability in regards to the dose related serum concentration. It is unknown if the serum level correlates with withdrawal symptoms during opiate withdrawal.

Methods 31 patients (24 male, 7 female) were included in the study. The duration of opiate addiction was 15.2 ± 11.3 years. 17 patients were included in a levomethadone substitution program on admission. Levomethadone serum levels were measured during the off-tapering of levomethadone (after dose finding, days 2, 6 and 11 during the tapering off). The Subjective Opiate Withdrawal Scale (SOWS), the Objective Opiate Withdrawal Scale (OOWS) and Clinical Global Impression (CGI) were also measured at the same time points. ECG monitoring and monitoring for adverse drug reactions (UKU side effect rating scale) were also conducted.

Results A significant correlation was found for the dose of levomethadone to its serum level (r = 0.531; p = 0.001) and also for SOWS and OOWS to levomethadone serum levels (correlation coefficient −0.290; p = 0.011 and −0.280; p = 0.014 respectively). QtcB was elevated in two patients. For male patients QtcB 425.4 ± 19.2 ms, for female patients 437.5 ± 14.7 ms. The most common side effects were gastrointestinal side effects (n = 13), restlessness (n = 11), increased perspiration (n = 10) which could also be withdrawal effects. All serum levels of levomethadone were with 0–241 ng/ml below the therapeutic range of the AGNP guideline (250–400 ng/ml).

Conclusion The correlation of withdrawal symptoms with plasma levels of levomethadone makes TDM useful to optimize opiate withdrawal by avoiding severe withdrawal symptoms and discontinuation of the withdrawal.

21 Therapeutic drug monitoring of antidepressants in chronic pain treatment

Authors Scherf-Clavel M[2], Breisinger S[1,2], Fischer M[1], Deckert J[2], Unterecker S[2,#], Rittner HL[1,#]
Institutes 1 Center for Interdisciplinary Pain Medicine, Department of Anesthesiology, University Hospital of Würzburg, Würzburg, Germany; **2** Department of Psychiatry, Psychosomatics and Psychotherapy, Center of Mental Health, University Hospital of Würzburg, Würzburg, Germany; # Unterecker S and Rittner HL contributed equally
DOI 10.1055/s-0040-1710129

Introduction Chronic pain is a major public health problem with epidemiological studies reporting about one fifth of the general population to be affected both in the USA and in Europe. Antidepressants are recommended for the treatment of chronic pain, however, target serum concentrations using therapeutic drug monitoring (TDM) are unknown. Moreover, treatment of chronic pain with antidepressants mostly is independent of a comorbid depression.

Methods A literature research on serotonin/norepinephrine reuptake inhibitors (SNRI) and tricyclic antidepressants (TCA) as treatment options in chronic pain is performed and studies on TDM in pain treatment are summarized.

Results SNRIs and TCAs are effective treatment options, especially in neuropathic pain and fibromyalgia. Regarding musculoskeletal pain only single studies are reported with inconsistent results. Particularly, higher doses of antidepressants are used to treat depression, whereas low doses are prescribed for chronic pain. TDM studies in musculoskeletal pain are not reported so far. Preliminary data show that responders in chronic musculoskeletal pain treatment with comorbid depression are treated with a 1.7-fold higher serum concentration of amitriptyline + nortriptyline compared to non-responders. They also show a 2.3-fold higher serum concentration compared to non-depressed responders.

Conclusion Antidepressants are effective in treatment of chronic pain; however, dosing should take comorbid depression into account. The determination of serum concentration of antidepressant drugs can guide treatment to a better outcome of pain relief in patients with comorbid depression.

22 Using TDM to improve efficacy and safety outcomes of antipsychotic treatment

Authors Schoretsanitis G[1], Haen E[1], Hiemke C[1], Gründer G[1], Paulzen M[1]
Institute 1 Department of Psychiatry Research, The Zucker Hillside Hospital, Northwell Health, Glen Oaks, NY, USA
DOI 10.1055/s-0040-1710130

Introduction The application of therapeutic drug monitoring (TDM), i. e. the quantification of drug levels in a human matrix, can be helpful in numerous

challenging clinical scenarios, such as lack of therapeutic response, relapse, or adverse drug reactions (ADRs) related to antipsychotic treatment.

Methods A selective review of invariably observational studies and case reports that highlight the value of TDM as clinical routine tool for clinicians prescribing antipsychotic medications.

Results Increasing literature demonstrates the usefulness of TDM in the appropriate dose selection for antipsychotics. Specific patient subgroups treated with antipsychotics, such as elderly, patients receiving polypharmacy, women under oral contraception and pregnant women may essentially benefit from the regular use of TDM. Moreover, TDM can be instrumental in the prevention of ADRs, with strength of evidence highly depending on data availability. For example, a dominant amount of evidence is available for clozapine compared to other antipsychotics. On the other hand, TDM evidence is practically absent for clinical scenarios such as transition between different formulations of antipsychotics, which have been less investigated, particularly for second-generation antipsychotics.

Conclusions TDM can be useful for: 1) monitoring drug compliance, 2) evolution of the relationship between the drug blood concentration and antipsychotic effect, 3) potential drug-interaction susceptibility and ultimately for identification of the therapeutic window for clinical efficacy of antipsychotic agents. The presentation will provide examples of condensed clinical decision-making scenarios to assist clinicians who routinely prescribe antipsychotics, to successfully apply TDM in routine clinical practice in order to optimize antipsychotic efficacy and safety.

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

Author Shipkova M[1,2]

Institutes **1** Competence Center for Therapeutic Drug Monitoring; **2** SYNLAB Holding Deutschland GmbH, Leinfelden-Echterdingen, Germany

DOI 10.1055/s-0040-1710131

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 reliable 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.

Conclusion 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.

24 Clinical validation study to derive conversion factors from capillary blood concentration to plasma concentration for venlafaxine and desvenlafaxine

Authors Stern M[1], Giebels M[2], Fey T[2], Lübking M[3], Alferink J[3], Hempel G[1]

Institutes **1** Institut für Pharmazeutische und Medizinische Chemie – Klinische Pharmazie, Westfälische Wilhelms-Universität, Münster, Germany; **2** Gerontopsychiatrie, LWL-Klinik Münster, Münster, Germany; **3** Damian-Klinik, Alexianer Münster GmbH, Münster, Germany

DOI 10.1055/s-0040-1710132

Introduction In the last years, several new products to enable TDM with capillary blood entered the market. To interpret capillary blood concentrations with current therapeutic reference ranges, conversion factors have to be established with clinical validation studies.

Methods A study for venlafaxine and desvenlafaxine has been conducted with volumetric absorptive microsampling (VAMS) as sampling device in two hospitals in Münster (Germany) with 49 patient samples over a period of one year. After giving written informed consent, blood out of the vein and an additional drop of blood out of the fingertip was drawn and analyzed by LC-MS. The obtained data was analyzed with Passing-Bablok regression and Bland-Altman analysis.

Results A good correlation between capillary blood and plasma concentrations could be achieved with a pearson's R above 0.93 and a conversion factor of 0.87 for venlafaxine and 0.75 for desvenlafaxine. The conversion factors passed the cross-validation test according to EMA guidelines with Bland-Altman analysis.

Conclusion After one year, 49 patient samples could be collected and analyzed. The resulting Passing-Bablok regressions and Bland-Altman analysis led to conversion factors, which are suitable for the application in routine healthcare. The established method can now be used to offer TDM to an ambulant setting by patient self-sampling or sampling in pharmacies or through nurses. This enables the opportunity of a faster, easier and more widespread use of TDM.

25 Pharmacogenetic diagnostics and therapeutic implications for genome medicine

Author Stingl JC[1]

Institute **1** Institute of Clinical Pharmacology, University Hospital of RWTH Aachen

DOI 10.1055/s-0040-1710133

Introduction The role of pharmacogenetic diagnostics has changed during the past decades with a more explorative role in the beginning explaining differences in drug metabolism and elimination, further looking at differences in individual drug response and safety, and nowadays developing to a therapy companion diagnostic for indications of drug therapies.

Methods With the knowledge on our pharmacogenome, also new methods for genetic diagnostics arose, and large genome analyses now became convenient, easy to handle, and relatively cheap. While in centralized countries like the United States, the development of guidelines and pharmacogenetic information in drug labels is already advanced, in Europe, the diversity of national health systems affects regulation for pharmacogenetic diagnostics.

Results Recently, a European referral was opened that should clear the question of a pretherapeutic testing of DPYD variants in therapy with fluoropyrimidines. The outcome of the referral (expected in 2020) could mean that for the first time in Europe, a pharmacogenetic test is mandatory before onset of a common drug therapy (so far, only genetic testing in rare disease therapy is mandatory).

Conclusion Genome medicine is now in the implication phase with the use of pharmacogenetic tests for drug therapy indication, for individualized dosing and for the avoidance of side effects. Depending also on national health systems, genetic tests for therapy decisions are/and will become more and more in use in realworld clinical practice.

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

Authors Toto S[1], Grohmann R[2], Bleich S[1]
Institutes 1 Department of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Germany; **2** Department of Psychiatry and Psychotherapy, Ludwig-Maximilian-University, Munich, Germany
DOI 10.1055/s-0040-1710134

Introduction The monitoring of adverse drug effects has become increasingly important within modern psychopharmacology. The AMSP ('Arzneimittelsicherheit in der Psychiatrie'), founded in 1993, is a drug safety monitoring program with special emphasis on severe and unusual adverse drug reactions during treatment with psychotropic drugs.

Methods Data were gathered from the AMSP data base. 54 psychiatric hospitals in Germany, Switzerland and Austria participated from 1993 to 2018. Data on psychotropic use were based on two reference days per year. Adverse drug reactions (ADRs) were determined using ASMP definitions and rating questionnaire. Causal relationship between observed symptoms and drugs given at that time were carefully assessed [1].

Results A total of 462,661 psychiatric inpatients were monitored from 1993 to 2016. Throughout this time, antipsychotics and antidepressants were the drug classes most commonly prescribed. Polypsychopharmacology has 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 total 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, is a useful tool in estimating the risk/benefit ratio of drug therapy within clinical setting.

References [1] Grohmann R. et al. Pharmacopsychiatry 37:4–11, 2004

27 Comparative study of suggested reference values and observed distributions in daily routine of a medical laboratory – lessons learned and open questions

Author Zurek G[1]
Institute 1 MVZ Medizinisches Labor Bremen GmbH, Bremen, Germany
DOI 10.1055/s-0040-1710135

Introduction The Consensus Guidelines of the TDM-AGNP working group contain a comprehensive list of suggested reference ranges based on the current literature [1]. The aim of the present study is to compare routinely observed drug concentration values in plasma with proposed reference ranges. Although no indication, dose information, comedication or adverse effects are known, the existing data holds a wealth of interesting information to be explored.

Methods Anonymized data was extracted from the routine archive and plotted as histograms. The observed frequency distribution is compared with the published reference ranges.

Results and Conclusion All analyzed drugs share the common observation of a significant number of concentrations in plasma below the limit of detection (LOD). Thus, TDM acts as a toll for compliance testing. Additional reasons of drug concentrations being below the LOD are a non-optimal pre-analytical phase or particular pharmacokinetics (agomelatine, methylphenidate).

Drugs with a clear indication of regular TDM due to its high toxicity and high prescription rates such as lithium exhibit a dense distribution. In very sparse data sets, this approach can only indicate an observed range of concentrations to be compared with the reference range.

References [1] Hiemke et al. Pharmacopsychiatry 2018; 51: 9–62.