Thieme

Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017

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ABSTRACT

Therapeutic drug monitoring (TDM) is the quantification and interpretation of drug concentrations in blood to optimize pharmacotherapy. It considers the interindividual variability of pharmacokinetics and thus enables personalized pharmacotherapy. In psychiatry and neurology, patient populations that may particularly benefit from TDM are children and adolescents, pregnant women, elderly patients, individuals with intellectual disabilities, patients with substance abuse disorders, forensic psychiatric patients or patients with known or suspected pharmacokinetic abnormalities. Non-response at therapeutic doses, uncertain drug adherence, suboptimal tolerability, or pharmacokinetic drug-drug interactions are typical indications for TDM. However, the potential benefits of TDM to optimize pharmacotherapy can only be obtained if the method is adequately integrated in the clinical treatment process. To supply treating physicians and laboratories with valid information on TDM, the TDM task force of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) issued their first guidelines for TDM in psychiatry in 2004. After an update in 2011, it was time for the next update. Following the new guidelines holds the potential to improve neuropsychopharmacotherapy, accelerate the recovery of many patients, and reduce health care costs.

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Abbreviations

BBB	blood-brain-barrier
C/D	concentration to dose ratio
CL	total clearance
CL/F	apparent total clearance
Cav	average concentration
Cmax	maximal concentration
Cmin	trough or minimal concentration
CYP	cytochrome P450
DRC	dose-related concentration
EMA	European Medicines Agency
F	bioavailability (fraction absorbed)
FDA	Food and Drug Administration
GeKO	German Commission Genetic Testing
MPR	metabolite to parent compound ratio
PET	positron emission tomography
P-gp	P-glycoprotein
t1/2	elimination half-life
TDM	therapeutic drug monitoring
tmax	time of maximal drug concentrations
tmin	time of minimal drug concentration

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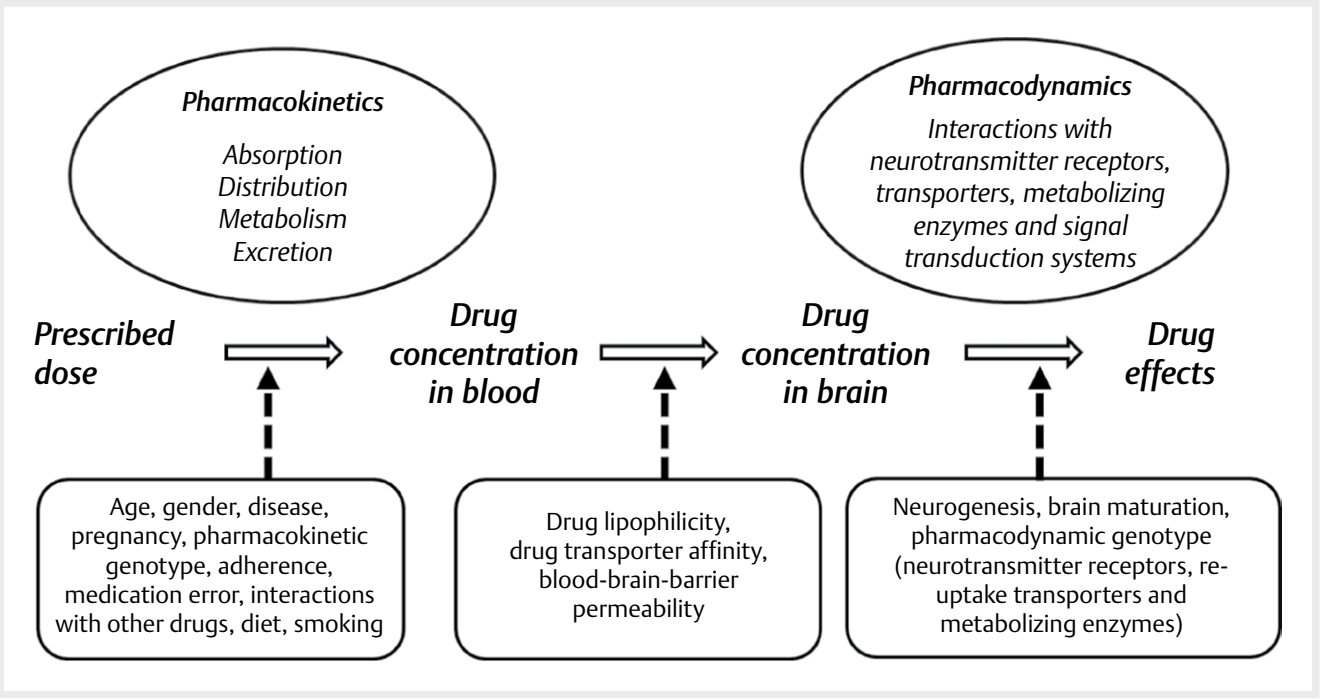

▶ **Fig. 1** From prescribed dose to drug effects modulated by multiple factors leading to marked pharmacokinetic and pharmacodynamic variability.

Background

For the treatment of psychiatric and neurologic patients, more than 200 drugs are available which have been discovered and developed during the last 60 years [89]. These drugs are effective and essential for the treatment of many neuropsychiatric/mental disorders and symptoms. Despite enormous medical and economic benefits, however, therapeutic outcomes are still far from satisfactory for patients and the prescribing physicians [6, 8, 709, 1206]. Therefore, after having focused clinical research on the development of new drugs [953, 954], growing evidence suggests that an improved application of available drugs may still bring substantial benefit to patients [75, 190, 248, 267, 1080]. Moreover, there is a gap between the available pharmacologic knowledge and its utilization in health care [1094]. The newest initiative to bridge this gap is "Precision Medicine". It considers individual variability to build the evidence base needed to guide clinical practice [229]. Therapeutic drug monitoring (TDM) is a patient management tool for precision medicine [565]. It enables tailoring the dosage of the medication(s) to the individual patient by combining the quantification of drug concentrations in blood, information on drug properties and patient characteristics. One major reason to use TDM for the guidance of neuropsychopharmacotherapy is the interindividual pharmacokinetic variability of the drugs in patients [957, 960]. At the very same dose, a more than 20-fold interindividual variation in the drug's steady-state concentration in the body may result, as patients differ in their ability to absorb, distribute, metabolize and excrete drugs due to concurrent disease, age, concomitant medication or genetic abnormalities [96, 328, 518, 520, 568, 569, 651]. Different pharmaceutic formulations of the same drug may also influence the degree and temporal pattern of absorption and, hence, drug concentrations in the body (▶ **Fig. 1**). TDM uses the quantification of a drug's concentration in blood plasma or serum to titrate the dosage of individual patients to a drug concentration in blood that is associated with the highest possible probability of response and a low risk of adverse drug reactions/toxicity. Moreover, TDM has the potential to enhance cost-effectiveness of neuropsychopharmacotherapy [13, 894, 961, 1204, 1267]. Despite TDM's potential, considerable disagreement was found between the information on TDM in official product information and existing medico-scientific evidence. Even for well-studied compounds, such as amitriptyline or clozapine, insufficient information on TDM was found in the product information (Summary of Product Characteristics, SPC) [1020, 1221]. For a large number of neuropsychopharmacological drugs, however, the quantification of blood concentrations has become clinical routine. Clear evidence of the benefits of TDM has been demonstrated for anticonvulsant drugs [912], tricyclic antidepressants [826], old (first generation or "typical") and new (second generation or "atypical") antipsychotic drugs [928] and mood stabilizing drugs [233]. For the mood stabilizer lithium, TDM has become a standard of care due to its narrow therapeutic range [230, 463, 707].

The benefits of TDM for optimization of pharmacotherapy, however, can only be obtained when the method is adequately integrated in the clinical treatment process. Current TDM use in neuropsychiatric care is often suboptimal as demonstrated by systematic studies [231, 462, 725, 1077, 1272, 1346]. The suboptimal use of TDM wastes laboratory resources and bears the risk of misleading results that will adversely influence clinical decision making [204]. A study on the clinical use of TDM for tricyclic antidepressants in psychiatric university hospital settings showed that 25 to 40 % of the requests for TDM were insufficiently filled out. Misinterpretation of the results led to about 20 % of incorrect dosage adjustments [1272, 1346, 1347]. Other typical errors were absence of steady-state conditions at the time of blood sampling and transcrip-

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tion errors on the request form. Studies on TDM for antidepressant and mood stabilizing drugs further specified the information on the imperfect use of TDM [757, 758]. For antiepileptic drugs, it was found that half of all requisitions were inappropriate [1077].

Against this background, the TDM task force of the working group on neuropsychopharmacology (Arbeitsgemeinschaft fuer Neuropsychopharmakologie und Pharmakopsychiatrie, AGNP) issued best practice guidelines for TDM in psychiatry with inclusion of recommendations for genotyping in 2004 [82]. In 2011, the guidelines were updated and considerably extended to include a large number of additional drugs, especially neurologic medications [524]. These guidelines were widely accepted by laboratories and practicing clinicians. The first guidelines [82] have been cited more than 300 times in the literature [1048]. The guidelines were translated into German [453, 521], Hungarian [523], French [85], Italian [522] and Chinese. Since 2011, knowledge about and acceptance of TDM has further advanced. The TDM task force of the AGNP therefore prepared this second updated version.

Objectives of the Consensus Document

This document addresses topics related to the theory and practice of TDM in psychiatry and neurology. The first part deals with theoretical aspects of monitoring neuropsychiatric drug concentrations in blood. The second part defines indications for TDM and gives orienting therapeutic concentrations in blood for dosage optimization. The third part describes best practice TDM, a process that starts with a request and ends in a clinical decision to either continue or change the pre-TDM pharmacotherapy.

To optimize the practice of TDM the following topics are addressed:

- definition of indications for using TDM in psychiatry and neurology
- definition of levels of recommendations to use TDM
- definition of therapeutic and dose-related reference ranges that laboratories can quote and clinicians can use to guide pharmacotherapy
- definition of alert levels for laboratories to warn the treating physician when drug concentrations are considered to be too high and potentially harmful
- recommendations and help for interpretative services
- recommendations for the combination of TDM with pharmacogenetic tests
- presentation of pharmacokinetic parameters required for interpretation of TDM results

Preparation of the Consensus Document

The updated consensus guidelines were prepared by the interdisciplinary TDM task force of the AGNP consisting of psychiatrists, neurologists, psychotherapists, pharmacologists including a court-certified pharmacology expert, biochemists, pharmacists and chemists from university hospitals and hospitals/institutions almost exclusively concerned with patient care in Germany, Switzerland, Austria, and Italy.

Data published in the previous AGNP consensus guidelines [82, 524] and other guidelines and recommendations for TDM of neuropsychiatric drugs [536, 587, 715, 869, 889–891, 912, 928, 932, 1304] were used. A systematic literature search was conducted, primarily in PubMed and in summaries of product characteristics (SPC), and also by hand in pharmacologic and clinical chemical journals to identify TDM-related information. More than two thousand articles were assessed. Finally, data were extracted from around 1400 articles identified as relevant for this 2nd update. A checklist (drug AND concentration AND (blood OR plasma OR serum)) was used to extract and analyse reported data. The search focused on therapeutic and dose-related drug concentrations in serum, plasma or blood. For the interpretative service of TDM, information on cytochrome P450 (CYP) substrate properties and metabolite parent compound ratios (MPR) were adopted or newly calculated. Moreover, CYP inducing and inhibiting properties of drugs and food constituents that are potentially relevant for pharmacokinetic drug-drug interactions were searched. Final decisions on the data presented in this update were made during five consensus conferences and by e-mail communication.

Therapeutic reference ranges are now listed for 154 neuropsychiatric drugs. Reference ranges were newly introduced for 25 drugs (levomilnacipran, tianeptine, vilazodone, vortioxetine, brexpiprazole, cariprazine, loxapine, lurasidone, N-desalkylquetiapine, brivaracetam, eslicarbazepine, perampanel, retigabine, diphenhydramine, doxylamine, gamma-hydroxy butyric acid, medazepam, modafinil, promethazine, zaleplone, heroin, morphine, nalmefene, nicotine and rotigotine) and revised for 18 drugs (bupropion, milnacipran, paroxetine, aripiprazole, asenapine, flupentixol, prothipendyl, felbamate, topiramate, lorazepam, temazepam, zolpidem, donepezil, galantamine, buprenorphine, disulfiram, methylphenidate and 3-O-methyldopa).

Special attention was given to the calculation of dose-related concentration (DRC) factors to compute dose-related reference ranges. They are used independently of the therapeutic reference range to identify adherence problems as well as individual pharmacokinetic abnormalities due to drug-drug interactions, poor or ultrarapid drug metabolism or altered liver or kidney function. The concept was introduced by Haen and colleagues [471] and adopted in the consensus guidelines 2011 for 83 neuropsychiatric drugs [524]. It was revised for this update and extended to 133 neuropsychiatric drugs, for 29 with inclusion of metabolites.

1. Pharmacokinetics and pharmacogenetics

1.1 Pharmacokinetic aspects

1.1.1 Absorption, distribution and elimination of neuropsychiatric drugs

Most neuropsychiatric drugs share a number of pharmacokinetic characteristics

- good absorption from the gastrointestinal tract into the blood compartment reaching maximal concentrations within 1–6 h
- highly variable systemic bioavailability ranging from 5 to essentially 100 %
- fast distribution from the blood compartment to the central nervous system with mostly higher levels in brain than in blood
- high apparent volume of distribution (about 10–50 L/kg)
- low trough drug concentrations in blood under steady-state conditions (about 0.1–500 ng/mL for psychiatric drugs and up to 20 µg/mL for neurologic drugs)
- elimination mainly by hepatic metabolism
- elimination half-life mostly between 12–36 h

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- linear pharmacokinetics at therapeutic doses with the consequence that doubling the daily dose will result in doubling the drug concentration in blood
- cytochrome P450 (CYP) and UDP-glucuronosyltransferases (UGT) as major metabolic enzyme systems

There are, however, numerous exceptions to this list of common pharmacokinetic features. For example, agomelatine, venlafaxine, trazodone, tranylcypromine, moclobemide, quetiapine, rivastigmine or ziprasidone display short (about 2–10 h) elimination half-lives, whereas aripiprazole and fluoxetine have long elimination half-lives (72 h for aripiprazole and 3–15 days for fluoxetine, taking into account its active metabolite norfluoxetine). Amisulpride, milnacipran, memantine, gabapentin, or sulpiride are only poorly metabolized in the liver and mainly excreted renally which may be advantageous for patients with impaired liver function. Paroxetine exhibits non-linear pharmacokinetics, due to inhibition of its own metabolism by a metabolite which is irreversibly bound to the enzyme resulting in its inactivation [108].

Many neuropsychopharmacological drugs are used as racemic compounds, and their enantiomers differ markedly in their pharmacodynamic and pharmacokinetic properties [88, 1104]. So far, however, methadone and methylphenidate are at present the only racemic psychotropic compounds for which TDM of the enantiomers has been introduced [68, 322]. The active enantiomer of racemic methadone is (R)-methadone, and l-methylphenidate (i. e., levorotary methylphendiate) is primarily responsible for the therapeutic effect of racemic methylphenidate. Flupentixol is available as a 1:1 mixture of the geometric cis- and trans-isomers (Z- and E-isomers, respectively) for oral administration, while the depot preparation flupentixol decanoate contains exclusively cis-flupentixol. Only the latter is considered to be pharmacologically active with regard to its affinity for dopamine (and serotonin) receptors, as shown in clinical studies in which clinical efficacy of cis-flupentixol (α-flupentixol; Z-flupentixol) was found to be superior to that of trans-flupentixol [83]. For research projects and other special situations, stereoselective analysis should be considered for parent drugs and/or metabolites, e. g., for citalopram, fluoxetine, venlafaxine, paliperidone or amitriptyline.

Inter- and intra-individual differences in blood concentrations of neuropsychopharmacological drugs (i. e., the pharmacokinetic variability) are caused by different activities of drug-metabolizing enzymes. The enzyme activity may decrease with age [651] and can be modified by renal and hepatic diseases. Most psychiatric or neurologic drugs undergo phase 1 metabolism by oxidative (e. g., hydroxylation, dealkylation, oxidation to N-oxides, S-oxidation to sulfoxides or sulfones), reductive (e. g., carbonyl reduction to secondary alcohols) or hydrolytic reactions [81]. Phase 1 reactions are predominantly catalyzed by CYP enzymes. They are proteins of a superfamily containing heme as a cofactor and function as terminal oxidases in electron transfer chains. The term P450 is derived from the spectrophotometric peak at the wavelength of the absorption maximum of the CYP enzymes (450 nm) in their reduced state complexed with carbon monoxide. CYP-catalyzed phase 1 reactions introduce a polar functional group that enables a phase 2 conjugation reaction with highly polar molecules such as glucuronic or sulphuric acid. For neuropsychopharmacological drugs possessing functional groups in the parent compound, glucuronidation of a hydroxyl (for example oxazepam or lorazepam) or an amine group to form N-glucuronides (for example olanzapine) may represent the essential metabolic pathway. According to their primary structure (sequence of amino acids) they are classified in 18 families of CYP genes and 43 subfamilies. In humans, 57 putatively functional genes and 58 pseudogenes are encoded by various gene clusters [1344]. For neuropsychopharmacological drugs, the most important isoenzymes are CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 (▶ **Table 1**) [59, 1344, 1351–1353]. Many CYP genes are highly susceptible to mutation. As explained below in more detail, genetic polymorphisms of CYP enzymes are major causes for the large interindividual variability of drug concentrations in the body, which gives rise to the need to measure them in blood.

Other enzymes may also be metabolic key determinants of drug action and toxicity [73]. Enzymes, such as aldo-keto reductases (AKRs), of the AKR superfamily catalyze reduction of aldehyde or ketone groups of endo- and exogenous compounds. In humans, 13 AKR proteins have been identified [73]. It was shown that they reduce ziprasidone to its dihydro derivative [93] and naltrexone to naltrexol [152]. Monoamine oxidase subtypes A and B (MAO-A and MAO-B) deaminate citalopram stereoselectively to an apparently inactive acidic metabolite [1007].

Actually, phase 2 enzymes are increasingly characterised with regard to substrate specificity. There is much overlap between the isoenzymes regarding affinity for substrates [245, 878]. Consequences for TDM are so far unclear.

Drugs are metabolized mainly in the liver and, to a minor degree, in extrahepatic tissues such as the intestinal mucosa or the brain [94, 402, 803].

When combining drugs that are inhibitors or inducers of drug metabolizing enzymes (▶ **Table 2, 3**), pharmacokinetic drug-drug interactions may occur if the comedication is a substrate of the inhibited or induced enzyme. Many interactions have been found by TDM either by chance or retrospective analysis of TDM data bases [183, 502, 918, 974, 1054, 1055, 1295]. Among environmental factors, smoking is of high clinical relevance for drugs that are substrates of CYP1A2 [336, 343]. CYP1A2 is dose-dependently induced by constituents of cigarette smoke (polycyclic aromatic hydrocarbons, not nicotine). When smoking 1–5, 6–10 and >10 cigarettes per day, the activity of CYP1A2 increases by 1.2-, 1.5- and 1.7-fold, respectively [342]. The increased activity returns to baseline within three days after smoking cessation. Smoking effects should therefore be considered at least when more than 10 cigarettes are smoked per day [343]. Cessation of heavy smoking under therapy with a CYP1A2 substrate (▶ **Table 1**) such as clozapine [133, 1232], duloxetine [375] or olanzapine [1357] may require dose reduction which should be controlled by TDM.

Besides enzymes involved in phase 1 and 2 metabolism, drug transporters play a role in the distribution pharmacokinetics of drugs [161, 301, 1214, 1320]. They are ATP-binding cassette (ABC) proteins located in cell membranes and function as efflux transporters to protect organs against xenobiotics. For many neuropsychopharmacological drugs, ABC transporters, especially P-glycoprotein (P-gp), the gene product of ABCB1, multidrug resistance protein (MRP) encoded by ABCC1 and breast cancer resistance protein (BCRP) encoded by ABCG2 have been identified as major de-

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▶ **Table 1** Enzymes and efflux transporters involved in the metabolism and distribution of neuropsychopharmacological compounds.

Drugs	Enzymes and transporters	References
Acamprosate	Not metabolized	[1033]
Agomelatine	**CYP1A2**, CYP2C19, CYP3A4	[126, 721]
Alprazolam	**CYP3A4**	[24, 905]
Amantadine	90 % is excreted unchanged via the kidney	[38]
Amisulpride	More than 90 % is excreted unchanged via the kidney	[1018]
Amitriptyline	CYP1A2, CYP2C9, **CYP2C19, CYP2D6**, CYP3A4, UGT1A3, UGT1A4, UGT2B10, P-gp (ABCB1)	[84, 150, 516, 878, 1187, 1215, 1216, 1293]
Amitriptyline oxide	FMO, **CYP2C19, CYP2D6**	[150, 276]
Amfetamine (dexamfetamine, lisdexamfetamine)	CYP2D6	[55]
Aripiprazole	**CYP2D6, CYP3A4**, P-gp (ABCB1)	[509, 639, 832, 1273]
Asenapine	**CYP1A2**, UGT1A4	[222, 1285]
Atomoxetine	**CYP2C19, CYP2D6**, P-gp (ABCB1)	[217, 805, 1354]
Benperidol	Unknown	[1068]
Benserazide	Hydroxylation, COMT	[594]
Biperiden	Unknown	[1146]
Brexpiprazole	**CYP3A4, CYP2D6**	[443]
Brivaracetam	CYP2C8, **renal elimination**	[1042]
Bromazepam	**CYP2C19**, **CYP3A4**	[26, 877]
Bromocriptine	**CYP3A4**	[938]
Bromperidol	**CYP3A4**	[388, 1156, 1176, 1337]
Brotizolam	**CYP3A4**	[1193]
Buprenorphine	CYP2C8, **CYP3A4**, UGT1A3, UGT2B7	[129, 817]
Bupropion	CYP2C19**, CYP2B6,** CR	[232, 514]
Buspirone	**CYP3A4**	[748]
Cabergoline	Unknown**,** CYP3A4, P-gp (ABCB1)	[54, 278]
Caffeine	**CYP1A2, CYP2A6**, xanthine oxidase, NAT	[15, 386, 475]
Carbamazepine	CYP1A2, CYP2C8, **CYP3A4**, UGT2B7, P-gp (ABCB1), BCRP (ABCG2), epoxide hydrolase	[586, 618, 730, 906, 1214, 1280]
Carbidopa	Loss of the functional hydrazine group, 1/3 not metabolized	[1030, 1261]
Cariprazine	CYP2D6, **CYP3A4**	[174, 840]
Chlordiazepoxide	**CYP3A4**	SPC
Chlorpromazine	CYP1A2, CYP2D6, P-gp (ABCB1)	[1277, 1316]
Chlorprothixene	Probably CYP2D6, CYP3A4	
Citalopram	**CYP2C19,** CYP2D6, CYP3A4, P-gp (ABCB1)	[158, 384, 1339]
Clobazam (norclobazam)	CYP2C19, **CYP3A4**	[271]
Clomethiazole	CYP2A6, CYP3A4	[189]
Clomipramine	CYP1A2, **CYP2C19, CYP2D6,** CYP3A4, UGT2B10	[412, 878]
Clonazepam	CYP3A4	[1070]
Clorazepate	CYP2C19, CYP3A4	
Clozapine	**CYP1A2, CYP2C19,** CYP3A4, P-gp (ABCB1)	[568, 884, 1232, 1278]
Cocain	**Carboxylesterase 1** and 2**,** pseudocholinesterase, CYP3A4	[776]
Codeine	**CYP2D6**, CYP3A4, UGT2B4, **UGT2B7**	[802, 878]
Cyamemazine	CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4	[45]
Dapoxetine	**CYP2D6**	[1333]
Desipramine	**CYP2D6**	[412]
Desvenlafaxine	CYP3A4, **CYP2C19, UGT**	[63]
Dextroamfetamine	CPY2D6	[55]
Diacetylmorphine (heroin)	**Carboxylesterase 2** and 1, UGT	[776, 802, 878]
Diazepam	CYP2B6, **CYP2C19, CYP3A4,** UGT2B7, P-gp (ABCB1)	[387, 846, 1275]
Dihydroergocryptine	**CYP3A4**	[29, 274]
Diphenhydramine	**CYP2D6**, UGT1A4, **UGT2B10**, P-gp (ABCB1)	[17, 846, 878]

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▶ **Table 1** Continued.

Drugs	Enzymes and transporters	References
Disulfiram	CYP1A2, CYP2A6, CYP2B6, CYP2E1, CYP3A4	[743]
Donepezil	**CYP2D6,** CYP3A4, P-gp (ABCB1)	[863, 1242]
Dothiepin (dosulepin)	**CYP2C19,** CYP2D6	[1341]
Doxepin	**CYP2C9, CYP2C19, CYP2D6**	[488, 633]
Doxylamine	Unknown	
Dronabinol	**CYP2C9, CYP3A4,** UGT1A9, UGT1A7, UGT1A8, UGT1A10	[119, 787, 878]
Duloxetine	**CYP1A2,** CYP2D6, P-gp (ABCB1)	[726, 1024]
Entacapone	**UGT1A9**	[687]
Escitalopram	**CYP2C19,** CYP2D6, CYP3A4, P-gp (ABCB1)	[166, 1207, 1268]
Ethanol	**Alcohol dehydrogenase, CYP2E1**	[193]
Felbamate	Renal excretion	[995]]
Flunitrazepam	CYP2C19, CYP3A4	[228, 392]
Flunarizine	**CYP2D6**	[841]
Fluoxetine	CYP2B6, **CYP2C9, CYP2C19, CYP2D6**, P-gp (ABCB1)	[723, 1064]
Flupenthixol	**CYP2D6**	[254, 633]
Fluphenazine	**CYP2D6**, P-gp (ABCB1)	[1352–1353]
Flurazepam	CYP2C19, CYP3A4	[1061]
Fluspirilene	Renal excretion, CYP3A4	[1113]
Fluvoxamine	**CYP2D6, CYP1A2**, P-gp (ABCB1)	[303, 611, 814]
Gabapentin	Not metabolized, renal excretion	[123]
Galantamine	CYP2D6, CYP3A4	[58]
Gammahydroxybutyric acid (GHB)	Beta-oxidation	[710]
Guanfacine	**CYP3A4**, epoxide hydratase, UGT	[623]
Haloperidol	**CYP2D6**, **CYP3A4**, AKR, UGT, P-gp (ABCB1)	[73, 154, 1176, 1277]
Heroin (diacetylmorphine)	**Carboxylesterase 2** and 1, UGT	[776, 802, 878]
Iloperidone	**CYP2D6,** CYP3A4	[175]
Imipramine	**CYP1A2, CYP2C19, CYP2D6,** CYP3A4, UGT1A4, UGT2B10	[412, 744, 878]
Lamotrigine	UGT1A4, UGT3B7, P-gp (ABCB1), BCRP (ABCG2)	[201, 1281]
Levetiracetam	Not metabolized, P-gp (ABCB1)	[849]
Levodopa	**DDC,** COMT, MAO	[1030]
Levomepromazine	**CYP3A**	[61, 1315]
Levomilnacipran	**CYP3A4**, P-gp (ABCB1)	[166, 901]
Levomethadone	CYP2B6, **CYP3A4,** CYP2D6	[249]
Levosulpiride	P-gp (ABCB1)	[214]
Lisdexamfetamine	Erythrocyte peptidase, CYP2D6	[668]
Lisuride	CYP3A4, **CYP2D6**	[975]
Lithium	Renal clearance	[424, 1125]
Lorazepam	UGT2B15	[275, 334, 878]
Loxapine	CYP3A4, CYP2D6, CYP1A2, CYP2C8, CYP2C19, FMO	[736]
Lurasidone	**CYP3A4**	[213]
Maprotiline	**CYP2D6**, CYP1A2	[140]
Medazepam	CYP2B6, **CYP2C19, CYP3A4**	SPC
Melatonin	**CYP1A2**	[489]
Melperone	Unknown	[135]
Memantine	Scarcely metabolized	[419]
Methadone	**CYP2B6, CYP3A4**, CYP2D6, ABCB1	[249, 718, 1082, 1203]
Methylphenidate	Carboxylesterase 1	[844]
Mianserin	**CYP2D6,** CYP1A2, CYP3A4	[664]
Midazolam	**CYP3A4**, UGT1A4	[372, 878]
Milnacipran	CYP3A4,ABCB1, **renal excretion**	[166, 704, 904, 968]
Mirtazapine	CYP3A4, CYP1A2, CYP2D6	[712, 1150]

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▶ **Table 1** Continued.

Drugs	Enzymes and transporters	References
Moclobemide	**CYP2C19,** CYP2D6	[423]
Modafinil	Amide hydrolase, CYP3A4	[1003, 1323–1324]
Morphine	CYP2C8, CYP3A4, **UGT2B7**	[262, 620, 776]
Nalmefene	UGT	[297]
Naloxone	UGT2B7, AKR1C	[73, 878]
Naltrexone	**AKR1C4**	[73, 152]
Nicotine	**CYP2A6,** UGT1A1, UGT1A2, UGT2B10	[104]
Nitrazepam	**CYP3A4**	[1171]
Nordazepam	CYP3A4, CYP2C19	[887, 1171]
Nortriptyline	**CYP2D6**, P-gp (ABCB1)	[675, 885, 1215, 1249]
Olanzapine	**UGT1A4**, UGT2B10, FMO, **CYP1A2**, CYP2D6, P-gp (ABCB1)	[176, 337, 878, 1277]
Opipramol	**CYP2D6**	SPC
Oxazepam	UGT1A9, UGT2B7, UGT2B15	[246, 878]
Oxcarbazepine	AKR, UGT2B15, P-gp (ABCB1)	[73, 878, 1279]
Paliperidone (9-hydroxyrisperidone)	60 % excreted unmetabolized, CYP3A4, UGT, P-gp (ABCB1), BCRP (ABCG2)	[273, 303, 461, 1250, 1277–1278]
Paroxetine	**CYP2D6**, CYP3A4, P-gp (ABCB1)	[303, 351, 596, 1215, 1256]
Perampanel	**CYP3A4,** CYP2B6, UGT1A1, UGT1A4	[910]
Perazine	CYP1A2, CYP2C9, CYP2C19, CYP3A4, FMO	[1149, 1316]
Pergolide	CYP3A4	[1329]
Perphenazine	CYP1A2, CYP2C19, **CYP2D6,** CYP3A4	[16, 886]
Phenytoin	CYP2C9, CYP2C19, UGT2B15	[730]
Phenobarbital	CYP2C19, UGT1A4	[34]
Pimozide	CYP1A2, **CYP2D6, CYP3A4**	[285, 1011]
Pipamperone	Unknown	
Piribedil	Demethylation, p-hydroxylation, and N-oxidation	[279]
Pramipexole	Not metabolized	[97]
Prazepam	**CYP2C19, CYP3A4**	SPC
Pregabalin	Not metabolized, renal excretion	[123]
Promazine	CYP1A2, CYP2A6, CYP2C19, CYP3A4	[1318]
Promethazine	**CYP2D6**	[839]
Quetiapine	**CYP3A4,** CYP2D6, P-gp (ABCB1)	[65, 1277]
Rasagiline	**CYP1A2**	[458]
Reboxetine	CYP3A4	[510, 1299]
Retigabine	NAT, UGT	[1197]
Risperidone	**CYP2D6,** CYP3A4, P-gp (ABCB1), BCRP (ABCG2)	[303, 461, 1278, 1330]
Rivastigmine	Cholinesterase	
Ropinirole	**CYP1A2**	[614]
Rotigotine	**CYP2C19**, CYP1A1, CYP1A2, CYP2D6, CYP3A4, SULT1A1, SULT1A2, SULT1A3, SULT1B1, SULT1C4, SULT1E1, UGT	[187, 279, 335, 579]
Rufinamide	Carboxylesterase	[936]
Selegiline	**CYP2B6**	[95]
Sertindole	**CYP2D6**, CYP3A4	[1322]
Sertraline	**CYP2B6, CYP2C19,** CYP2C9, CYP2D6, CYP3A4, UGT1A1, P-gp (ABCB1)	[876, 1215, 1276]
Sulpiride	Not metabolized, renal excretion, P-gp (ABCB1)	[214]
Temazepam	CYP219, UGT2B7	[622, 887]
Tetrahydrocannabinol (THC)	**CYP2C9**, CYP3A4	[776, 1151]
Thioridazine	**CYP1A2, CYP2D6,** CYP3A4	[1184, 1294]
Tianeptine	Beta-oxidation	[449]
Tiapride	Not metabolized	[865]

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▶ **Table 1** Continued.

Drugs	Enzymes and transporters	References
Tolcapone	COMT, CYP2A6, CYP3A4, UGT	[687]
Topiramate	UGT, P-gp (ABCB1)	[730]
Tranylcypromine	MAO, unclear	[64]
Trazodone	**CYP3A4,** CYP2D6	[442, 1019]
Triazolam	**CYP3A4**	[439]
Trifluoperazine	UGT1A4	[878]
Trimipramine	**CYP2C19, CYP2D6,** CYP2C9, CYP3A4, UGT2B10	[319, 878]
Valproic acid	UGT1A3, UGT1A6, UGT2B7, CYP2A6, CYP2B6, CYP2C9, CYP219, beta-oxidation	[878, 1169]
Venlafaxine	**CYP2C19**, **CYP2D6,** CYP2C9, CYP3A4, P-gp (ABCB1)	[367, 606, 788]
Vilazodone	**CYP3A4,** P-gp (ABCB1)	[128, 166]
Vortioxetine	**CYP2D6,** CYP3A4, CYP2A6, CYP2C9, P-gp (ABCB1)	[548]
Zaleplone	Aldehyde oxidase, **CYP3A4**	[993]
Ziprasidone	CYP3A4, aldehyde oxidase	[93, 950]
Zolpidem	CYP1A2, CYP2C9, **CYP3A4**	[1269]
Zopiclone	CYP2C8, **CYP3A4**	[92, 1202]
Zotepine	CYP1A2, CYP2D6, **CYP3A4**	[1083]
Zuclopenthixol	**CYP2D6**	[559]

ABC: ATP-binding cassette; AKR: aldo-keto reductase; COMT: catechol-O-methyltransferase; CR: carbonyl reductase; CYP: cytochrome P450; DDC: dopadecarboxylase (= aromatic amino acid decarboxylase); FMO: flavin monooxygenase; MAO: monoamine oxidase; NAT: N-acetyltransferase; SPC: summary of product characteristics; SULT: sulfotransferase; UGT: UDP-glucuronosyltransferase; P-glycoprotein (P-gp) is encoded by the ABCB1 gene and breast cancer resistance protein (BCRP) by the ABCG2 gene. Indicated CYP substrate properties are based primarily on in vivo studies in humans, whereas ABC substrate properties rely on animal or cell line studies. When compounds are combined with strong or moderate inhibitors (See ▶ **Table 2**) or inducers (See ▶ **Table 3**) and enzymes are indicated in bold, then the compounds' concentrations in blood will significantly increase or decrease.

terminants of drug distribution kinetics (▶ **Table 1**) [1320]. Drugs that are ABC transporter substrates are taken up by passive diffusion into cells and then expelled via ABC transporters into the extracellular space by ATP-dependent conformational changes. P-gp is highly expressed in the blood brain barrier (BBB) and the small intestine and thus plays a significant role in governing drug trafficking into and out of distinct organs [1320]. Animal studies give evidence that P-gp controls the availability rate of many antidepressant and antipsychotic drugs like nortriptyline, citalopram or risperidone in the brain [303, 1157, 1215]. It is suggested that high P-gp function is responsible for inefficacious concentrations, and low P-gp function is associated with high drug concentrations and tolerability problems [111, 146, 147, 160, 263, 850, 978, 1217]. Similar to CYP enzymes, multiple genetic mutations have been identified for ABC transporters [1320]. Moreover, the expression of ABC transporters is up- and down-regulated in a variety of ways, e. g., by pathophysiological stressors, xenobiotics, hormones or dietary factors [809].

Gender differences have also been reported for the pharmacokinetics of neuropsychopharmacological drugs [9–11, 762, 1088, 1107, 1127, 1340], most likely due to effects of female sex hormones on the pharmacokinetic processes of absorption, distribution, metabolism, and excretion [256, 656]. However, findings are still inconsistent and their clinical relevance is not yet clear. Although body weight should, on pharmacokinetic principle [77], be a major determinant of the blood concentration of a medication after administration of a certain dose, some studies found the impact of body weight to be less than predicted by pharmacokinetic principles [9, 1088, 1226]. Systematic research in these fields is still required.

1.1.2 Drug concentrations in blood

▶ **Fig. 2** shows the concentration time curve after oral application of a hypothetical drug. At steady-state, drug intake equals drug elimination over a defined time frame. Concentrations will fluctuate during the day, especially in the case of drugs with short elimination half-lives (< 12 h) and depending on the dosing scheme (i. e., dosage) which must be considered for interpretations of TDM results [1134]. In TDM, trough concentrations (Cmin) at steady-state (therapy with constant dose for at least 4 to 6 half-lives) have been used as the standard procedure for the vast majority of drugs. The procedure of trough sampling immediately prior to the next dose has been chosen for practicality. Deviations from the correct sampling time immediately prior to the next dose are less critical for trough samples than during other phases after dose application, since the concentration time curve is relatively flat towards the end of the dosing interval (terminal ß-elimination phase).

Therapeutic ranges are determined in clinical studies correlating these trough concentrations with clinical outcomes. A frequent problem is, that blood sampling at different time points throughout the dosing interval leads to concentrations that may be misinterpreted as conferring an enhanced risk for adverse drug reactions when in reality true trough levels would be lower and no benchmark (therapeutic range) is available for such mistimed samples. As explained below, the expected trough concentration can and should then be computed.

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▶ **Table 2** Inhibitors of CYP enzymes involved in drug metabolism.

Inhibiting drugs	Inhibited enzymes	References
Amiodarone	**CYP2C9**, CYP2D6, CYP3A4	[790]
Amprenavir	**CYP3A4**	[1313]
Aprepitant	**CYP3A4**	[749]
Atazanavir	**CYP3A4**	[1266]
Boceprevir	**CYP3A4**	[407]
Bupropion	**CYP2D6**	[663]
Cimetidine	CYP1A2, CYP2D6, CYP3A4	[769]
Ciprofloxacin	**CYP1A2, CYP3A4**	[76]
Clarithromycin	**CYP3A4**	[969]
Clomethiazole	**CYP2E1**	[296]
Clopidogrel	CYP2B6	[996]
Crizotinib	**CYP3A4**	[761]
Diltiazem	**CYP3A4**	[1154]
Disulfiram	**CYP2E1**	[619]
Duloxetine	**CYP2D6**	[1096]
Enoxacin	**CYP1A2**	[1112]
Erythromycin	**CYP3A4**	[883]
Esomeprazole	**CYP2C19**	[879]
Felbamate	CYP2C19	[981]
Fluconazole	**CYP2C9, CYP3A4**	[860]
Fluoxetine and norfluoxetine	**CYP2D6**, **CYP2C19**, CYP3A4	[572]
Fluvoxamine	**CYP1A2**, CYP2C8, CYP2C9, **CYP2C19**, CYP3A4	[572]
Fosamprenavir	**CYP3A4**	[1313]
Gemfibrocil	**CYP2C8**	[59]
Grapefruit juice	**CYP3A4**	[1128]
Indinavir	**CYP3A4**	[1270]
Isoniazid	CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP3A4, **MAO**	[859]
Itraconazol	**CYP3A4**	[1173]
Ketoconazol	**CYP3A4**	[293]
Levomepromazine	**CYP2D6**	[1258]
Melperone	**CYP2D6**	[502]
Metoclopramide	CYP2D6	[724]
Miconazol	**CYP2C9**, CYP3A4	[860]
Moclobemide	**CYP2C19**, **CYP2D6**, **MAO-A**	[215, 423, 485]
Nelfinavir	**CYP3A4**	[629]
Norfloxacine	CYP1A2	[385]
Omeprazole	**CYP2C19**	[1282]
Paroxetine	**CYP2D6**	[572]
Perazine	**CYP1A2**	[360, 1317]
Phenylpropanolamine	**CYP1A2**	[182]
Posaconazole	**CYP3A4**	[667]
Propafenon	CYP1A2, CYP2D6	[804]
Quinidine	**CYP2D6**	[142]
Ritonavir	CYP2D6, **CYP3A4**	[72, 629, 1270]
Saquinavir	**CYP3A4**	[72]
Telaprevir	**CYP3A4**	[394]
Telithromycine	**CYP3A4**	[601]
Ticlopidine	CYP2B6, **CYP2C19**	[996]
Tranylcypromine	**CYP2A6, MAO**	[411]
Valproic acid	CYP2C9	[291, 460]
Verapamil	**CYP3A4**	[692]
Voriconazol	**CYP2B6**, CYP2C9, **CYP2C19**, **CYP3A4**	[179]
Zileuton	**CYP1A2**	[426]

Drugs that are primarily metabolized by an inhibited enzyme are potential victim drugs. Combination with these inhibitors can lead to clinically relevant drug-drug interactions (www.mediq.ch or www.psiac.de). Inhibition of enzymes indicated in bold will increase plasma concentrations of victim drugs by more than 50 % (See ▶ **Table 1**). CYP: cytochrome P450, MAO: monoamine oxidase.

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▶ **Table 3** Inducers of enzymes and efflux transporters involved in drug metabolism and distribution.

Inducing drugs	Induced enzymes or ABC transporters	Comments	References
Bosentan	**CYP3A4**		[764]
Carbamazepine	CYP1A2, **CYP2B6,** CYP2C9, **CYP3A4, P-gp (ABCB1), UGT**	Increase of CYP3A4 activity within 3 weeks, induction of its own metabolism	[12, 266, 409, 882, 1122]
Efavirenz	**CYP2B6, CYP3A4**		[1004]
Ethanol	**CYP2E1**	Induction may lead to metabolic tolerance.	[590, 708]
Isoniazide	**CYP2E1**	Initial inhibition and then induction of CYP2E1	[1069, 1343]
Lamotrigine	**UGT**		[266]
Modafinil	CYP1A2, CYP2B6, **CYP3A4**		[1002]
Oxybutynin	**CYP3A4**		[452]
Phenobarbital	CYP1A2, **CYP2B6,** CYP2C9, CYP2C19, **CYP3A4, UGT1A1**		[742]
Phenytoin	CYP1A2, **CYP2B6,** CYP2C9, CYP2C19**, CYP3A4, UGT**		[60, 266]
Primidone	CYP2C9, CYP2C19, **CYP3A4**		[935]
Rifabutin	**CYP3A4**	Induction of own metabolism	[1349]
Rifampicin	**CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4**	After induction by rifampicin, CYP2C19 and CYP3A4 activities remain elevated for 4 days after discontinuation and return to baseline levels within 8 days.	[552, 742]
Ritonavir	**CYP2C9,** CYP3A4 (high dose), UGT		[368]
Smoke	**CYP1A2**	Maximal increase by 10 or more cigarettes per day, decrease of CYP1A2 activity within 3 days after smoking cessation	[342–343]
St. John's wort	**CYP3A4,** CYP2C9, **P-gp (ABCB1)**		[466]

ABC: ATP-binding cassette transporter; CYP: cytochrome P450; UGT: UDP-glucuronosyltransferase; P-glycoprotein (P-gp) is encoded by the ABCB1 gene. Induction of enzymes that are indicated in bold will decrease plasma concentrations of victim drugs (See▶ **Table 1**) by more than 50 %.

▶ **Fig. 2** shows that drug concentrations in blood depend on the choice of dosing. It is, therefore, mandatory to consider the dosing scheme used in clinical studies to derive therapeutic ranges. Clearly, the therapeutic ranges reported are only valid for the dosing scheme used in the respective study and cannot easily be transferred to other dosing schemes and application forms (iv, intramuscular depot etc.). Interpretation of TDM results becomes even more complicated when dosing schemes are used that distribute the daily dose in an unequal fashion, e. g., higher doses in the evening than during the day to achieve sedation during the night. Therefore, the dosing schemes relevant for therapeutic ranges are important for proper interpretation of the TDM result.

1.1.3 Drug concentrations in brain and cerebrospinal fluid

The pharmacologic activity of psychiatric and neurologic drugs depends on their availability at the target sites within the brain. The delivery of drugs from blood to brain takes place across brain capillary endothelial cells comprising the BBB [481]. The BBB controls the brain environment by efficiently restricting the exchange of solutes, e. g., by hindering the influx of potentially harmful xenobiotics including many drugs. The permeability of the BBB for a particular molecule defines the rate at which a drug enters brain interstitial fluid (ISF) from where the molecules will then be further distributed to and equilibrated within the brain cells [481]. Drug transportation from blood to cerebrospinal fluid (CSF) and vice versa takes place at the blood-CSF barrier (BCSFB) supplemented by an exchange between CSF and brain ISF. The CSF is an accessible sampling site for measuring drug concentrations of unbound drugs. Two systematic studies of 39 compounds by Fridén et al. [376] and 25 compounds by Kodaira et al. [652] demonstrated a good correlation between CSF and ISF drug concentrations for compounds that show a high permeability and little or no drug efflux via transporters. The role of CSF as a site for measuring unbound drug concentrations in brain, however, is still under discussion [481].

Drugs that are efficiently eliminated from the brain at the BBB are primarily P-gp substrates like risperidone, aripiprazole or venlafaxine [303, 639, 1217]. For these compounds, brain ISF concentrations are much lower than blood concentrations. When drugs are substrates of P-gp, the brain to blood concentration ratios vary widely for drugs with similar physicochemical properties. Animal studies found ratios ranging from 0.22 for risperidone [44] to 34 for fluphenazine [42]. Despite highly variable ratios of brain to blood concentrations of the different neuropsychiatric drugs, animal studies have shown that steady-state concentrations in blood correlate well with concentrations in brain, and much better than they correlate to the prescribed dosages. This has been shown, e. g., for tricyclic antidepressants [417], trazodone [287], or olanzapine [43]. In patients, it has been shown by magnetic resonance spectroscopy that brain concentrations of fluoxetine and norfluoxetine parallel concentrations in blood [607]. For carbamazepine and its epoxide, a linear relationship between brain and blood concentrations was found in patients undergoing brain surgery [821]. For neuropsychiatric medications, drug concentrations in blood can therefore be considered a valid marker of concentrations in brain.

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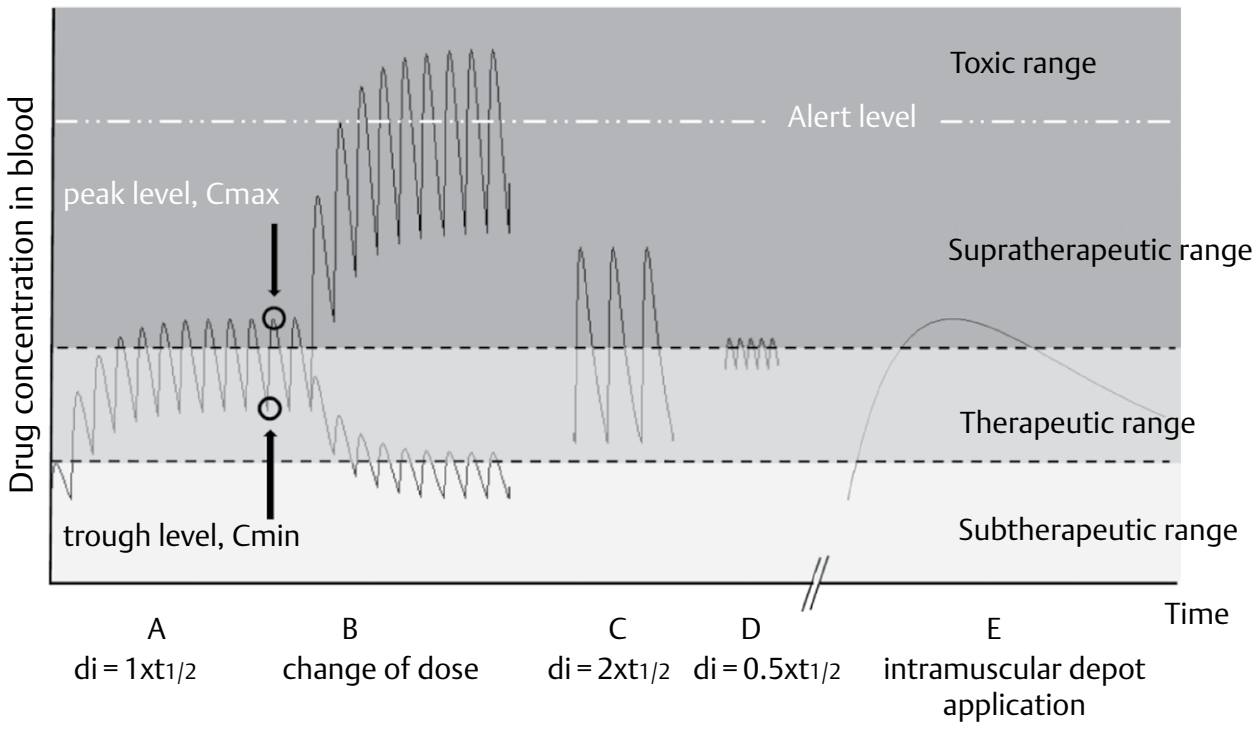

▶ **Fig. 2** Concentration time curve after oral or intramuscular depot medication. A: 94 % of steady state (therapy with constant dose) is reached after four elimination half-lives (t1/2) of the drug. At steady-state, drug intake equals drug elimination over a defined time frame. Trough levels (Cmin) at steady state are usually quantified and recommended for TDM. The figure shows a hypothetical drug with a dosing interval (di) equal to its half-life ($di = t_{1/2}$), a situation found similar for many drugs (e. g., $t_{1/2} = 12$ h, di = 12 h, curve A). Trough concentrations are right in the middle of the therapeutic range, i. e., on target, despite the fact that the drug's concentrations during the dosing interval sometimes exceed the therapeutic range. B: Modification of drug concentrations by doubling or halving the dose without change of the dosing interval. C: Doubling the dose interval ($di = 2 \times t_{1/2}$) and administering the entire daily dose once daily results in curve C. The area under the blood concentration versus time curve (AUC) representing the total drug exposition is identical for curves A and C, however, trough concentrations in curve C (24 h after the daily dose) are significantly lower than in curve A (12 h after a half daily dose). High differences between trough and peak levels can be associated with tolerability problems during the phases of high drug concentrations. D: Curve D illustrates the intake of four equal doses per day, resulting in the same daily dose as for curves A to C. Again the AUC is identical to curves A and C but this time we observe higher trough concentrations. Using this application form, even low doses can be effective, since sufficient drug concentrations are available at the target structures. E: Intramuscular application of depot: Peak concentrations may be achieved after as early as 1 day or as late as 4 weeks depending on the formulation. Concentrations comparable to trough values after oral application can only be obtained immediately prior to the next application. Blood sampling during the elimination phase after full absorption (maximum) will result in higher values compared to trough sampling after oral application despite equal AUC. Please note the time scale for curve E is different from curves A to D.

Positron emission tomography (PET) enables analysis of central nervous receptor occupancy in vivo. PET studies have demonstrated that blood concentrations correlate well with the occupancy of target sites in the brain [347, 456, 457, 836, 837, 1213]. Antipsychotic drugs exert most of their therapeutic actions by blockade of dopamine D2-like receptors [625]. Blockade of D2 receptors by antipsychotic drugs reduces the binding of radioactive PET ligands [347, 454, 1213]. Using this approach and by quantifying the displacement of dopamine receptor radioligands, it has been shown that receptor occupancy correlates better with concentrations of antipsychotic drugs in blood than with daily doses [525]. It is even possible to predict dopamine D2 receptor occupancy based on the concentration of an antipsychotic drug in blood [1213]. Optimal clinical response was seen at 70–80 % D2 receptor occupancy, and 80 % D2 receptor occupancy was defined as the threshold for extrapyramidal symptoms [347, 868]. PET was also used to characterize in vivo serotonin transporter (SERT or 5HTT) occupancy by serotonin reuptake inhibitors (SSRIs) [46, 69, 800, 801, 864, 1118, 1165]. Using a serotonin transporter radioligand, concentrations of citalopram, paroxetine, fluoxetine and sertraline in blood were shown to correlate well with serotonin transporter occupancy. At least 70 % occupancy should be attained for optimal clinical outcome [800, 801]. PET studies have thus brought about highly relevant information to determine therapeutically effective drug concentrations in blood for a considerable number of psychoactive drugs [456].

1.2 Pharmacogenetic aspects

The clinical importance of pharmacogenetic factors in the pharmacokinetics and pharmacodynamics of neuropsychiatric drugs is increasingly recognized [269, 341, 823, 1041]. As already mentioned above, drug-metabolizing enzymes, especially CYP isoen-

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zymes, exhibit genetic variability [1351–1353]. Extensive metabolizers (EM) are defined as wild-type with two active alleles. Poor metabolizers (PM) lack functional alleles. Intermediate metabolizers (IM) are either genetically heterozygous, carrying an active and an inactive allele or have one or two alleles with reduced activity. Ultrarapid metabolizers (UM) carry alleles with increased activity or multiplications of functional alleles [105]. Genetic polymorphisms of drug-metabolizing enzymes are clinically important. On the one hand, unexpected adverse drug reactions and toxicity may occur in PM due to increased blood concentrations. On the other hand, non-response may occur in UM due to subtherapeutic blood concentrations [272]. Prodrugs are activated by metabolism via CYP enzymes, e. g., codeine to morphine and tramadol to desmethyltramadol by CYP2D6 [547, 892]. In this situation, UMs are at risk for adverse drug reactions and PM patients will not be able to produce pharmacologically active metabolites. A new promising approach is the determination of mRNA encoding CYP1A2, CYP2C9 and CYP2C19 in leukocytes, mRNA levels were found to correlate well with hepatic CYP activities as shown by parallel probe drug phenotyping of CYP enzymes [1182].

Historically, the metabolizer status was determined with probe drugs such as caffeine for CYP1A2, omeprazole for CYP2C19, metoprolol or dextromethorphan for CYP2D6, or midazolam for CYP3A4/5 [722, 1170]. These phenotyping tests measure the metabolic situation of the patient at the moment of the test and allow detection of metabolic changes. They can thus be used to study the influence of environmental factors such as smoking or comedications on CYP activities [342, 343, 1098, 1357]. Over the last years, CYP genotyping has become more and more available. The clear advantage of genotyping is that it represents a "trait marker" and that its result is not influenced by environmental factors. It can be carried out in any situation and its result has a lifetime value. However, despite the fact that functional significance of the genetic variations for CYP enzymes is very well characterized [389], there is still appreciable variability caused by rare genetic variants which allows a probable prediction of the individual enzyme activity by genetic analyses focusing on the common variants only [774].

Other metabolizing enzyme systems such as UDP glucuronosyltransferases (UGT) also display genetic polymorphisms [245, 268], but their clinical relevance in pharmacotherapy and for dose adjustments is less well characterized than for CYP polymorphisms [1144].

With regard to ABCB1 transporters and the functional role of its gene product P-gp for drug distribution in the body, the ABCB1 genotype has been suggested to affect antidepressant and antipsychotic drug response. Patients may respond differently to P-gp substrate antidepressants and ABCB1 genotyping can be useful for improving antidepressant treatment outcome. Meanwhile, over 30 studies have investigated whether genetic variants within ABCB1 predict clinical efficacy and/or tolerability of antidepressants in humans. In particular, minor allele carriers of the single nucleotide polymorphisms (SNPs) rs2032583 and rs2235040 were repeatedly found to be more susceptible to the effects of antidepressants than major allele carriers [146, 147, 263, 978, 1001, 1043, 1217]. Several other studies, however, did not observe better response rates or more adverse drug reactions among minor allele carriers than non-carriers [111, 301, 927, 1051]. A pilot clinical trial with different doses of antidepressants that were P-gp substrates showed superior efficacy in carriers of the minor allele of rs2235083 at doses in the recommended dose range [147, 160]. A dose increase strategy for the carriers of the major allele proved not effective. However, other strategies as switching to an antidepressant that is not substrate of the P-gp transporter have not yet been evaluated. Larger studies are therefore necessary before coming to a final conclusion as to the relevance and practical consequences of ABCB1 genotypic variation.

In addition to the pharmacokinetic aspects reviewed above, there is increasing evidence for genetic factors driving pharmacodynamic processes such as interactions of drugs with receptors, enzymes, transporters, carrier proteins, structural proteins or ion channels to be crucially involved in mediating treatment response in mental disorders. In affective disorders, the serotonin transporter gene (5HTT; SLC6A4) is the most widely studied gene in this context. Results, however, have been inconclusive so far [610, 1071, 1181]. Applying a hypothesis-free approach, genome-wide association studies (GWAS) have been conducted in the STAR * D, the Munich Antidepressant Response Signature (MARS) and the Genome-based Therapeutic Drugs for Depression (GENDEP) samples. These studies, however, failed to discern genome-wide significant markers of antidepressant treatment response [553, 680]. Response to lithium has also been investigated in the largest meta-analysis so far in a cohort of more than 2,500 patients from 22 research centers worldwide. While results may provide the basis for a better understanding of lithium mechanisms, they are not relevant as yet for clinical decision making [541, 679, 789, 1059]. In psychotic disorders, variation in the dopamine receptor genes DRD2, DRD3 and DRD4 have extensively been investigated regarding antipsychotic treatment response; these studies, however, did not yield robustly replicable results (for review see [143]). In alcohol dependent patients, recent meta-analytic data support a considerable role of the functional A118G polymorphism of the μ opioid receptor gene (OPRM1) via a differential response to naltrexone [192]. However, more research is needed to determine the clinical validity (e. g., sensitivity, specificity, positive/negative predictive value) and utility profiles for pharmacogenetic approaches based on OPRM1 variation in the treatment of alcohol use disorders [508].

Pharmacogenetic analyses at the pharmacodynamic level revealed promising first results regarding the genetic underpinnings of relevant adverse drug reactions of psychoactive drugs. The human leukocyte antigen markers HLA-B * 1502 and HLA-A * 3101 were consistently reported to confer a higher risk to develop Stevens-Johnson syndrome under carbamazepine treatment in patients of Asian descent [354, 1328]. Some pharmacogenetic tests have been piloted in a clinical context such as the PGxPredict: CLOZAPINE test designed to predict agranulocytosis risk based on HLA-DQB1 gene variation, which, however, has been stopped given a high specificity (98.4 %), but a low sensitivity (21.5 %) [143]. 5-HTR2C, melanocortin 4 receptor (MC4R), neuropeptide Y (NPY), cannabinoid receptor 1 (CNR1) and leptin gene variations have been shown to mediate antipsychotic-induced weight gain (for review see [447]). Well-replicated gene variations have been described in antipsychotic-induced dystonia/tardive dyskinesia: Variations in RGS2 (regulator of G-protein signaling 2), a gene which

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modulates dopamine receptor signal transduction [429, 430], as well as variations in the serotonin receptor genes HTR2C [18, 19, 1067] and possibly also HTR2A [694, 1066]. A variation in the serotonin receptor gene HTR1A (rs6295; C-1019G) has consistently been associated with the antipsychotic treatment response of negative symptoms in schizophrenia [822, 1168].

To overcome the limitations of previous studies, the following strategies have been proposed: Focusing on one specific pharmacologic class and concentrating on more narrowly defined phenotypes (e. g., the International SSRI Pharmacogenomics Consortium, ISPC [112]), including pharmacokinetic variables (i. e. blood levels [965, 1227]) and environmental influences [649], completing genetic coverage by including structural variation (e. g., copy number variation, CNV [873]), analysing interactive effects of multiple risk genes ('epistasis', e. g., [770]) and including epigenetic variation [300, 798]. Along these lines, large worldwide consortia are currently being established in an attempt to conduct large-scale pharmacogenetic studies applying state-of-the-art techniques such as genome-wide association studies and exome sequencing, e. g., the International Consortium on Lithium Genetics (ConLiGen) [1059].

2. Drug Concentrations in Blood to Guide Neuropsychopharmacotherapy

To guide neuropsychopharmacotherapy, TDM considers pharmacodynamic and pharmacokinetic aspects. It has to be checked (1) whether the drug concentration is within the therapeutic reference range so that therapeutic efficacy and acceptable tolerability can be expected and (2) whether the blood concentration fits to the prescribed dosage to find out if the medication is taken as prescribed and/or if pharmacokinetic abnormalities are present. It must therefore be discriminated between therapeutically effective and expected dose-related drug concentrations [470, 471]. Moreover, determination of metabolite to parent compound ratios and probe drug phenotyping enable evaluation of the individual pharmacokinetic phenotype.

2.1 The therapeutic reference range

The law of mass action implies that pharmacologic effects are concentration related [50]. TDM is based on this assumption with respect to both, therapeutic improvement and adverse drug reactions. TDM also assumes that there is a concentration range of the drug in blood for maximal effectiveness and acceptable safety, the so-called "therapeutic reference range". Studies on relationships between drug concentration in blood and clinical improvement have supported this concept since the 1960s for lithium, tricyclic antidepressants and first-generation antipsychotic drugs. Systematic reviews and meta-analyses that were based on adequately designed studies demonstrated a significant relationship between clinical outcome and drug concentration in blood for nortriptyline, imipramine and desipramine, which are associated with a high probability of response [82]. For amitriptyline as a model compound, a meta-analysis of 45 studies has shown that various statistical approaches provided almost identical therapeutic reference ranges [1222, 1224]. For new antipsychotic drugs like aripiprazole [1115], olanzapine [933] or risperidone [1336], relationships between drug concentration in blood and clinical effectiveness have been reported [729].

The therapeutic reference range is an essential target range for TDM guided pharmacotherapy. Its estimation requires determination of a lower and an upper limit of therapeutically effective and tolerable drug concentrations in blood. A generally accepted method to estimate these limits does not exist, and methodological restrictions such as placebo response or treatment resistance must be considered [50, 329, 958]. PET studies were most helpful to define these limits for antipsychotic and antidepressant drugs. The PET technique, however, is highly expensive and available only in few centers. Fixed dose studies are the most appropriate way to determine therapeutic reference ranges. Their determination, however, is actually not legally required for drug approval. We strongly advise that drug monitoring should be implemented into the development process of new drugs during the clinical research phase. To do this, established concepts of clinical trials (fixed dose studies) must be supplemented by measuring drug concentrations in blood.

For "therapeutic reference range", there are a lot of synonymous terms like "therapeutic window", "therapeutic range", "optimal plasma concentration", "effective plasma concentration", "target range", "target concentration", or "orienting therapeutic range", the term used in the first TDM consensus [82]. The AGNP TDM task force decided in 2011 to use the term "therapeutic reference range" following the convention of TDM guidelines published for antiepileptic drugs [912], and to use the term "drug concentration in blood" which includes plasma concentration, serum concentration or plasma level, serum level or blood level.

Definition

The "therapeutic reference ranges" reported in these guidelines (▶ **Table 4**) define ranges of drug concentrations in blood that specify a lower limit below which a drug induced therapeutic response is relatively unlikely to occur and an upper limit above which tolerability decreases or above which it is relatively unlikely that therapeutic improvement may be still enhanced. The therapeutic reference range is an orienting, population based range, which may not necessarily be applicable to all patients. Individual patients may show optimal therapeutic response under a drug concentration that differs from the therapeutic reference range. Ultimately, neuropsychopharmacotherapy can be best guided by identification of the patient's individual therapeutic concentration. The therapeutic reference ranges as recommended by the TDM group of the AGNP are given in ▶ **Table 4**.

Therapeutic reference ranges shown in ▶ **Table 4** are evidence-based and derived from the literature by the structured review process described above. Therapeutic reference ranges that are based on randomized clinical trials were found for only 17 neuropsychiatric drugs in the literature. For most drugs, reference ranges were obtained from studies with therapeutically effective doses. The reference ranges listed in ▶ **Table 4** are generally those for the primary indication. A number of drugs, however, are recommended for several indications. For example, antidepressant drugs are also used

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▶ **Table 4** Recommended therapeutic reference ranges (consensus), elimination half-life (t1/2) ranges and laboratory alert levels for neuropsychopharmacological drugs and levels of recommendation to use TDM as clinical routine for dose optimization without specific indications (see ▶ **Table 7**).

Drugs and active metabolites	Therapeutic reference range	t1/2	Laboratory alert level	Level of recommendation to use TDM	Conversion factor, CF	Comments	References
Antidepressant drugs							
Agomelatine	7–300 ng/mL (1–2 h after 50 mg)	1–2 h	600 ng/mL	4	4.11	Because of rapid elimination, trough drug concentrations are not measurable under chronic treatment; determinations, preferentially of Cmax, should be restricted to specific indications.	[126]
Amitriptyline plus nortriptyline	80–200 ng/mL	10–28 h 18–44 h	300 ng/mL	1	3.60 3.80	Increased toxicity in children and PM of CYP2D6, concentration-related impairment of driving performance	[451, 465, 557, 924, 1101, 1222]
Amitriptyline oxide amitriptyline plus nortriptyline	80–200 ng/mL	1.1–2.5 h 5–17 h 18–44 h	300 ng/mL	1	3.41 3.60 3.80	Prodrug, active moiety is the sum of amitriptyline and nortriptyline	[357]
Bupropion plus hydroxybupropion	850–1,500 ng/mL	1–15 h 17–47 h	2,000 ng/mL	2	4.17 3.91	Hydroxybupropion is the major active compound exhibiting about 50 % of bupropion's activity, other metabolites exhibit 20 % of the activity of bupropion at best. Since bupropion is unstable, the therapeutic range refers to hydroxybupropion only.	[259, 260, 570, 678, 963, 1160]
Citalopram	50–110 ng/mL	38–48 h	220 ng/mL	1	3.08	The N-demethylated metabolite might weakly contribute to pharmacological actions.	[71, 117, 180, 413, 581, 688, 800, 852, 895, 896, 988, 990, 1036, 1087, 1228]
Clomipramine plus N-desmethyl-clomipramine	230–450 ng/mL	16–60 h 37–43 h	450 ng/mL	1	3.18 3.32	Differential pharmacological profile of parent drug (preferential serotonin reuptake inhibition) and metabolite (preferential noradrenaline uptake inhibition)	[403]
Desipramine	100–300 ng/mL	15–18 h	300 ng/mL	2	3.75	Metabolites possibly active in vivo	[924]
Desvenlafaxine	100–400 ng/mL	10–17 h	800 ng/mL	3	3.80	No active metabolites	[952]
Dothiepin (dosulepin)	45–100 ng/mL	18–21 h	200 ng/mL	2	3.39	Adverse reactions correlate with drug concentrations in blood.	[165, 550, 745, 979, 1008]
Doxepin plus N-desmethlydoxepin	50–150 ng/mL	15–20 h	300 ng/mL	2	3.58 3.77		[277, 286, 697, 799, 1035]
Duloxetine	30–120 ng/mL	9–19 h	240 ng/mL	2	3.36	No active metabolites, renal disease associated with elevated concentrations	[1, 33, 198, 670, 727, 1167, 1274]
Escitalopram	15–80 ng/mL	27–32 h	160 ng/mL	2	3.08	N-demethylated metabolites may weakly contribute to pharmacological actions.	[413, 733, 1228, 1235]
Fluoxetine plus N-desmethyl fluoxetine	120–500 ng/mL	4–6 days 4–15 days	1,000 ng/mL	3	3.23 3.39	Long elimination half-life leads to long-lasting potent inhibition of CYP2D6.	[120, 136, 318, 654, 734, 801, 984, 1036, 1228]
Fluvoxamine	60–230 ng/mL	21–43 h	500 ng/mL	2	3.14	Inhibition of CYP1A2, CYP2C19 and age dependent elevation, maximum in vivo inhibition of CYP1A2 and CYP2C19 attained at 60 ng/mL	[608, 888, 1063, 1152, 1158, 1166]
Imipramine plus desipramine	175–300 ng/mL	11–25 h 15–18 h	300 ng/mL	1	3.57 3.75	Hydroxylated metabolites with uncertain pharmacological activity	[3, 115, 414, 934]

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▶ **Table 4** Continued.

Drugs and active metabolites	Therapeutic reference range	t1/2	Laboratory alert level	Level of recommendation to use TDM	Conversion factor, CF	Comments	References
Levomilnacipran	80–120 ng/mL	6–9 h	200 ng/mL	3	2.24	Reference range refers to steady-state concentrations expected under a therapeutic dose of 100 mg/d.	[202–203]
Maprotiline	75–130 ng/mL	20–58 h	220 ng/mL	2	3.60	Active metabolite N-desmethylmaprotiline	[390, 542, 674]
Mianserin	15–70 ng/mL	14–33 h	140 ng/mL	3	3.78		[326, 816]
Milnacipran	100–150 ng/mL	5–8 h	300 ng/mL	2	2.24	Reference range refers to drug concentrations for a therapeutically recommended dose of 100 mg/day; optimal concentrations may be higher, since concentrations in blood required to attain 80 % serotonin and noradrenaline transporter occupancy are > 200 ng/mL.	[346, 528, 698, 864, 1021]
Mirtazapine	30–80 ng/mL	20–40 h	160 ng/mL	2	3.77	N-demethylated metabolite does not contribute to pharmacological actions.	[428, 567, 636, 712, 796, 831, 991, 1073]
Moclobemide	300–1,000 ng/mL	2–7 h	2,000 ng/mL	3	3.72	Metabolites are pharmacologically inactive.	[380, 485, 549, 555]
Nortriptyline	70–170 ng/mL	18–44 h	300 ng/mL	1	3.80	Hydroxylated metabolites, PM of CYP2D6 and low CYP3A4 activity is associated with increased risk of toxicity.	[51, 52, 597, 929, 932, 934]
Paroxetine	20–65 ng/mL	12–44 h	120 ng/mL	3	3.04	Inhibition of CYP2D6	[359, 406, 410, 801, 1036, 1196, 1335]
Reboxetine	60–350 ng/mL	8–12 h	700 ng/mL	3	3.19		[880, 881]
Sertraline	10–150 ng/mL	22–36 h	300 ng/mL	2	3.27	N-demethylated metabolite has a 2-fold longer elimination half-life than sertraline, but only 1/20 of the activity of sertraline, similar concentrations in children and adolescents.	[20, 80, 464, 734, 801, 984, 1177, 1228, 1265]
Tianeptine	30–80 ng/mL	2.5-3 h	160 ng/mL	3	2.89		[427]
Tranylcypromine	≤ 50 ng/mL	1–3 h	100 ng/mL	4	7.51	Due to irreversible inhibition of monoamine oxidase, concentrations in blood do not correlate with drug actions.	[558]
Trazodone	700–1,000 ng/mL	4–11 h	1,200 ng/mL	2	2.69		[791, 1072]
Trimipramine	150–300 ng/mL	23–24 h	600 ng/mL	2	3.40	Active metabolite N-desmethyltrimipramine	[244, 319, 377, 554]
Venlafaxine plus O-desmethyl venlafaxine	100–400 ng/mL	4–14 h 10–20 h	800 ng/mL	2	3.61 3.80	O-desmethylvenlafaxine is the predominant active compound in most patients; concentrations above 222 ng/mL were found to be predictive for response; N-demethylated venlafaxine does not contribute to pharmacological actions. At active moiety concentrations below 100 ng/mL, the drug acts preferentially as an SSRI, t1/2 given for extended release formulation.	[137, 405, 535, 801, 919, 921, 984, 989, 1036, 1074, 1129, 1245]
Vilazodone	30–70 ng/mL	18–32 h	140 ng/mL	3	2.26	Major metabolites represent 27 % of total circulating vilazodone, no data on TDM, reference range refers to steady state concentrations at therapeutic doses	[756]
Vortioxetine	10–40 ng/mL	57–66 h	80 ng/mL	2	3.35	At least four inactive metabolites	[47, 200, 548, 834, 1137, 1186]

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▶ **Table 4** Continued.

Drugs and active metabolites	Therapeutic reference range	t1/2	Laboratory alert level	Level of recommendation to use TDM	Conversion factor, CF	Comments	References
Antipsychotic drugs							
Amisulpride	100–320 ng/mL	12–20 h	640 ng/mL	1	2.71	No metabolites, some patients may need concentrations above 320 ng/mL to attain sufficient improvement.	[102, 148, 739, 797, 829, 966, 1114, 1253]
Aripiprazole Aripiprazole plus dehydroaripiprazole	100–350 ng/mL 150–500 ng/mL	60–80 h	1,000 ng/mL	2	2.23	Dehydroaripiprazole concentrations amount to about 45 % of the parent drug. Apparent elimination half-life 30–47 days	[57, 455, 509, 625, 637, 711, 729, 815, 1115, 1157]
Asenapine	1–5 ng/mL	13–39 h	10 ng/mL	4	3.50		[917, 1285]
Benperidol	1–10 ng/mL	4–8 h	20 ng/mL	3	2.62	Higher levels may be tolerated in patients under long-term high-dose therapy due to adaptive changes.	[666, 853, 1068]
Brexpiprazole	40–140 ng/mL	91 h	280 ng/mL	3		Major metabolite amounts to 23–48 % of the parent drug, does not contribute to therapeutic effects.	[223]
Bromperidol	12–15 ng/mL	20–36 h	30 ng/mL	2	4.38		[1108, 1194, 1337]
Cariprazine	10–20 ng/mL	48–120 h	40 ng/mL	3	2.34	Active metabolites are N-desmethylcariprazine and N,N-didesmethylcariprazine.	[174, 840, 1257]
Chlorpromazine	30–300 ng/mL	15–30 h	600 ng/mL	2	3.14		[181, 210, 999]
Chlorprothixene	20–300 ng/mL	8–12 h	400 ng/mL	3	3.17		[650, 980]
Clozapine	350–600 ng/mL	12–16 h	1,000 ng/mL	1	3.06	Major metabolite N-desmethylclozapine with unclear antipsychotic activity, the therapeutic reference range seems likely to be lower in pediatric patients.	[241, 242, 290, 900, 930, 1241, 1314]
Flupentixol	0.5–5 ng/mL (cis-isomer)	20–40 h	15 ng/mL	2	2.30	Apparent t1/2 for flupentixol decanoate 17 days	[67, 83, 982, 1015]
Fluphenazine	1–10 ng/mL	16 h	15 ng/mL	1	2.29	Apparent half-life for fluphenazine decanoate 14 days	[1015, 1237]
Fluspirilene	0.1–2.2 ng/mL	7–14 days	4.4 ng/mL	3	2.10		[1111]
Haloperidol	1–10 ng/mL	12–36 h	15 ng/mL	1	2.66	Higher levels can be tolerated in patients under long-term high-dose therapy due to adaptive changes; apparent t1/2 for haloperidol decanoate 17 days.	[118, 363, 505, 868, 902, 931, 941, 1224, 1237]
Iloperidone	5–10 ng/mL	18–33 h	20 ng/mL	3	2.34		[225, 861, 917, 1031]
Levomepromazine	30–160 ng/mL	16–78 h	320 ng/mL	3	3.04		[255, 1194]
Loxapine	5–10 ng/mL	6–8 h	20 ng/mL	3	3.05	Delivered by means of a thermally generated aerosol	[1164]
Lurasidone	15–40 ng/mL	20–40 h	120 ng/mL	3	2.03		[213, 225, 917, 951]
Melperone	30–100 ng/mL	4–6 h	200 ng/mL	3	3.80	QTc prolongation is suggested to correlate with drug concentrations.	[135, 546, 1148]
Olanzapine	20–80 ng/mL	30–60 h	100 ng/mL	1	3.20	Under olanzapine pamoate, patients have a high risk for a post injection syndrome when drug concentrations exceed 100 ng/mL. Apparent half-life for olanzapine pamoate 30 days	[56, 91, 101, 114, 116, 226, 349, 404, 754, 778, 780, 866, 933, 1099, 1289]
Paliperidone (9-hydroxyrisperidone)	20–60 ng/mL	17–23 h	120 ng/mL	2	2.35	Apparent half-life for paliperidone palmitate 25–49 days	[40, 110, 224, 842]

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▶ **Table 4** Continued.

Drugs and active metabolites	Therapeutic reference range	t1/2	Laboratory alert level	Level of recommendation to use TDM	Conversion factor, CF	Comments	References
Perazine	100–230 ng/mL	8–16 h	460 ng/mL	1	2.95		[151]
Perphenazine	0.6–2.4 ng/mL	8–12 h	5 ng/mL	1	2.48	Apparent half-life for perphenazine enanthate 4–6 days	[642, 1015, 1161, 1237]
Pimozide	15–20 ng/mL	23–43 h	20 ng/mL	3	2.17		[1065]
Pipamperone	100–400 ng/mL	17–22 h	500 ng/mL	3	2.66		[134, 947]
Prothipendyl	30–80 ng/mL	2–3 h	500 ng/mL	4	3.35	For acute sedation, 12 h after 240 to 320 mg	[792, 1050]
Quetiapine N-desalkylquetiapine	100–500 ng/mL 100–250 ng/mL	6–11 h 10–13 h	1,000 ng/mL	2	2.61 3.39	When the patient has taken the extended release (ER) formulation in the evening and blood was withdrawn in the morning, expected concentrations are 2-fold higher than trough levels.	[25, 183, 356, 400, 482, 492, 851, 907, 1100, 1252, 1312]
Risperidone plus 9-hydroxy-risperidone	20–60 ng/mL	2–4 h 17–23 h	120 ng/mL	2	2.44 2.35	Adverse reactions correlate with drug concentrations. To avoid neurological adverse reactions, >40 ng/mL should be targeted only in cases of insufficient or absence of therapeutic response. Apparent half-life for long acting injection formulation 26 days	[257, 350, 728, 777, 793, 845, 857, 920, 992, 997, 1056, 1120, 1240, 1336]
Sertindole	50–100 ng/mL	55–90 h	200 ng/mL	2	2.27	Active metabolite dehydrosertindole (concentration at therapeutic doses 40–60 ng/mL), concentration dependent increase of QT interval by blockade of potassium channels.	[113, 177, 178, 1191, 1321]
Sulpiride	200–1,000 ng/mL	8–14 h	1,000 ng/mL	2	2.93	No metabolites, renal elimination	[221, 828, 1194]
Thioridazine	100–200 ng/mL	30 h	400 ng/mL	1	2.70	Contraindicated in PM of CYP2D6	[324, 1194]
Ziprasidone	50–200 ng/mL	4–8 h	400 ng/mL	2	2.55	The drug should be taken with a meal, otherwise absorption is reduced and drug concentrations will be lower than expected.	[208, 755, 781, 1251, 1264]
Zotepine	10–150 ng/mL	13–16 h	300 ng/mL	3	3.01		[657, 1172]
Zuclopenthixol	4–50 ng/mL	15–25 h	100 ng/mL	3	2.49	Apparent half-life for zuclopenthixol decanoate 19 days and 1–2 days for the acetate	[144, 258, 559, 645, 1062, 1260]
Mood stabilizing drugs							
Carbamazepine	4–10 µg/mL	10–20 h	20 µg/mL	1	4.23	The metabolite, known as the epoxide is equipotent to carbamazepine and contributes to clinical effects, especially to side effects.	[763, 937]
Lamotrigine	1–6 µg/mL	14–104 h	20 µg/mL	2	3.90	So far, no specific reference range for mood stabilizing effect; in patients with treatment resistant depression, concentrations should be above 3.25 µg/mL; valproic acid increases the elimination half-life to 45–75 h, carbamazepine, phenytoin or phenobarbital decrease it to 9–14 h due to induction of UDP-glucuronosyltransferase.	[600, 609, 819, 838, 1225]
Lithium	0.5–1.2 mmol/L (4–8 µg/mL) acute up to 1.2 mmol/L chron. 0.5–0.8 mmol/L	14–30 h	1.2 mmol/L (8 µg/mL)	1	125.8	Age dependent increase of elimination half-life (30–36 h); lithium concentrations should be up to 1.2 mmol/L for acute treatment and 0.5–0.8 mmol/L for maintenance treatment.	[1076, 1307]
Valproic acid	50–100 µg/mL	11–17 h	120 µg/mL	1	6.93	In individual cases 120 µg/mL are also tolerated in acute mania.	[23, 366, 497, 740, 1244]

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▶ **Table 4** Continued.

Drugs and active metabolites	Therapeutic reference range	t1/2	Laboratory alert level	Level of recommendation to use TDM	Conversion factor, CF	Comments	References
Anticonvulsant drugs							
Brivaracetam	0.5–0.9 µg/mL	7–11 h	1.8 µg/mL	3	4.72	For a dose of 2x 50 mg/d	[1014, 1042, 1147]
Carbamazepine	4–12 µg/mL	10–20 h	20 µg/mL	1	4.23	The epoxide metabolite is equipotent to carbamazepine and contributes to clinical effects, especially to adverse reactions.	[141, 577, 912]
Clobazam N-desmethyl-clobazam	30–300 ng/mL 300–3,000 ng/mL	36–42 h 71–82 h	500 ng/mL 5,000 ng/mL	3	3.33 3.49		[271, 459, 912]
Clonazepam	20–70 ng/mL	30–40 h	80 ng/mL	3	3.17	Clonazepam accumulates after repeated dosing, the 7-aminoclonazepam is slightly active.	[74, 835, 912]
Ethosuximide	40–100 µg/mL	33–55 h	120 µg/mL	3	7.08		[98, 144, 912]
Eslicarbazepine acetate	10–35 µg/mL	20–40 h	70 µg/mL	3	3.37	Prodrug metabolized to the active compound eslicarbazepine	[562]
Felbamate	30–80 µg/mL	15–23 h	100 µg/mL	3	4.20	Clearance and prolonged half-life affected by diminished renal function	[484, 587, 912]
Gabapentin	2–20 µg/mL	5–7 h	25 µg/mL	3	5.84		[121, 123, 145, 587, 713, 912]
Lacosamide	1–10 µg/mL	10–15 h	20 µg/mL	3	2.66		[78, 99, 145, 186, 234, 765, 1045]
Lamotrigine	3–15 µg/mL	14–104 h	20 µg/mL	2	3.90	Valproic acid increases the elimination half-life to 45–75 h, carbamazepine, phenytoin or phenobarbital decrease it to 9–14h.	[144, 145, 531, 587, 600, 819, 820, 912, 1109, 1225]
Levetiracetam	10–40 µg/mL	6–8 h	50 µg/mL	4	5.88	Clearance significantly declines with age requiring an about 30 to 50 % lower dose, age dependent increase of t1/2.	[144, 235, 587, 912, 1139, 1290]
Methsuximide N-desmethyl-methsuximide	10–40 µg/mL	1–3 h 36–45 h	45 µg/mL	2	4.92 5.29	Elimination half-life increases in case of severe renal impairment. The metabolite is the active compound in vivo	[144]
Oxcarbazepine 10-hydroxycarbazepine	10–35 µg/mL	5 h 10–20 h	40 µg/mL	2	3.96 3.73	The metabolite is the active compound in vivo.	[144, 539, 587, 782, 912]
Perampanel	180–980 ng/mL	48–105 h	1,000 ng/mL	3	2.86	Carbamazepine and other CYP3A4 inducers reduce elimination half-life to 25 h.	[408, 910]
Phenobarbital	10–40 µg/mL	80–120 h	50 µg/mL	1	4.31		[144, 912]
Phenytoin	10–20 µg/mL	20–60 h	25 µg/mL	1	3.96		[144, 665, 912]
Pregabalin	2–5 µg/mL	6 h	10 µg/mL	3	6.28		[107, 123, 144, 587, 785, 912]
Primidone phenobarbital	5–10 µg/mL 10–40 µg/mL	14–15 h 70–140 h	25 µg/mL 50 µg/mL	2	4.58	Phenobarbital is the active metabolite of primidone. TDM-guided therapies should refer to phenobarbital concentrations.	[144, 912]

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▶ **Table 4** Continued.

Drugs and active metabolites	Therapeutic reference range	t1/2	Laboratory alert level	Level of recommendation to use TDM	Conversion factor, CF	Comments	References
Retigabine	0.45–0.90 µg/mL	8–10 h	1.8 µg/mL	3	3.29	Therapeutic reference range refers to concentrations that are expected under therapeutic doses of 600 mg/d.	[355, 911]
Rufinamide	5–30 µg/mL	6–10 h	40 µg/mL	2	4.20		[100, 145, 936]
Stiripentol	1–10 µg/mL	4–13 h	15 µg/mL	2	4.27		[926]
Sulthiame	2–8 µg/mL	3–30 h	12 µg/mL	2	3.46		[144, 655, 783]
Tiagabine	20–200 ng/mL	7–9 h	300 ng/mL	2	2.66		[144, 397, 587, 912]
Topiramate	2–10 µg/mL	19–23 h	16 µg/mL	3	2.95		[144, 145, 382, 587, 784, 912]
Valproic acid	50–100 µg/mL	17–30 h	120 µg/mL	1	6.93		[23, 144, 366, 497, 912, 1243]
Vigabatrin	2–10 µg/mL	5–8 h	20 µg/mL	4	7.74		[144, 587, 713, 912, 1305]
Zonisamide	10–40 µg/mL	49–77 h	40 µg/mL	2	4.71		[415, 811, 813]
Anxiolytic drugs and drugs for treatment of sleep disorders							
Alprazolam	5–50 ng/mL 20–40 ng/mL (panic disorder)	12–15 h	100 ng/mL	3 3	3.22		[1058, 1248]
Bromazepam	50–200 ng/mL	15–35 h	300 ng/mL	4	3.16	In chronic users drug concentrations can be markedly higher than in non-users. High concentrations may indicate misuse.	[369, 476, 1058]
Brotizolam	4–10 ng/mL (at 1 h)	3–6 h	20 ng/mL	4	2.53	Drug concentration required for sleep induction	[585, 1218]
Buspirone plus major metabolites	1–4 ng/mL	1–5 h 4–7 h	30 ng/mL	3	2.59 2.49	Major metabolites are 6-hydroxybuspirone and 1-(pyrimidinyl) piperazine (1-PP).	[298, 299, 1037, 1058]
Chlordiazepoxide	400–3,000 ng/mL	5–30 h	3,500 ng/mL	4	3.48		[732, 1058]
Clonazepam	4–80 ng/mL	19–30 h	100 ng/mL	4	3.17	In chronic users drug concentrations can be markedly higher than in non-users.	[305, 1058]
Diazepam plus N-desmethyldiazepam	100–2,500 ng/mL	24–48 h 80–103 h	3,000 ng/mL	4	3.51	In chronic users drug concentrations can be markedly higher than in non-users. High concentrations may indicate misuse. In blood samples from 1000 people arrested for impaired driving, the median concentration of diazepam plus N-desmethyldiazepam was 500 ng/mL (range 110–7,600 ng/mL).	[378, 435, 437, 591, 1058]
Diphenhydramine	10–30 ng/mL	7–12 h	60 ng/mL	4	3.92	Concentration required for sleep induction	[1091]
Doxylamine	200–350 ng/mL (at 2 h) 50–160 ng/mL (at 12 h)	9–17 h	320 ng/mL	4	2.57	Concentration required for sleep induction	[1262]
Flunitrazepam	6–12 ng/mL (sedation) 12–15 ng/mL (sleep induction)	10–30 h	50 ng/mL	4	3.20	In chronic users drug concentrations can be markedly higher than in non-users. If high concentrations above 15 ng/mL are required for sedation or sleep induction, misuse may be suggested.	[130, 775]
Flurazepam N-1-desalkylflurazepam	0–4 ng/mL (at 1–3 h) 10–22 ng/mL (at 1–3 h) 75–165 ng/mL (at 10 h after drug intake under steady-state)	2–3 h 47–100 h 2–3 h	330 ng/mL	4	2.58	Concentration required for sleep induction, N-desalkyl flurazepam at steady state. In chronic users drug concentrations can be markedly higher than in non-users. If higher concentrations are required misuse may be suggested.	[431, 604]

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▶ **Table 4** Continued.

Drugs and active metabolites	Therapeutic reference range	t1/2	Laboratory alert level	Level of recommendation to use TDM	Conversion factor, CF	Comments	References
Gammahydroxybutyric acid (GHB, sodium oxabate)	0.5–1.0 µg/mL 50–100 µg/mL 100–200 µg/mL	0.4–0.8 h	200 µ/mL	4	9.60	Endogenous concentration in blood Concentration required for sedation or sleep induction Concentration in blood to induce unconsciousness	[170]
Lorazepam	30–100 ng/mL	12–16 h	300 ng/mL	4	3.20	In chronic users drug concentrations can be markedly higher than in non-users.	[334, 369, 441, 1058, 1239]
Lormetazepam	2–10 ng/mL (at 1.5 h)	8–14 h	100 ng/mL	4	2.98	Drug concentration required for sleep induction	[4, 940]
Medazepam desmethyldiazepam, temazepam plus oxazepam	200–2,500 ng/mL	24–48 h	3,000 ng/mL	4	3.69 3.19 3.49	Prodrug, active compounds are the metabolites desmethyldiazepam, temazepam and oxazepam.	[474, 1058]
Midazolam	6–15 ng/mL 60–80 ng/mL (at 1 h)	1–3 h	1,000 ng/mL	4	3.07		[60, 435, 545]
Modafinil	1,000–1,700 ng/mL after 200 mg/day	10–12 h	3,400 ng/mL	3	4.21		[1003, 1323, 1324, 1332]
Nitrazepam	30–100 ng/mL (at 0.5 -2 h)	18–30 h	200 ng/mL	4	3.56	Drug concentration usually required for sleep induction. In chronic users concentrations can be markedly higher than in non-users. High concentrations may indicate misuse.	[843, 1058]
Nordazepam	120–800 ng/mL	50–90 h	1,500 ng/mL	4	3.69	In chronic users drug concentrations can be markedly higher than in non-users.	[1058]
Opipramol	50–500 ng/mL	11 h	1,000 ng/mL	3	2.87		[684]
Oxazepam	200–1,500 ng/mL	4–15 h	2,000 ng/mL	4	3.49	In chronic users drug concentrations can be markedly higher than in non-users.	[1058]
Pregabalin	2–5 µg/mL	5–7 h	10 µg/mL	3	6.28	TDM recommended in pregnant women, high concentrations can be an indicator for misuse.	[122, 123, 1052, 1199]
Prothipendyl	5–20 ng/mL (12 h after 40–80 mg)	2–3 h	500 ng/mL	4	3.35	For the indication sleep disorder	[792, 1050]
Promethazine	2–18 ng/mL (at 1.5–3 h)	10–14 h	100 ng/mL	4	3.47	Drug concentration usually required for sleep induction	[1180]
Temazepam	600–1,100 ng/mL (at 1 h)	5–13 h	2,000 ng/mL	4	3.19	Drug concentration usually required for sleep induction	[1058, 1239]
Triazolam	2–20 ng/mL (at 0.7–2 h)	1–5 h	40 ng/mL	4	2.91	Drug concentration usually required for sleep induction	[1058]
Zaleplone	20–40 ng/mL (at 1–2 h)	1–2 h	200 ng/mL	4	3.28	Drug concentration usually required for sleep induction	[309, 438]
Zolpidem	80–160 ng/mL (at 1–3 h)	1–4 h 1–3 h in children	320 ng/mL	4	3.25	Drug concentration usually required for sleep induction	[309, 1040, 1058]
Zopiclone	55–85 ng/mL (at 1.5–2 h)	2–6 h	300 ng/mL	4	2.57	Drug concentration usually required for sleep induction, unstable at room temperature	[352, 1058]

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▶ **Table 4** Continued.

Drugs and active metabolites	Therapeutic reference range	t1/2	Laboratory alert level	Level of recommendation to use TDM	Conversion factor, CF	Comments	References
Antidementia drugs							
Donepezil	50–75 ng/mL	70–80 h	100 ng/mL	2	2.64	Positive correlation between donepezil concentration in blood and inhibition of AChE activity of red blood cell membranes and clinical improvement.	[499, 653, 898, 1012, 1013, 1190]
Galantamine	10–40 ng/mL	8–10 h	90 ng/mL	3	3.48	Adverse drug reactions reported under 32 mg/day	[543, 566, 1334]
Memantine	90–150 ng/mL	60–100 h	300 ng/mL	3	5.58	Most patients are underdosed under conditions of clinical routine	[419, 472, 659–660]
Rivastigmine	8–20 ng/mL (1–2 h after oral dose) 5–13 ng/mL (1 h before application of a new patch)	1–2 h	40 ng/mL	3	4.00	Because of short elimination half-life Cmax has to be determined for oral applications. For patch application Cmin may be determined as usual. Positive correlation between rivastigmine concentration and inhibition of AChE activity of red blood cell membranes.	[252, 253, 691, 1086, 1309]
Drugs for treatment of substance related disorders							
Acamprosate	250–700 ng/mL	3–33 h	1,000 ng/mL	3	8.68		[144, 479, 480, 771]
Buprenorphine	1–3 ng/mL	2–5 h	10 ng/mL	2	2.38	Effective concentrations vary from patient to patient. Chronic users of opioids may require higher concentrations in blood to avoid the occurrence of withdrawal symptoms. Under recommended maximal doses of 24 mg buprenorphine per day expected trough concentrations are 3 to 6 ng/mL for buprenorphine and 6 to 15 ng/mL for norbuprenorphine.	[163, 199, 220, 672]
Bupropion hydroxybupropion	550–1,500 ng/mL	1–15 h 17–47 h	2,000 ng/mL	2	4.17 3.91	In a clinical trial 300 mg was the most effective dose leading to the therapeutic reference range as indicated which refers to hydroxybupropion, since bupropion is unstable.	[163, 589]
Clomethiazole	100–5,000 ng/mL (at 4 to 8 h)	2–5 h		4	6.19	In heavy alcohol dependent patients much higher concentrations may be required. Detoxification should be guided by clinical symptoms.	[163, 189, 1220, 1355]
Diacetylmorphine (heroin) morphine	70–350 ng/mL (at 1 h) 5–30 ng/mL (at 24 h)	8 min 2–5 h		4	2.71 3.50	Concentrations given for inhalation or injection of 600–900 mg diacetylmorphine at 1 or 24 h after injection of 300 to 1,000 mg. Non-users of opioids would be intoxicated at these concentrations. In opioid users effective and toxic concentrations differ between patients depending on the level of tolerance. Cmax concentrations of 60–110 ng/mL at 1 h after oral intake of 50 mg diacetylmorphine in healthy subjects.	[310–311]
Disulfiram Diethylthiomethylcarbamate-methyl ester	50–400 ng/mL 270–310 ng/mL	6–9 h	500 ng/mL -	3	3.37	Disulfiram (DSF) is a prodrug, its active metabolite diethylthiomethylcarbamate-methyl ester (DDTC-Me) has been suggested as a possible marker for proper dose titration of disulfiram; in a pharmacokinetic study under 300 mg/d DSF mean ± SD steady state concentrations of DSF amounted to 170 ± 10 ng/mL, those of DDTC-Me to 290 ± 20 ng/mL.	[163, 345, 588, 1058, 1095, 1124]

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▶ **Table 4** Continued.

Drugs and active metabolites	Therapeutic reference range	t1/2	Laboratory alert level	Level of recommendation to use TDM	Conversion factor, CF	Comments	References
Levomethadone	250–400 ng/mL	14–55 h	400 ng/mL	2	3.23	In non-users of opiates, effective or toxic concentrations are markedly lower than in users. Chronic users may need higher concentrations in blood to avoid the occurrence of withdrawal symptoms.	[163, 249, 251]
Methadone	400–600 ng/mL	24–48 h	600 ng/mL	2	3.23	In non-users of opiates, effective or toxic concentrations are markedly lower (300 ng/mL) than in users. Risk of QT-prolongation increases with drug concentrations in blood. Above 656 ng/mL high risk of QTc time above 450 ms.	[36, 144, 163, 250, 251, 321, 418, 477, 1082, 1255]
Morphine	10–100 ng/mL (pain) 50–200 ng/mL (substitution)	11–21 h	100 ng/mL	4	6.17	For pain suppression In hospice inpatients concentrations for cancer pain suppression ranged between 6 and 356 ng/mL; higher concentrations are required for opioid substitution treatment with daily doses of 500 to 800 mg morphine sulfate.	[53, 131, 812, 1058]
Nalmefene	10–20 ng/mL (at 2 h)	5–11 h	200 ng/mL	4	3.26	Acute use on-demand or as-needed when there is a perceived risk of relapse to high alcohol drinking. TDM may be useful for distinct cases after a single dose.	[297, 551]
Naltrexone plus 6β-naltrexol	25–100 ng/mL	2–5 h 7–13 h	200 ng/mL	2	3.06 3.04	Therapeutic effects rely primarily on the metabolite.	[163, 353, 420, 771]
Nicotine	5–20 ng/mL	2 h	400 ng/mL	4	6.16	Application of patch containing 35 mg. Highly variable for oral applications.	[282]
Varenicline	4–5 ng/mL	23–39 h	10 ng/mL	3	4.73		[163, 344, 967]
Drugs for treatment of attention deficit hyperactivity syndrome							
Atomoxetine	200–1,000 ng/mL 60–90 min after intake of 1.2 mg/kg/day	2–5 h	2,000 ng/mL	3	3.91	Recommended reference ranges indicate Cmax measured in remitters. Elimination half-life is 21 h in PM of CYP2D6.	[395, 498, 805, 1046]
Dexmethylphenidate	13–23 ng/mL 4 h after 20 mg	2 h	44 ng/mL	3	4.29	5.2–5.5 ng/mL are associated with 50 % dopamine transporter blockade.	[1209]
Methylphenidate	For children and adolescents: 6–26 ng/mL 2 h after 20 mg IR or 4–6 h after 40 mg XR formulations For adults: 12–79 ng/mL 2 h after 20 mg IR or 4–6 h after 40 mg XR formulations	2 h	50 ng/mL	3	4.29	Methylphenidate is unstable at room temperature. The drug is available as immediate release (IR) and retarded formulations (XR) by Osmotic Controlled Release Delivery Systems (OROS) or bi-modal release by Spheroidal Drug Absorption Systems (SODAS). Values given indicate Cmax ranges at therapeutically effective doses.	[7, 227, 560, 766, 909, 1009, 1085, 1116, 1117, 1208–1209]

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▶ **Table 4** Continued.

Drugs and active metabolites	Therapeutic reference range	t1/2	Laboratory alert level	Level of recommendation to use TDM	Conversion factor, CF	Comments	References
Antiparkinson drugs							
Amantadine	300–600 ng/mL	10–14 h	1,200 ng/mL	3	5.98	Drug concentrations increased in case of impaired renal function. Conc. >3,000 ng/ml cause adverse reactions, i. e. myoclonus, delirium, hallucinations.	[540, 592, 858, 1327]
Biperiden	1–6.5 ng/mL (0.5–2 h after 4 mg)	18–24 h	13 ng/mL	3	3.21		[155, 448]
Bornaprine	0.7–7.2 ng/mL (1–2 h after 4 mg)	30 h	14 ng/mL	3	3.04		[786]
Bromocriptine	Low dose (2.5 mg): 0.1–0.3 ng/mL Max. dose (25 mg): 1.0–4.0 ng/mL	38 h	8 ng/mL	3	1.53	Levodopa 250 mg + 25 mg DCI diminishes bromocriptine concentration by about 50 %.	[279, 971]
Cabergoline	58–144 pg/mL (at 0.5–4 h after drug intake for 4 weeks)	63–68 h	390 pg/mL	3	2.21	Unstable at room temperature, plasma or serum should be stored frozen (< − 20 °C).	[279]
Carbidopa	20–200 ng/mL (at 2 h)	2 h	400 ng/mL	3	4.42	Unstable at room temperature, plasma or serum should be stored frozen (< − 20 °C).	[422, 1029]
Entacapone	0.4–1.0 µg/mL (1 h)	0.5 h	2 µg/mL	3	3.28	Unstable at room temperature, plasma or serum should be stored frozen (< − 20 °C).	[504, 830, 1005, 1006, 1025]
Levodopa 3-O-Methyldopa	0.9–2.0 µg/mL 0.7–10.9 µg/mL (at 1 h after 250 mg and combined with 25 mg carbidopa)	1–3 h 2 h	5 µg/mL 20 µg/mL	3	5.07 3.28	Unstable at room temperature, plasma or serum should be stored frozen (< − 20 °C), elimination half-life and concentrations in blood increase under comedication with carbidopa or benserazide.	[5, 236, 348, 701, 867, 870, 871, 899, 942, 1029]
Pramipexole	0.4–7.2 ng/mL	8–12 h	15 ng/mL	3	4.73	Optimal concentrations may be different for different diagnoses or under combination with L-dopa.	[97, 1326]
Ropinirole	0.4–6.0 ng/mL	3–10 h	12 ng/mL	3	3.84		[495, 1198]
Rotigotine	0.1–0.7 ng/mL	5–7 h	2 ng/mL	3	3.17	Transdermal application. Multiple metabolites that do not contribute to pharmacological actions because of fast elimination.	[335]
Tolcapone	3–6 µg/mL (at 2 h)	2 h	12 µg/mL	3	3.66		[294, 593]

Unless otherwise indicated, reference ranges and alert levels refer to trough concentrations (Cmin). For interpretation of TDM results it has to be checked whether measured drug concentrations are within the therapeutic reference range. Concentrations below or above the range are indicative that treatment failure or adverse reactions may occur; AChE: acetylcholine esterase, CL: clearance, DCI: L-dopa/decarboxylase inhibitor; PM: poor metabolizer; Drug concentrations given in mass units can be converted to molar units by multiplication with the conversion factor (CF) nmol/L = ng/mL × CF; For bupropion, carbamazepine, lamotrigine and valproic acid recommended reference ranges are listed twice in accordance with the 2 different indications

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for the treatment of anxiety or obsessive compulsive disorder or chronic pain, and antipsychotic drugs are approved for the treatment of affective disorders. Little information is available on optimal drug concentrations in blood for these indications. Exceptions are carbamazepine, lamotrigine and valproic acid (valproate), which are therefore sometimes listed twice in ▶ **Table 4**. It should be mentioned that studies are on the way to evaluate therapeutic reference ranges for children or adolescent patients [328, 399, 654, 1177, 1314]. For elderly patients, there is an urgent need to conduct similar studies.

When new drugs become available, it is a major handicap for TDM guided pharmacotherapy that therapeutic reference ranges are unclear. Estimation of therapeutic reference ranges is not required for drug approval, and therefore they are rarely established. To be able to make a meaningful use of TDM in spite of this missing link, we propose for these situations to establish a provisional reference range.

Recommendation

As long as valid data on therapeutic reference ranges do not exist, we recommend determination of the arithmetric mean ± standard deviation of drug concentrations in blood of responders to the neuropsychiatric medication. The mean ± SD range should be used as preliminary therapeutic reference range. Further (prospective or observational) studies must verify or correct this range.

2.1.1 Estimation of the lower limit of the therapeutic reference range

Whenever possible, the lower limit of a drug's therapeutic range should be based on studies estimating the relationship between a drug's concentration in blood and clinical effectiveness. Below the lower limit, drug effects are not significantly different from placebo. The optimal study design to evaluate the lower limit is a prospective double-blind randomized controlled trial where patients are treated with drug doses that result in a predefined blood concentration range of the drug. An almost optimal study design was applied by Van der Zwaag and co-workers on patients treated with clozapine [1241]. Clozapine concentrations in blood were titrated to 50–150 ng/mL, 200–300 ng/mL or 350–450 ng/mL. Significant therapeutic superiority was found for middle and high concentrations compared to low concentrations of clozapine. A similar design was applied to a blood level study comparing imipramine and mirtazapine [162]. To conduct such studies, however, is a considerable logistic challenge. Fixed dose studies are feasible and therefore preferable for the evaluation of the lower limit [1222, 1224].

To estimate the threshold value of a therapeutic reference range, receiver operating characteristic (ROC) analysis has proven helpful [483]. A ROC plot allows the identification of a cut-off value that separates responders from non-responders and estimates the sensitivity and specificity of the parameter "drug concentration in blood". The usefulness of ROC analysis has been demonstrated for a number of antipsychotic and antidepressant drugs [829, 928, 934, 1274].

2.1.2 Estimation of the upper limit of the therapeutic reference range

In the first study on TDM in psychiatry [52], an inverse U-shaped relationship between blood concentrations and clinical effects was reported for nortriptyline. The lack of therapeutic improvement at high concentrations was attributed to the mechanism of action of the tricyclic antidepressant drug on monoaminergic neurons. According to current knowledge, however, it seems more likely that reduced amelioration at high concentrations is due to nortriptyline's adverse reactions. The upper limit of the therapeutic range is therefore often defined by the increased risk of adverse drug reactions, also in these guidelines. Correlations to drug concentrations in blood were shown for motor symptoms of antipsychotic drugs [973] and for unwanted effects of tricyclic antidepressant drugs [261, 465]. For paroxetine, a positive correlation was found between the drug concentration in blood and serotonin syndrome symptoms [503]. For citalopram, it was shown that adverse drug reactions correlated inversely with clearance of the drug [1339]. When such data are available, it is possible to apply ROC analysis for the calculation of the upper limit of the therapeutic range [829]. For many neuropsychiatric drugs listed in ▶ **Table 4**, however, valid data on both the concentration in blood and the incidence of adverse drug reactions, are lacking. Case reports on tolerability problems or intoxications mostly do not include drug concentration measurements. Sporadic reports on fatal cases and intoxications are of limited value. When reported blood concentrations have caused death, the drug level is mostly far above the concentration that is associated with maximal therapeutic effects [983, 1132]. Moreover, post mortem redistribution of drugs from or into the blood can lead to dramatic changes in blood levels [671, 948], and the direction of the change does not follow a general rule [616]. Because of these limitations estimation of an upper threshold level above which tolerability decreases or the risk of intoxication increases is more difficult than estimation of the lower threshold level, especially for drugs with a broad therapeutic index like SSRIs. Therefore, many upper threshold values listed in ▶ **Table 4** refer to concentrations where maximum efficiency is expected. In these guidelines, upper limit threshold levels were mostly obtained by calculation of expected dose-related drug concentrations in blood (Cmin) attained under approved maximal doses.

2.1.3 From population-based to subject-based reference values

All therapeutic reference ranges listed in ▶ **Table 4** are population-based. The population-derived ranges constitute descriptive statistical values not necessarily applicable to all patients. Optimal neuropsychopharmacotherapy should try to identify a patient's "individual optimal therapeutic concentration range" to guide the treatment [96, 955]. Furthermore, the stage of the mental disorder also determines the optimal drug concentration. For lithium, it has been shown that the optimal concentration range depends on whether the patient is in an acute manic episode or under maintenance therapy [1076]. For clozapine, Gaertner and colleagues [391] determined individual optimal drug concentrations in blood required for stable remission for every patient under maintenance therapy in a relapse prevention study and found that the antipsychotic drug concentration in maintenance therapy can be up to 40 % lower than that needed for the treatment of an acute schizophrenic episode.

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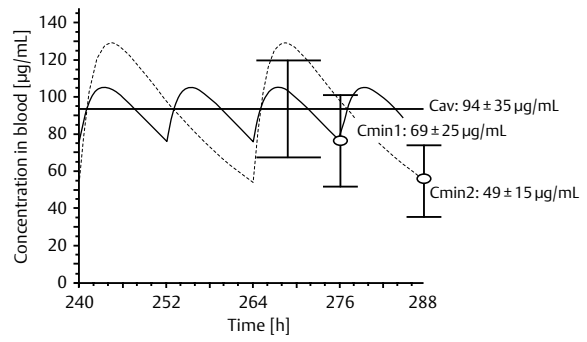

▶ **Fig. 3** Time to concentration curves expected under steady state conditions for valproic acid in blood after daily oral doses of 900 mg with dosing intervals of either 12 h (solid, Cmin1) or 24 h (hatched, Cmin2). The average elimination half-life (t1/2) of valproic acid is 14 h. Circles and error bars indicate expected trough (Cmin) and average concentrations (Cav) ± standard deviation (SD).

Recommendation

It can be useful to measure the drug concentration in blood when the patient has attained the desired clinical outcome. This drug concentration can be regarded as optimal concentration for the individual patient. In case of symptom aggravation, relapse or adverse drug reactions, the value is helpful to find out whether non-adherence or pharmacokinetic alterations have occurred that can explain clinical impairment.

2.1.4 Laboratory alert level

For most neuropsychiatric drugs shown in ▶ **Table 4,** concentrations in blood with an increased risk of toxicity are normally much higher than the upper threshold levels of the therapeutic reference ranges. In the present guidelines, a "laboratory alert level" is defined as follows:

Definition

The "laboratory alert levels" reported in this guideline (▶ **Table 4**) indicate drug concentrations above the recommended therapeutic reference range that oblige the laboratory to feedback immediately to the prescribing physician. For some drugs, the alert levels are based on reports on severe adverse drug reactions or intoxications that were supplemented by concentration measurements. Mostly, however, the alert level was arbitrarily defined as a drug concentration in blood that is 2-fold higher than the upper limit of the therapeutic reference range. The laboratory alert should lead to dose reduction when the patient exhibits signs of adverse drug reactions. When the high drug concentration is well tolerated by the patient and if a dose reduction bears the risk of symptom exacerbation, the dose should remain unchanged. The clinical decision, especially in case of unchanged dosage in the face of an alert level that was reached or exceeded, needs to be documented in the medical file.

2.2 The dose-related reference range

For the interpretation of TDM results, there is a second concentration range besides the therapeutic reference range, the so called dose-related reference range. The use of the therapeutic reference range is a pharmacodynamic approach. Application of the dose-related reference range is a pharmacokinetic approach. It compares a measured drug concentration with a theoretically expected drug concentration range. Referring to pharmacokinetic studies, preferentially on a population of patients without co-medication or pharmacogenetic abnormalities ("normal" patients), the average steady-state concentration (Cav) of a drug expected in a normal patient can be calculated when the daily maintenance dose (Dm), the dosing interval (di), the total clearance (CL) and the bioavailability (F) are known:

$$Cav = (Dm/di) \times (F/CL) \quad (1)$$

Dose and dosing interval are known from the prescription, pharmacokinetic parameters are available from pharmacokinetic trials. Using the daily dose (1 mg/24 h = 1,000,000 ng/1440 min), the standard deviation (SD) of the total apparent clearance CL/F (mL/min), that is also reported in the literature, it is possible to calculate Cav ± SD (ng/mL) by Eq. (1). For the calculation, the dimensions of the different parameters must be considered and all doses have to be converted to ng, all volumes to mL and time intervals to min. When a CL/F value of 100 ± 50 mL/min was reported, the coefficient of variation is 50 %, then Cav amounts to 139 ng/mL for a dose of 20 mg/day (i. e., (20,000,000 ng/1440 min) * (1/(100 mL/min)) = 139 ng/mL), SD of Cav will be 69 ng/mL and the Cav ± SD ranges from 70 to 208 ng/mL. Assuming a dosing interval of 24 h, i. e., once daily (quaque die, q.d.) dosing , the Cav ± SD range was proposed as dose-related reference range by Haen and colleagues [470, 471]. The mean - SD was considered as lower and the mean + SD as upper limit of this range. Statistically, this range contains 68 % of concentrations determined under normal conditions in the blood of a population that consists of 18–65 years old individuals. For the 2011 guidelines [524], apparent total clearance (CL/F) data ± SD were extracted from the literature for 83 neuropsychiatric drugs for calculation of dose factors. Multiplying these factors ± SD by the daily dose, dose-related reference ranges were calculated and used for the interpretation of TDM results. When a patient's drug concentration measured by TDM was found within the dose-related reference range, the concentration was defined as normal. Concentrations above or below the range were considered as signals indicating potential abnormalities such as partial non-adherence, drug-drug interactions, genetic polymorphisms of drug metabolizing enzymes or diseases of organs involved in drug elimination.

The concept of the dose-related reference range worked. Many incompletely adherent patients or patients with pharmacokinetic abnormalities could be identified [470]. The average steady-state concentration equation is valid and useful when the drug's elimination half-life (t1/2) is long compared to the dosing interval. However, when t1/2 is short and the dosing interval is longer than t1/2, values calculated by Eq. (1) are poorly predictive for the Cmin values used for TDM. This problem is illustrated in ▶ **Fig. 3** for valproic acid which has a t1/2 of 14 h and is applied either once or twice daily.

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Under daily doses of 900 mg, the dose-related reference range of valproic acid computed by Eq. (1) amounts to 94 ± 35 µg/mL, independent of the dosing interval. Time to concentration curves, however, show that the trough concentrations are lower than Cav, 49 ± 15 µg/mL if the dosing schedule is a single 900 mg dose per day. It amounts to 69 ± 25 µg/mL if the daily dose of 900 mg/d is administered in two doses of 450 mg each. Cav ± SD ranges match with Cmin ± SD ranges for dosing intervals < 14 h. Therefore, computed Cav can be considered as an appropriate predictor for an expected drug concentration in blood. Under a single dose per day schedule, however, Cmin at 24 h after the last dose is by 54 % lower than Cav. As explained here for valproic acid as an example, this limitation must be considered when using Eq. (1) based calculations of dose-related reference ranges. Depending on the dosing interval, this limitation can be relevant for multiple drugs, e. g., duloxetine, paroxetine, venlafaxine, amisulpride, paliperidone, quetiapine, lithium, valproic acid, zopiclone, atomoxetine or naltrexone. When dosing intervals are longer than t1/2, computed values are by more than 30 % lower for Cmin than for Cav. Overall, this applies for 32 % of the compounds listed in ▶ **Table 5**.

Moreover, there is another limitation of Cav based calculations. The validity of the dose-related reference range cannot be easily verified by measurements which, in contrast, is possible for Cmin, because TDM is based on the measurement of a drug's minimal ("trough") blood concentration. Cav is by definition the area under the time to concentration curve (AUC) divided by the dosing interval. It cannot be attributed to a distinct time point like Cmin which is necessary for the timing of venipuncture. Another limitation of Cav based calculations is neglection of fluctuations of drug levels over the day as shown in ▶ **Fig. 2** which can be important for a drug's tolerability and efficacy [206].

Because of these limitations, it was decided to modify the calculation of dose-related reference ranges for this update. Without going into the details described in textbooks on pharmacokinetics (see e. g., [77, 306]), steady-state concentrations can be calculated by extension of Eq. (1) and applying the Bateman function. Gex-Fabry and colleagues [404] used this approach and described a function for the postabsorptive phase, which is the interval between tmax, the time of maximal drug concentration, and tmin, the time of Cmin, to calculate concentration during the elimination phase.

Assuming a one-compartment model and an exponential decrease of drug concentration in blood, an expected steady-state drug concentration Ct can be computed for any time point during the postabsorptive phase as follows:

$$Ct = [(Dm/di) \times (F/CL)] \times [(ke \times di)/(1 - e^{-ke \times di})] \times (e^{-ke \times t}) \quad (2)$$

where Dm is the dose under steady-state conditions, termed maintenance dose, CL/F apparent total clearance (for calculation used as reciprocal value), di dosing interval, ke elimination rate constant, to be calculated from the elimination half-life, $t_{1/2}$, by $ke = \ln 2 / t_{1/2,}$ and t the time of blood withdrawal.

Assuming di as 24 h and t as time interval between intake of the last dose and blood withdrawal as Δt, Eq. (3) can be used to estimate an expected Cmin as follows:

$$Cmin = (Dm/24) \times (F/CL) \times \left[(ke \times 24)/(1 - e^{-ke \times 24})\right] \times (e^{-ke \times \Delta t}) \quad (3)$$

Drug concentrations expected by TDM measurements can thus be computed by daily dose, CL/F, $t_{1/2}$ and time interval between last dose and blood withdrawal Δt. As for the calculation of Cav, the pharmacokinetic parameters CL/F and t1/2 are available from pharmacokinetic trials, daily dose and Δt are fixed by the prescriber.

Using part of Eq. (3), a DRC factor can be defined and computed, e. g., by MS-Excel software, for drugs with known CL/F and t1/2 as follows.

$$\text{DRC factor} = (F/CL) \times \left[(ke \times 24)/(1 - e^{-ke \times 24})\right] \times (e^{-ke \times \Delta t}) \quad (4)$$

Expected Cmin of a given dose can then be calculated by multiplying the DRC factor by the daily dose. The limitations for prediction of theoretically expected Cmin in comparison to Cav are the more complex calculation procedure and the need to implement t1/2 which also varies between individuals. Since variability of t1/2 is probably caused by the same factors as variability of clearance, it was assumed for the TDM guidelines that the SD of mean drug concentrations measured in a population of adherent patients reflects normal variability of apparent total clearance (CL/F). Based on this assumption it was defined that the interindividual variability of a population's CL/F equals the variability of Cmin. The SD reported in the literature for CL/F was thus propagated to Cmin to calculate expected mean ± SD as dose-related reference range as done previously for Cav based calculations [471]. It was empirically tested whether this way of calculation predicts expected drug concentrations.

▶ **Table 5** lists DRC factors for 172 compounds with inclusion of parent drugs, metabolites and active moiety. Factors were computed by Eq. (4) using pharmacokinetic data reported in the literature. Following recommended schedules of drug application, decisions were made to define Δt. For a drug like citalopram or extended release (XR) venlafaxine given once per day in the morning, Δt was 24 h. For drugs like amitriptyline that is given normally in the morning and the evening, Δt was set at 12 h. For hypnotic drugs given shortly before bedtime and blood withdrawal in the next morning, Δt was set at 10 h. Listed factors can be used for calculation of the lower and the upper limit of the range by multiplying DRC factors low (= DRC factor – SD) and high (= DRC factor + SD) by the daily dose to obtain the dose-related reference range. When drugs are given once or twice daily, DRC factors are given in ▶ **Table 5** for Δt at 12 and 24 h, respectively. For drugs like clomethiazole or modafinil where blood concentrations are not measured at tmin (no trough levels), DRC factors are given in ▶ **Table 5** at distinct time points when blood withdrawal is recommended.

The validity of these calculations, based on eqs. [(2]) to ([4]) and the pharmacokinetic parameters CL/F and ke of pharmacokinetic studies on normal patients reported in the literature as well as recommended dosing interval and daily doses according to the SPC provided by the manufacturer, was controlled for plausibility using empirically obtained Cmin values reported for normal patients in TDM studies. Computed dose-related reference ranges were accepted when theoretical values were confirmed by empirical data. This was the case when the empirical mean Cmin value was within the theoretical dose-related reference range.

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▶ **Table 5** Apparent total clearance (i. e., clearance/bioavailability, CL/F), bioavailability (F), average elimination half-life (t1/2), time interval between last dose and blood withdrawal (Δt) and and dose related concentration (DRC) factors for calculation of dose related reference ranges of parent drugs, metabolites and active moieties.

Drugs and metabolites	CL/F ± SD	F	t1/2	Δt	DRC factors			Comments	References
	[mL/min]	[%]	[h]	[h]	mean	low	high		
Antidepressant drugs									
Agomelatine	1,100 ± 500	3	1.5	2	2.78	1.52	4.04	Trough level at Δt = 24 h are not measurable because of rapid elimination, CL affected by CYP1A2.	[126, 1110]
Amitriptyline nortriptyline active moiety	1,043 ± 301 1,435 ± 609	50	19 30	12	0.65 0.48 1.12	0.46 0.28 0.73	0.83 0.68 1.51	CL affected by CYP2C19 and CYP2D6 and age	[515, 1143, 1228, 1259]
Amitriptyline oxide amitriptyline nortriptyline active moiety	485 ± 133 3,947 ± 1,316 3,488 ± 969	64	2 19 31	12	0.20 0.17 0.20 0.37	0.14 0.11 0.14 0.26	0.26 0.23 0.25 0.48	Prodrug, active compounds are amitriptyline and nortriptyline. CL affected by CYP2C19 and CYP2D6	[276, 357]
Bupropion hydroxybupropion	2,260 ± 870 147 ± 91	90	19 28	24	0.19 3.46	0.12 1.32	0.27 5.60	Bupropion is unstable at room temperature, the metabolite is the major active compound. CL/F affected in patients with renal impairment and by CYP2B6	[534, 621, 678, 1211]
Citalopram N-desmethylcitalopram	360 ± 105 622 ± 384	80	40 50	24	1.52 0.94	1.07 0.36	1.96 1.52	CL affected by CYP2C19 and age	[195, 515, 578, 984, 1119, 1228, 1339]
Clomipramine N-desmetylclomipramine active moiety	1,120 ± 667 622 ± 384	50	21 36	12	0.60 1.11 1.71	0.24 0.42 0.67	0.96 1.79 2.75	CL affected by CYP2D6 and CYP2C19	[340, 517, 984, 1079, 1143]
Desipramine	1,750 ± 1,248	38	17	12	0.39	0.11	0.66	CL affected by CYP2D6	[517, 1143]
Desvenlafaxine	315 ± 82	80	14	24	1.15	0.85	1.45	CL affected by CYP2C19, not by CYP2D6	[63, 848, 952]
Dothiepin = Dosulepin	2,450 ± 1,867	30	20	24	0.18	0.04	0.32	CL affected by CYP2C19	[643, 745]
Doxepin N-desmethyldoxepin active moiety	1,706 ± 938 1,750 ± 940	27	17 51	12	0.39 0.40 0.79	0.18 0.18 0.36	0.61 0.61 1.22	CL affected by CYP2C19 and CYP2D6, age and gender	[517, 799, 1143, 1228]
Duloxetine	750 ± 264	60	12	24	0.43	0.28	0.58	CL affected by smoking due to induction of CYP1A2, higher in Asian patients	[727, 1097, 1188]
Escitalopram N-desmethylescitalopram	495 ± 218 622 ± 384	80	30 52	24	1.05 0.95	0.59 0.36	1.51 1.53	CL affected by CYP2C19, age and gender	[195, 544, 578, 583, 584, 854, 987, 1106, 1228]
Fluoxetine N-desmethylfluoxetine active moiety	126 ± 93 111 ± 72	90	120 240	24	5.14 6.04 11.18	1.35 2.12 3.47	8.93 9.96 18.89	CL calculated from trough steady state concentrations in blood	[27, 984, 985, 1228]
Fluvoxamine	1,907 ± 504	53	20	24	0.23	0.17	0.29	CL affected by CYP2D6	[984, 1143, 1259]

Thieme

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▶ **Table 5** Continued.

Drugs and metabolites	CL/F ± SD	F	t1/2	Δt	DRC factors			Comments	References
	[mL/min]	[%]	[h]	[h]	mean	low	high		
Imipramine desipramine active moiety	1,733 ± 578 933 ± 117	39	12 21	12	0.37 0.73 1.10	0.25 0.63 0.88	0.49 0.82 1.31	CL affected by CYP2D6 and CYP2C19	[673, 1038, 1143, 1163]
Levomilnacipran	176 ± 43	90	8	12	1.71	1.12	2.30	CL reduced by renal impairment but not affected by CYP enzymes	[202, 203, 1021]
Maprotiline	741 ± 410	70	40	12	0.93	0.42	1.45	CL affected by CYP2D6 and age	[140, 746, 1228]
Mianserin	664 ± 258	30	32	12	1.03	0.63	1.44	CL affected by CYP2D6	[238, 326, 984]
Milnacipran	592 ± 95	85	8	12	0.99	0.83	1.14	CL similar in Asians and Caucasians, not affected by CYP enzymes	[1021]
Mirtazapine	261 ± 80	50	30	12	2.63	1.82	3.43	CL affected by age, gender and smoking status, and lower in Asian patients	[567, 831, 984, 1150, 1189, 1228]
Moclobemide	208 ± 82	70	2.5	12	0.80	0.48	1.11	CL affected by CYP2C19	[295, 549]
Nortriptyline	970 ± 242	50	30	12	0.71	0.53	0.88	CL affected by CYP2D6	[515, 576, 1143, 1210]
Paroxetine	724 ± 274	64	19	24	0.60	0.37	0.83	CL affected by CYP2D6, nonlinear pharmacokinetics due to inhibition of CYP2D6	[515, 808, 1092, 1143, 1228, 1231]
Reboxetine	58 ± 26	60	10	12	10.8	5.94	15.6		[243, 925]
Sertraline N-desmethylsertraline	1,167 ± 450 822 ± 278	66	26 70	24	0.42 0.75	0.26 0.50	0.58 1.00	CL decreases during pregnancy and increases in patients aged > 60 years	[288, 374, 1228]
Tianeptine	222 ± 58	100	3	12	1.09	0.80	1.38	Metabolism does not involve CYPs	[307]
Tranylcypromine	1,152 ± 607	100	3	12	0.21	0.10	0.32	Metabolism does not involve CYPs	[753]
Trazodone	115 ± 35	100	7	12	4.82	3.35	6.29	CL decreases with age, affected by CYP3A4	[702, 791, 806–807]
Trimipramine	1,113 ± 330	41	24	12	0.61	0.43	0.79	CL affected by CYP2D6 and CYP2C19	[632, 1143]
Venlafaxine IR O-desmethylvenlafaxine active moiety N-desmethylvenlafaxine Venlafaxine XR O-desmethylvenlafaxine active moiety N-desmethylvenlafaxine	1,250 ± 433 300 ± 67 367 ± 267 1,196 ± 576 422 ± 107 704 ± 264	40 40 	6 11 7 11 20 7	24 24 	0.10 0.99 1.09 0.46 0.24 1.04 1.28 0.24	0.06 0.77 0.83 0.13 0.12 0.78 0.90 0.15	0.14 1.21 1.35 0.80 0.36 1.30 1.67 0.33	Data for immediate and extended release formulations (IR and XR), which differ in tmax, 1 h for IR and 6 h for XR For the XR formulation, CL/F computed from Cmin; CL affected by CYP2D6 and CYP2C19 and by age	[339, 405, 512, 598, 602, 646, 984, 1074, 1143]

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▶ **Table 5** Continued.

Drugs and metabolites	CL/F ± SD	F	t1/2	Δt	DRC factors			Comments	References
	[mL/min]	[%]	[h]	[h]	mean	low	high		
Vilazodone	415 ± 129	70	32	24	1.28	0.88	1.67	CL affected by CYP3A4	[127–128]
Vortioxetine	550 ± 83	80	66	24	1.11	0.94	1.28	CL affected by CYP2D6	[47, 548, 834]
Antipsychotic drugs									
Amisulpride	586 ± 174	50	16	24	0.67	0.47	0.87	CL not affected by CYP enzymes, renal excretion	[138, 827, 829, 1018]
Aripiprazole dehydroaripiprazole active moiety	53 ± 16 132 ± 49	90	70 94	24	11.72 4.82 16.54	8.15 3.04 11.19	15.29 6.60 21.89	CL affected by CYP2D6 and CYP3A4.	[626, 751–752]
Asenapine	2,761 ± 1,783	35	24	12	0.25	0.09	0.41	CL similar in patients elder or younger than 65 years	[197, 312]
Benperidol	1,266 ± 513	50	6	12	0.40	0.24	0.56		[1068]
Brexpiprazole	23 ± 13	95	91	24	27.4	11.6	43.2	CL affected by CYP2D6	[443]
Bromperidol	1,598 ± 607	30	20	12	0.42	0.26	0.58		[690, 1155]
Cariprazine N-desmethylcariprazine N-didesmethylcariprazine	279 ± 67 869 ± 178 125 ± 32	100	44 37 446	24	2.05 0.63 5.45	1.56 0.50 4.06	2.54 0.76 6.85	CL affected by CYP3A4	[840]
Chlorpromazine	623 ± 203	30	30	24	0.83	0.56	1.10		[1338]
Chlorprothixene	2,507 ± 478	50	10	12	0.25	0.20	0.30		[62, 970]
Clozapine N-desmethylclozapine	637 ± 367 667 ± 283	50	12 8	12 24 12 24	1.01 0.50 0.87 0.31	0.43 0.21 0.50 0.18	1.59 0.79 1.25 0.44	CL may be enhanced in smokers due to induction of CYP1A2 and decreased during inflammation. CL/F is twofold higher in Asian than Caucasian patients, for clozapine, t1/2 is prolonged to 30 h in intoxicated patients.	[133, 216, 240, 290, 575, 703, 1075]
Flupentixol	2,148 ± 814	50	35	12	0.32	0.20	0.44	CL associated with CYP2D6	[2, 595, 914]
Fluphenazine	9,990 ± 2,820	35	16	12	0.07	0.05	0.09	CL affected by CYP2D6	[944]
Fluspirilene	No data								
Haloperidol	826 ± 203	60	18	12	0.81	0.61	1.01	CL affected by CYP2D6	[205, 381, 914, 941]
Iloperidone	1,258 ± 425	100	18	12	0.53	0.35	0.71	CL affected by CYP2D6	[175, 1031]
Levomepromazine	2,630 ± 1,580	50	28	12	0.26	0.10	0.42		[255, 779]
Levosulpiride	425 ± 140	30	8	12	1.35	0.90	1.79	CL affected by P-gp (ABCB1)	[214, 1331]
Loxapine	807 ± 138	30	7	4 24	1.51 0.21	1.26 0.17	1.78 0.25	Aerosol application	[1126, 1164]
Lurasidone	3,902 ± 702	20	18	24	0.11	0.09	0.13	CL affected by food intake (fat content)	[225, 358, 951]
Melperone	2,555 ± 476	60	5	12	0.18	0.14	0.21		[135]

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▶ **Table 5** Continued.

Drugs and metabolites	CL/F ± SD	F	t1/2	Δt	DRC factors			Comments	References
	[mL/min]	[%]	[h]	[h]	mean	low	high		
Olanzapine	372 ± 132	80	33	12	1.85	1.19	2.50	CL higher in males than in females and elevated in smokers due to induction of CYP1A2	[106, 176, 226, 404, 1292]
Paliperidone	112 ± 54	30	20	24	3.98	2.06	5.90	Extended release formulation	[617, 842]
Perazine	3,671 ± 2,134	10	12	12	0.17	0.07	0.27	Data based on single dose study	[153]
Perphenazine	12,567 ± 6,417	40	10	12	0.05	0.02	0.08	CL enhanced in smokers, affected by CYP2D6	[330, 574, 582]
Pimozide	1,400 ± 467	40	33	12	0.49	0.33	0.65	CL affected by CYP2D6	[284, 1039]
Pipamperone	644 ± 207	100	20	12	1.05	0.71	1.38		[947]
Prothipendyl	910 ± 300	12	2.5	6	0.96	0.64	1.28		[792]
Quetiapine IR desalkylquetiapine Quetiapine XR desalkylquetiapine	1,072 ± 461 2,094 ± 621 596 ± 421 1,137 ± 646	9 9 	8 18 8 18	12 12 12 24 12 24	0.54 0.32 0.97 0.34 0.59 0.37	0.31 0.23 0.29 0.10 0.25 0.16	0.78 0.41 1.66 0.58 0.92 0.58	Data for immediate and extended release formulations (IR and XR), with tmax of 1 and 6 h, respectively; for XR, CL/F computed from Cmin, CL affected by gender and age	[66, 183, 356, 361, 400, 482, 492, 705, 897, 1312, 1350]
Risperidone 9-hydroxyrisperidone active moiety	1,447 ± 1,038 140 ± 47	70	3 20	12	0.57 4.82 5.39	0.34 3.20 3.54	0.80 6.44 7.24	CL affected by CYP2D6 and age, potentially decreased during inflammation	[172, 693, 728, 1105, 1240, 1336]
Sertindole	317 ± 211	70	73	24	1.95	0.65	3.25	CL affected by CYP2D6	[178, 1321–1322]
Sulpiride	1,186 ± 240	35	8	12	0.49	0.39	0.59	CL reduced in case of impaired renal function	[149, 828, 1300]
Thioridazine	693 ± 289	60	30	12	0.99	0.58	1.40	CL affected by CYP2D6	[191]]
Ziprasidone	350 ± 98	60	7	12	1.58	1.14	2.03	F affected by food intake	[208, 478, 956, 1296]
Zotepine	5,367 ± 4,900	90	15	12	0.12	0.01	0.24		[1172]
Zuclopenthixol	1,584 ± 717	50	18	12	0.42	0.23	0.61	CL affected by CYP2D6	[574]
Anticonvulsant and mood stabilizing drugs									
Brivaracetam	54 ± 13	100	9	12	11.2	8.5	14.0		[1014, 1042, 1053, 1147]
Carbamazepine	132 ± 39	70	15	12	4.99	3.52	6.47	CL increases over time due to induction of CYP3A4/5, t1/2 decreases from 36 h after acute doses to 15 h under chronic treatment	[109, 132, 333]
Clobazam N-desmethylclobazam	42 ± 25 13 ± 6	90	32 57	12	16.6 53.6	6.8 28.4	26.3 78.8	CL affected by CYP2C19	[271, 1044, 1195]
Felbamate	35 ± 9	90	19	24	12.4	9.1	15.7		[995]

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▶ **Table 5** Continued.

Drugs and metabolites	CL/F ± SD	F	t1/2	Δt	DRC factors			Comments	References
	[mL/min]	[%]	[h]	[h]	mean	low	high		
Lamotrigine	35 ± 13	100	14	24	10.3	6.50	14.17	Markedly affected by comedication with inducing properties, valproic acid increases the mean elimination half-life to 70 h and carbamazepine, phenytoin or phenobarbital decreases it to 9–14 h.	[194, 750, 998]
Levetiracetam	62 ± 10	99	7	12	8.94	7.50	10.39		[530, 972]
Lithium	25.0 ± 9.5	100	24	12 24	27.2 19.3	16.9 11.9	37.6 26.6	For calculation of expected dose-related concentrations, DRC must be multiplied by daily dose in mmol, resulting concentrations are µmol/L.	[31, 1174, 1283]
Oxcarbazepine 10-monohydroxy-carbamazepine	3,383 ± 1,680 40 ± 8	100	2 9	12	0.03 15.1	0.01 12.1	0.04 18.1		[539, 1263, 1342]
Primidone	38.5 ± 8.5	90	20	12	17.5	13.7	21.4	Active metabolite phenobarbital	[768]
Rufinamide	5.6 ± 3.7	80	8	24	86.0	29.2	142.8		[936]
Topiramate	26 ± 5	90	8	12	22.4	18.1	26.8		[302, 599]
Valproic acid	6.65 ± 2.45	100	14	12 24	98.5 54.4	62.2 34.4	134.8 74.4	CL reduced in UGT1A3 * 5 carriers	[219, 1243]
Anxiolytic drugs and drugs for treatment of sleep disorders									
Alprazolam	58 ± 13	80	13	10	12.5	9.7	15.2	CL affected by CYP3A4	[905, 1103]
Bromazepam	57.6 ± 12.7	85	23	10	12.5	9.8	15.3	CL affected by CYP3A4 and CYP2C19 and gender	[605, 877]
Brotizolam	273 ± 72	70	5	10	2.19	1.62	2.77	CL affected by CYP3A4	[585, 893]
Buspirone 1-pyrimidinylpiperazine 6-hydroxybuspirone	42,409 ± 11,438 5,574 ± 2,573 3,149 ± 880	10	3 5 6	10	0.01 0.11 0.21	0.00 0.06 0.15	0.01 0.16 0.26	CL affected by CYP3A4	[70, 299]
Chlordiazepoxide	16.1 ± 3.1	100	22	10	44.9	36.1	53.6	CL affected in patients with alcoholic hepatitis and by CYP3A4	[818]
Clonazepam	76.5 ± 13.5	80	25	10	9.42	7.76	11.08	CL affected by CYP3A4	[432]
Clorazepate dipotassium N-desmethyldiazepam	 19 ± 5	13	2 53	10	 38.0	 28.5	 47.5	Prodrug, N-desmethyldiazepam is the active compound	[865]

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▶ **Table 5** Continued.

Drugs and metabolites	CL/F ± SD	F	t1/2	Δt	DRC factors			Comments	References
	[mL/min]	[%]	[h]	[h]	mean	low	high		
Diazepam N-desmethyldiazepam active moiety	25 ± 16 22 ± 9	80	43 65	10	28.5 32.8 61.3	10.2 19.4 29.6	46.9 46.1 93.0	CL affected by CYP2C19	[511]
Diphenhydramine	1,631 ± 658	50	10	10	0.44	0.26	0.61	CL affected by CYP2D6 and age	[1091]
Doxylamine	232 ± 69	100	10	10	3.07	2.16	3.99		[1262]
Flunitrazepam	245 ± 56	85	26	10	2.94	2.27	3.61		[308]
Flurazepam N-desalkylflurazepam hydroxyethylflurazepam	47,881 ± 15,960 85 ± 36 10,085 ± 3,362	70	3 75 3	10	0.01 8.31 0.04	0.01 4.79 0.03	0.01 11.82 0.05		[433]
Hydroxyzine	686 ± 224	70	14	10	1.05	0.71	1.40	Reduced CL in patients with primary biliary cirrhosis	[1090]
Lorazepam	73 ± 37	94	14	10	9.91	4.89	14.93		[440]
Lormetazepam	216 ± 36	80	12	10	3.34	2.78	3.89		[529]
Medazepam diazepam N-desmethyldiazepam oxazepam Active moiety	 25 ± 16 22 ± 9 98 ± 42	80	2 43 65 20	10	 28.5 32.8 7.4 68.6	 10.2 19.4 4.2 33.8	 46.9 46.1 10.5 103.5	Prodrug metabolized to active compounds diazepam, N-desmethyldiazepam and oxazepam; CL affected by CYP2C19 and CYP3A4	[474]
Midazolam	380 ± 61	70	2	10	0.48	0.40	0.56	CL affected by CYP3A4	[1238]
Nitrazepam	82 ± 34	78	28	10	8.77	5.13	12.41	CL affected by CYP3A4	[1234]
Opipramol	4,329 ± 2,473	94	11	10	0.17	0.07	0.26	CL affected by CYP2D6	[684, 855]
Oxazepam	98 ± 42	85	20	10	7.38	4.22	10.54		[434]
Pregabalin	75 ± 14	90	6	10	8.61	6.99	10.24		[122, 211]
Prazepam N-desmethyldiazepam	167 ± 50 22 ± 9	70	1 65	10	0.26 32.2	0.18 19.0	0.33 45.3	Prodrug metabolized to the active compound N-desmethyl-diazepam	[22, 563]
Promethazine	1,140 ± 410	25	12	10	0.63	0.40	0.86	Oral dose, CL affected by CYP2D6	[1180]
Temazepam	767 ± 312	95	8	10	0.90	0.53	1.27		[1102]
Triazolam	440 ± 60	85	3	10	0.87	0.75	0.99	CL affected by CYP3A4	[436, 1102]
Zaleplon	1,099 ± 231	70	1	10	0.01	0.01	0.01	CL affected by CYP3A4	[309, 438]
Zolpidem	315 ± 49	70	2	10	0.57	0.48	0.66	CL affected by CYP3A4	[309, 438]
Zopiclone	567 ± 317	70	4	10	0.91	0.40	1.43	CL affected by CYP3A4	[738]
Antidementia drugs									
Donepezil	128 ± 23	100	70	12	5.40	4.42	6.38	CL affected by CYP2D6	[499, 627, 833]
Galantamine	334 ± 66	90	9	12	1.81	1.45	2.17		[943, 1284, 1348]

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▶ **Table 5** Continued.

Drugs and metabolites	CL/F ± SD	F	t1/2	Δt	DRC factors			Comments	References
	[mL/min]	[%]	[h]	[h]	mean	low	high		
Memantine	125 ± 34	100	64	24	4.86	3.55	6.17		[720, 862]
Rivastigmine	2,214 ± 2,584 1,341 ± 1,046	36	2 -	12 24	0.04 0.69	0.00 0.36	0.09 1.02	Oral application Transdermal patch application, DRC calculated from TDM data	[691]
Drugs for treatment of substance related disorders									
Acamprosate	2,981 ± 1,240	11	13	12	0.22	0.13	0.31	F reduced by food intake	[480, 1033]
Buprenorphine N-desmethyl buprenorphine	3,201 ± 3,676 1,470 ± 1,533	40	28 69	24	0.16 0.42	0.00 0.00	0.34 0.85	HCV infection is associated with elevated concentrations in blood, CL affected by CYP3A4	[719, 737, 772]
Bupropion Hydroxybupropion	2,250 ± 870 147 ± 91	90	20 28	24	0.20 3.46	0.12 1.32	0.28 5.60	Bupropion is unstable at room temperature, the metabolite is the major active compound, CL affected in patients with renal impairment and by CYP2B6	[534, 621, 678, 1211]
Clomethiazole	733 ± 167	32	4	6	1.41	1.09	1.74		[189, 1220, 1355]
Diamorphine (heroin) 6-acetylmorphine morphine	15,500 1,227 ± 503	100	0.1 0.4 2	6	 0.59	 0.35	 0.83	Diamorphine and 6-acetylmorphine are not measurable due to rapid elimination	[1017]
Disulfiram Diethyldithiomethyl-carbamate	829 ± 169 585 ± 138	80	7 22	24	0.20 0.79	0.16 0.61	0.24 0.98		[345, 588]
Levomethadone	161 ± 68	82	35	24	3.37	1.95	4.79	CL associated with CYP3A4	[167, 371]
Methadone	182 ± 43	80	34	24	2.96	2.26	3.66	CL associated with CYP2B6 and CYP3A4	[320, 322, 323, 699, 700, 856, 1049, 1319]
Morphine sulfate, SR morphine	2,577 ± 1,933	30	21	12 24	0.26 0.18	0.06 0.05	0.46 0.31	Data for morphine given for slow release (SR). Apparent $t_{1/2,}$ and CL calculated from Cmin. Calculation of dose-related concentrations must be corrected for salt preparation (sulfate, sulfate pentahydrate or hydrochloride).	[812]
Nalmefene	1,007 ± 188	41	13	2 6 12 12	0.79 0.26 0.19 0.64	0.65 0.21 0.16 0.52	0.94 0.31 0.23 0.76	Factors for single doses applied “as needed” Factors for daily drug intake	[383, 551, 676]
Naltrexone 6β-naltrexol	2,334 ± 300 1,083 ± 157	35	4 11	24	0.02 0.27	0.02 0.23	0.02 0.31	CL increased in alcohol dependent patients by about 20 %	[163, 313]
Nicotine	1,333 ± 450	30	2	3 -	1.53 1.05	1.01 0.70	2.05 1.40	Nicotine chewing gum During patch application	[282, 735]

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▶ **Table 5** Continued.

Drugs and metabolites	CL/F ± SD	F	t1/2	Δt	DRC factors			Comments	References
	[mL/min]	[%]	[h]	[h]	mean	low	high		
Varenicline	83.7 ± 14.9	100	24	12 24	8.13 5.75	6.69 4.73	9.58 6.77	CL linearly related to renal clearance	[624, 977]
Drugs for treatment of attention deficit hyperactivity syndrome									
Atomoxetine	288 ± 103	79	4	6 24	3.54 0.11	2.28 0.07	4.81 0.15	CL affected by CYP2D6 and CYP2C19	[1046]
Dextroamfetamine	428 ± 107	89	9	6 24	2.24 0.56	1.68 0.42	2.80 0.70		[507, 1000]
Dexmethylphenidate	3,530 ± 1,072	23	3	6	0.27	0.19	0.36	Bimodal release formulation	[1208, 1209]
Guanfacine	630 ± 198	81	18	6	1.34	0.92	1.76	CL affected by CYP3A4	[1010]
Lisdexamfetamine d-amfetamine	20,579 ± 9,245 1,155 ± 268	50	1 11	6	0.80	0.61	0.98	Active metabolite d-amfetamine	[125, 338, 767, 1010]
d,l-Methylphenidate, IR XR for children XR for adults	3,177 ± 1,023	0.14	2 4.3 3.5	3 6 6	0.64 0.31 0.21	0.44 0.24 0.15	0.85 0.38 0.27	Factors given for Cmax of immediate and extended release formulations (IR and XR) for children (IR and XR) and for adults (only XR)	[7, 227, 560, 1010, 1085, 1209, 1301]
Modafinil	51 ± 11	33	14	6	17.3	13.6	21.0		[1323, 1324, 1332]
Antiparkinson drugs									
Pramipexole	483 ± 64	90	8	10	1.44	1.25	1.63	CL given for dexpramipexole	[97, 139, 571, 1326]
Ropinirol	956 ± 412	50	6	10	0.68	0.39	0.97	CL enhanced in smokers due to induction of CYP1A2	[495, 614, 1198]
Rotigotine	5,553 ± 2,600	-	-	-	0.66	0.55	0.77	Factors given for transdermal application and calculated from TDM data, CL affected by CYP2C19	[188, 335]

DRC factors were computed as described in the text. Decisions for Δt followed recommended schedules of drug application. Dose-related reference ranges are calculated by multiplying DRC factors low and high by the daily dose. They are the mean–SD to mean + SD range and refer to trough concentrations unless otherwise indicated; CYP related comments and other comments are given, when the information was considered as useful for TDM and other laboratory tests, especially genotyping. Pharmacokinetic parameters have been compiled to the best of our knowledge. However, we take no responsibility for their correctness in the legal sense.

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When Δt is different from values listed in ▶ **Table 5**, an expected drug concentration can be computed by Eq. (2) for any time point during the postabsorptive phase (time from maximal drug concentration).

Derived from the original concept of the dose-related reference range for average drug concentrations [471], the dose-related reference range is now defined as a Cmin range that can be calculated from the prescribed dosage and pharmacokinetic parameters.

Definition

The "dose-related reference range" reported in the present guidelines is defined as the mean–SD to mean + SD range of the trough concentration of a drug under steady-state conditions. The mean ± SD includes 68 % of a population of "normal" patients who ingested their medication, are aged 18–65 years, with a body weight of 70 kg and without pharmacokinetically relevant comorbidity, comedication or genetic abnormalities in drug metabolism. Dose-related reference ranges are obtained by multiplying DRC factors low and high of ▶ **Table 5** by the daily dose.

The dose-related reference range is a discriminating reference range to identify patients with abnormal drug concentrations in blood. When practicing TDM, measured drug concentrations reported by a TDM laboratory should be compared with computed theoretical values by using data of ▶ **Table 5** in these guidelines (see also cases below). When a patient's drug concentration is within the expected dose-related range, the concentration can be considered as "normal", i. e. the concentration is in accordance with the prescribed dose. Concentrations above or below the expected range are signals that indicate potential abnormalities such as partial non-adherence, drug-drug interactions, genetic polymorphisms of drug metabolizing enzymes or diseases of organs involved in drug elimination. Based on own experiences, abnormalities are assumed for about 1/3 of the patients. Therefore, the mean ± SD range (68 % of the patients) was considered as the range that is expected in "normal" patients. The validity of this assumption, however, still needs to be confirmed by studies. In case of observed abnormalities, suggested reasons should be explained in the clinical pharmacological TDM comment (see below) and causes should be clarified.

2.3 Concentration to dose ratio

The ratio of drug concentration to dose (Cmin/D, usually abbreviated as C/D) is a further parameter to analyse pharmacokinetic abnormalities [271, 500]. C/D can be easily calculated from TDM data by dividing the drug trough steady-state concentration by the dose that the patient is taking. C/D ratios are inversely related to total clearance [271, 292]. A high C/D ratio indicates slow and a low C/D ratio rapid drug clearance.

C/D ratios were used to detect drug-drug interactions by comparing different patient groups (e. g., [169, 586, 918, 1054, 1055]). Jerling and co-workers measured intraindividual C/D ratios of amitriptyline and nortriptyline and found interacting effects of levomepromazine, perphenazine and carbamazepine by showing that on and off of concomitant drugs corroborated previous C/D results [573]. Repeated measurement of C/D ratios in the same patients also helps to detect partial non-adherence to medication as it was shown for clozapine [1142]. Intraindividual variability of C/D should be below 20 %. Variability exceeding 20 % points to adherence problems or pharmacokinetic alterations due to drug-drug, drug-food or drug-disease interactions.

The C/D ratio can also be used to estimate the dose required to achieve a desired target concentration of the drug in blood [48]. Given, for example, that a C/D ratio of 0.5 (ng/mL)/mg was determined and the drug's therapeutic reference range is 30–100 ng/mL, a daily dose of 60 (=30/0.5) mg is required to reach 30 ng/mL and 200 (=100/0.5) mg to reach 100 ng/mL.

2.4 Metabolite to parent compound ratios

Biotransformation of neuropsychiatric drugs by phase 1 enzymes may lead to metabolites with similar or different pharmacodynamic properties as their respective parent compounds. Examples for metabolites with similar properties are nortriptyline (parent compound: amitriptyline), N-desmethyldoxepin (parent compound: doxepin), desipramine (parent compound: imipramine), norfluoxetine (parent compound: fluoxetine), O-desmethylvenlafaxine (parent compound: venlafaxine), or 9-hydroxyrisperidone (parent compound: risperidone). For these drugs, the sum of the concentrations of parent compound and active metabolite, i. e., the active moiety, is relevant for TDM-guided dosing. Examples for metabolites with different pharmacodynamic characteristics compared with their parent drugs are carbamazepine-10,11-epoxide (more toxic than carbamazepine), N-desmethylclomipramine (noradrenergic activity: parent compound: clomipramine), N-desmethylclozapine (cholinomimetic activity; parent compound: clozapine) or N-desalkylquetiapine (noradrenergic activity; parent compound: quetiapine). Major metabolites of olanzapine, sertraline or citalopram seem unlikely to contribute to the parent drugs' efficacy or tolerability. It can be argued that the monitoring of metabolites is useless when metabolites are devoid of pharmacodynamic activity. From a pharmacokinetic perspective, however, determination of active and non-active metabolites can be informative. The metabolite to parent compound ratio (MPR) is a direct measure of metabolizing enzyme(s) activity in vivo [265, 580, 602, 693, 759, 760, 1074]. When a distinct CYP isoenzyme is predominantly involved in a phase 1 reaction, MPR even reflects the phenotype of this CYP enzyme (▶ **Table 6**). MPR allows identification of abnormal metabolism caused by pharmacokinetic interactions or genetic abnormalities. For venlafaxine and risperidone, a low MPR is indicative for a poor metabolizer (PM) genotype of CYP2D6. PM genotypes can be differentiated from extensive metabolizer (EM) genotypes with a sensitivity of 91 % [759]. A high MPR points to enhanced enzymatic activity and thus indicates an ultrarapid metabolizer (UM) status. Moreover, enzyme inducing effects, e. g., of CYP1A2 by cigarette smoke, can be identified by an MPR enhancing effect. For sertraline, it has been shown how to use MPR of N-desmethylsertraline to sertraline for identification of patients' adherence to the prescribed medication [173, 985, 1023].

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▶ **Table 6** Metabolite to parent compound ratios (MPR) for neuropsychopharmacological drugs. MPR ranges are mean ratios − SD to mean ratios + SD under steady-state for trough levels.

Parent drugs	Metabolites	Metabolite to parent compound ratios	Major CYP enzymes involved	Comments	References
Amitriptyline	Nortriptyline	0.2–1.8 (n = 83)	CYP2C19		[984]
Aripiprazole	Dehydroaripiprazole	0.3–0.5 (n = 283)	CYP2D6, CYP3A4	Similar ratio for oral and long-acting injectable form	[509, 637, 751, 815]
Bromperidol	Reduced bromperidol	0.11–0.51 (n = 31)	CYP3A4		[1108, 1156]
Buprenorphine	N-desmethylbuprenorphine	1.58–2.36 (n = 29)	CYP3A4		[772]
Bupropion	Hydroxybupropion	11.2–21.0 (n = 10)	CYP2B6	Bupropion is unstable at room temperature.	[259, 260, 421, 570, 621]
Buspirone	6-hydroxybuspirone	25–53 (n = 20)	CYP3A4		[298]
Carbamazepine	Carbamazepine-10,11-epoxide	0.07–0.25 (n = 14)	CYP3A4		[577]
Cariprazine	N,N-didesmethyl-cariprazine	3–6 (n = 38)	CYP3A4		[174, 840]
Citalopram	N-desmethylcitalopram	0.31–0.60 (n = 2 330)	CYP2C19		[988]
Clobazam	N-desmethylclobazam	2–10 (n > 150)	CYP3A4		[271, 661]
Clomipramine	N-desmethylclomipramine	0.8–2.6 (n = 115)	CYP1A2, CYP2C19		[984]
Clozapine	N-desmethylclozapine	0.45–0.79 (n = 40 non-smokers)	CYP1A2, CYP2C19	Ratios lower in smokers than in non-smokers	[241, 513, 569, 922]
Diazepam	N-desmethyldiazepam	0.94–1.92 (n = 7)	CYP2C19, CYP3A4		[511]
Dothiepin = Dosulepin	N-desmethyldothiepin	0–1.4 (n = 50)	CYP2C19		[550]
Doxepin	N-desmethyldoxepin	0.6–1.6 (n = 12)	CYP2C9, CYP2C19, CYP2D6		[286, 631, 799]
Escitalopram	N-desmethylescitalopram	0.3–1.0 (n = 243)	CYP2C19		[987]
Fluoxetine	N-desmethylfluoxetine	0.7–1.9 (n = 334)	CYP2B6, CYP2C9, CYP2C19		[984]
Fluvoxamine	Fluvoxamino acid	0–1.2 (n = 49)	CYP2D6		[401]
Haloperidol	Reduced haloperidol	0.14–0.42 (n = 5)	CYP2D6		[914, 1223]
Imipramine	Desipramine	0.6–3.2 (n = 14)	CYP2C19		[156, 157, 1153]
Maprotiline	N-desmethylmaprotiline	1.1–3.7 (n = 76)	CYP2D6		[1271]
Mianserin	N-desmethylmianserin	0.5–0.8 (n = 182)	CYP2D6		[984]
Mirtazapine	N-desmethylmirtazapine	0.2–1.2 (n = 100)			[1073]
Moclobemide	Moclobemide N-oxide	0.8–2.5 (n = 6)			[485]
Olanzapine	N-desmethylolanzapine	0.1–0.3 (n = 76, non-smokers)	CYP1A2		[1099]
Perazine	N-desmethylperazine	1.1–3.3 (n = 27)	CYP2C19		[151]
Perphenazine	N-desalkylperphenazine	0.6–2.8 (n = 54)	CYP2D6		[1161]
Quetiapine	N-desalkylquetiapine	0.54–3. 10 (n = 601)	CYP3A4	Similar in children and adults	[66, 361, 897, 1312]
Reboxetine	O-desethylreboxetine	< 0.1 (n = 38)	CYP3A4		[881]

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▲ **Table 6** Continued.

Parent drugs	Metabolites	Metabolite to parent compound ratios	Major CYP enzymes involved	Comments	References
Risperidone	9-Hydroxyrisperidone	3.6–22.7 (n = 168)	CYP2D6	Oral ingestion	[693, 759, 1233]
Risperidone	9-Hydroxyrisperidone	1.2–4.3 (n = 30)	CYP2D6	Intramuscular long-acting form	[845]
Sertindole	Dehydrosertindole	1.1–2.7 (n = 6)	CYP2D6		[177, 1322]
Sertraline	N-desmethylsertraline	1.7–3.4 (n = 348)	CYP2B6		[985, 1016]
Trazodone	m-Chlorophenylpiperazine (mCPP)	0.04–0.22 (n = 43, total range)	CYP3A4		[556]
Trimipramine	N-desmethyltrimipramine	0.26–0.56 (n = 17)	CYP2C19		[325]
Venlafaxine	O-desmethylvenlafaxine N-desmethylvenlafaxine	2.7–7.7 (n = 217) 0.28–0.85 (n = 145)	CYP2D6 CYP2C19		[759, 788, 989, 1074]

Indicated MPR ranges are those of "normal" individuals without genetic abnormalities in drug metabolizing enzymes or comedications with inhibitors or inducers of drug metabolizing enzymes. For interpretation of TDM results of compounds listed in this table it must be checked if measured ratios are above or below the mean ± SD range. Outliers are indicative for adherence problems or pharmacokinetic abnormalities which should be clarified. Information given in this table refers to distinct metabolic degradations, whereas ▲ **Table 1** considers metabolizing CYP enzymes for all degrading pathways.

When using MPR to characterize a patient's metabolic phenotype, confounding factors must be well controlled to avoid false conclusions. Especially the correct timing of blood sampling is essential when parent drug and metabolite have different elimination half-lives.

The validity of MPR to predict CYP gene variants has been proven for risperidone and venlafaxine [602, 760, 1074, 580, 759]. For risperidone and its metabolite 9-hydroxyrisperidone, the cut-off MPR for EM and PM of CYP2D6 was 1.0. Its sensitivity was 91 %, its specificity 86 % and its positive predictive value 35 %, while the negative predictive value was 99 % [759]. Similar results were found for venlafaxine and its major metabolite O-desmethylvenlafaxine. The cut-off MPR of 1.0 had a sensitivity of 93 %, a specificity of 86 %, a positive predictive value of 40 % and a negative predictive value of 99 % [759]. To discriminate UM and EM, the MPR value was less sensitive. Phenotypes of these genotypes overlap. Thereby it has to be considered that UM genotypes of CYP2D6 explains only 30 % of UM phenotypes. Despite some limitations, we recommend to determine MPR for the characterization of the patient's metabolic phenotype.

Definition

The term "metabolic ratio" is used inconsistently in the literature, either as ratio of concentration of parent compound to metabolite or vice versa metabolite to parent compound. To avoid confusion, we use the term metabolite to parent compound ratio (MPR). MPR values shown in ▶ **Table 6** for 35 neuropsychiatric drugs are in vivo estimates of the enzymatic activities involved in the metabolism of the respective drugs. Assuming normal distribution, mean MPRs ± standard deviation (SD) were calculated for standard dosages. Outliers of the mean ± SD range may point to partial non-adherence or abnormalities in drug metabolism which should be clarified.

2.5 Probe drug phenotyping

The pharmacokinetic phenotype is measured by so-called 'probe drug' tests. They were introduced in the past when it was observed that the metabolism of drugs is genetically determined. This was found for a number of drugs like debrisoquine, mephenytoin, sparteine and also for the antidepressant drug nortriptyline [21]. Systematic research identified compounds that are preferably metabolized by distinct CYP enzymes. Using this knowledge, phenotyping tests were developed and validated with specific probe drugs, e. g., caffeine for CYP1A2, efavirenz for CYP2B6, losartan or tolbutamide for CYP2C9, omeprazole or mephenytoin for CYP2C19, dextromethorphan, debrisoquine or metoprolol for CYP2D6, midazolam or erythromycin for CYP3A4, and chloroxazone for CYP2E1 [218, 283, 343, 373, 425, 527, 533, 644, 722, 847, 1121, 1170]. Subjects ingest the probe drug, whenever possible in a pharmacodynamically ineffective dose, and concentrations of parent compound and metabolite formed by the indicator reaction are determined. Their concentrations or ratios of concentrations reflect the in vivo activity of the respective CYP enzyme. Progress in drug ana-

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▶ **Table 7** Typical indications for measuring drug concentrations in blood of psychiatric or neurologic patients.

Obligatory TDM
– Dose optimization after initial prescription or after dose change for drugs with a high level of recommendation to use TDM (see ▶ **Table 4**)
– Drugs for which TDM is mandatory for safety reasons (e. g., lithium or carbamazepine)
Specific indications for TDM
– Uncertain adherence to medication
– Relapse prevention because of uncertain adherence to medication
– Lack of clinical improvement under recommended doses
– Relapse under maintenance treatment
– Determination of optimal individual drug concentration when the patient has attained the desired clinical outcome
– Recurrence of symptoms under adequate doses
– Clinical improvement and adverse effects under recommended doses
– Combination treatment with a drug known for its interaction potential or suspected drug interaction
– Use of counterfeit medications by the patient
– Presence of a genetic peculiarity concerning drug metabolism (genetic deficiency, gene multiplication)
– Patient with differential ethnicity
– Patient with abnormally high or low body weight
– Pregnant or breast feeding patient
– Children or adolescent patient
– Elderly patient (>65 y)
– Patient with intellectual disability
– Forensic psychiatric patient
– Court case related to neuropsychiatric medications
– Patient with pharmacokinetically relevant comorbidity (hepatic or renal insufficiency, cardiovascular disease)
– Patient with acute or chronic inflammations or infections
– Patient with restrictive gastrointestinal resection or bariatric surgery
– Problem occurring after switching from an original preparation to a generic form (and vice versa)
– Use of over the counter (OTC) drugs by the patient
– Pharmacovigilance programs

lysis by mass spectrometry enabled the use of cocktails containing six or more probe drugs. They allow quantifying the activity of several isoenzymes by a single test. One practical idea for probe drug phenotyping was to measure the optimal dose of an intended drug. Such assays, however, were not successful so far. Since only few drugs are metabolized by a single isoenzyme, it is difficult to compute the optimal dose based on phenotyping tests. It was found more appropriate to analyze the drug concentration of the prescribed drug, i. e. to use TDM for dose finding. Phenotyping tests, however, are well established for evaluation of pharmacokinetic interactions, preferentially during drug development. When evidence is given by in vitro data that a new drug has CYP inhibiting or inducing properties, a phenotyping test is recommended for clarification [370]. Moreover, phenotyping by probe drugs can be helpful as add-on for TDM. Using caffeine as probe drug, the inducing effect of smoke on CYP1A2 activity was characterized. It could be shown that the inducing effect disappears within four days after cessation of heavy smoking [342].

2.6 Indications for measuring drug concentrations in blood

▶ **Table 7** presents a list of indications for TDM in psychiatry and neurology. The validity of these indications has to be examined and evaluated for each case individually. Similar to any diagnostic test, TDM should only be requested when there is evidence that the result will provide an answer to a well-defined question.

For drugs with established therapeutic reference ranges or with a narrow therapeutic index, it makes sense to measure drug concentrations in blood for dose titration after initial prescription or after dose change. Even without a specific problem, there is sufficient evidence that TDM has beneficial effects for patients treated with the following drugs: lithium, tricyclic antidepressants, several antipsychotics or anticonvulsants (▶ **Table 4**). For lithium, TDM is even mandatory for safety reasons.

Problems with adherence (non-adherence, partial adherence), a politically more correct term than compliance, since 'adherence' presupposes the patient to be a hierarchically equal partner in therapeutic decision making [49], are common and costly in pharmacotherapy. On average, 50 % of medications for chronic diseases in general are not taken as prescribed [1356]. In studies on patients with schizophrenia [90, 603] and in patients with depression or bipolar disorder, non-adherence ranged from 10 to 69 % [264, 716, 795, 1345]. In a large sample of patients with dementia who were treated with choline esterase inhibitors, it was found that 34 % were adherent within an observation period of 12 months [473]. Incomplete or total non-adherence impairs the effectiveness of treatment. According to a report of the World Health Organization [1325] it is suggested that improvement of adherence may have a far greater impact on the health of the population than any improvement in specific medical treatments. Methods used to measure adherence include pill-counting, addition of colouring agents detectable in urine, examining case-note recordings, interviewing patients or noting the attending physicians' clinical judgment about adherence [14, 612, 1034, 1246, 1247, 1286]. Studies

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have shown that clinicians cannot reliably predict their patients' adherence [171, 725, 1034]. Measuring drug concentrations in blood is advantageous compared to other methods, since it tells the prescribing physician whether the drug is in the body at a concentration that is potentially sufficient to provide the expected clinical response. In patients with epilepsy, drug concentration monitoring confirmed more often non-adherence than adequate seizure control. For antiepileptic drugs, subtherapeutic levels were found in most patients attending hospitals due to seizures [1138]. Deviations from the expected dose-related reference range (▶ **Table 5**) indicate whether the patient has taken his medication and/or is a rapid or poor metabolizer. Concomitant determination of metabolites is another approach to clarify drug adherence. For interpretation, however, possible interactions with co-medications exhibiting enzyme inhibiting or inducing properties must be considered (▶ **Table 2, 3**). Reis and coworkers [985, 986] analysed the adherence of patients who were treated with sertraline by repeated determination of serum drug concentrations of the parent compound and of the metabolite. Variations of the N-desmethylsertraline/sertraline ratio were highly indicative of hidden and partial non-adherence. As reported above, this consensus gives metabolite to parent compound ratios for 35 neuropsychiatric drugs (▶ **Table 6**). By taking several blood samples per day and by calculating the observed and expected time dependent drug concentrations in blood, it can be differentiated if a low drug concentration is due to reduced bioavailability, enhanced degradation or poor adherence. Pharmacokinetic modelling of the expected time dependent drug and metabolite concentration in blood enables identification of different types of non-adherence [5, 584, 1141, 1192].

Relapse prevention is a major goal of maintenance treatment. Reduction of relapse rates by TDM is highly cost-effective, as relapses can lead to re-hospitalization [124, 658, 1142]. In schizophrenic patients, it has been shown that fluctuations of clozapine concentrations in blood are predictive for relapses [391, 1219]. TDM may thus reduce the risk of relapse or recurrence by increasing the doctor's alertness concerning the patient's adherence to the medication.

Recommendation

We recommend regular monitoring of drug concentrations in blood under maintenance therapy, at least every 3–6 months, to prevent relapses and re-hospitalizations. The frequency of TDM requests may be increased if the patient is suspected to be non-adherent to the medication or in case of changes of co-medications or of smoking that affect the pharmacokinetics of the prescribed drug.

When clinical improvement under recommended doses is insufficient and the drug is well tolerated, TDM will clarify whether the drug concentration is too low and whether it makes sense to increase the dose.

When adverse drug reactions coincide with clinical improvement under recommended doses, measurement of the drug concentration in blood may clarify if these reactions are related to excessively high drug levels in the blood and if the dose can be decreased without loss of efficacy.

When combining compounds that are inhibitors or inducers of drug metabolizing enzymes (▶ **Table 2, 3**) with a drug that is a substrate of the inhibited or induced enzyme (▶ **Table 1**), dosing should be guided by TDM to avoid loss of action, poor tolerability or intoxication due to a pharmacokinetic drug-drug interaction [364, 412, 1081, 1236]. Effects of smoking should be considered when patients are under therapy with a CYP1A2 substrate such as clozapine, duloxetine, mirtazapine, olanzapine, rasagiline or ropinirol (▶ **Table 1**).

In patients exhibiting genetic abnormalities of drug metabolizing enzymes, it may be necessary to adapt doses or apply therapeutic alternatives. Kirchheiner (Stingl) and coworkers [630, 633, 1145] calculated doses for PM or UM of CYP2D6 based on pharmacokinetic and pharmacodynamic findings. These dose adjustments on pharmacogenetic evidence has been further adopted by international consortia such as the Pharmacogenetic Clinical Implementation consortium (CPIC), and evidence based guidelines on how to adjust therapy in the case of pharmacogenetic variants have been issued for tricyclics and SSRIs [516]. However, even in the case of a confirmed abnormal CYP genotype, TDM is recommended, because most CYP isoenzymes are not substrate-specific and genotyping can only roughly predict to which extent the drug concentrations in blood may be changed in the individual patient [905, 906, 1136].

Any neuropsychopharmacotherapy of pregnant or breastfeeding women should assure that the blood concentration of the drug is held in the therapeutic reference range to minimize the risk of relapse on the mother's side and, at the same time, minimize risks associated with drug exposure of the fetus or the infant [35, 280, 289]. Renal clearance and the activity of the CYP isoenzymes 2A6, 2C9, 2D6 and 3A4, and uridine 5′-diphosphate glucuronosyltransferase (UGT) 1A4 and 2B7 are increased during pregnancy, whereas activities of CYP1A2 and CYP2C19, and N-acetyltransferase 2 (NAT2) decrease [532, 773, 903]. TDM in pregnant women and/or mothers should be carried out at least once per trimester and within 24 h after delivery [103, 681].

Many neuropsychiatric drugs are not approved for use in children or adolescents [416, 1308]. To date, therapeutic reference ranges for most neuropsychopharmacological drugs are based upon studies performed in adults, and data about the correlation of concentration with therapeutic response or adverse drug reactions in the paediatric population are scarce [327, 1298]. The relative lack of clinical trials and the resultant off-label use could lead to a higher risk of dosing errors and adverse drug reactions. Pharmacokinetics and pharmacodynamics change during development [328, 794, 939, 945, 1230], suggesting that dosing regimens as well as possible clinical effects in minors cannot be extrapolated from the evidence obtained in adults. Increasing prescription numbers in paediatric patients contrast with these uncertainties about safety and efficacy [327], and heavy responsibility is imposed upon both physicians and caregivers. Under these conditions, TDM is strongly recommended to individualize drug treatment and optimize drug safety. In adolescents suffering from psychotic disorders, comorbid drug abuse is very common, and adherence to antipsychotic treatment is generally marginal [538]. Therefore, TDM is

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even highly recommended for these patients. The extrapolation of therapeutic reference ranges - which have been established in adult patients - to paediatric patients, especially to young children, has to be investigated for every single substance, as preliminary TDM studies in paediatric neuropsychiatry provided divergent results. Fortunately, however, several studies have demonstrated similar therapeutic reference ranges for children/adolescents and adults (e. g., sertraline [1177], aripiprazole [949, 1311], fluvoxamine [677]). For most substances, a high interindividual variability in drug concentrations after administration of the same dose was shown in children and adolescents. Similar to adult patients concentrations were broadly related to prescribed dosages [56, 57, 240, 654, 1177, 1185]. Finally, there is evidence indicating the necessity for higher weight-normalized dosages to achieve the concentrations within the reference range for adults, or suggesting that reference ranges are different from those for adults for drugs like quetiapine [400], clozapine [1314] or risperidone [647].

However, the implementation of TDM in the paediatric population is more difficult than in adults because sampling procedures often are invasive and require the cooperation of the patient [939]. As described below in more detail, ongoing research investigates the suitability of alternative matrices, e. g., saliva, and more convenient sampling techniques (e. g., bloodspot) in routine TDM to minimize inconvenience and patient discomfort in paediatric patients [362].

Besides a plea for more clinical trials and more pharmacokinetic-pharmacodynamic studies in children and adolescents, active and standardized surveillance and follow-up (i. e., patient monitoring) of children and adolescents starting drug treatment is necessary. A registry that captures such observations, assessments, and measurements including TDM of many patients in a standardized way was established to generate pharmacovigilance data (evidence) on dosing regimens, serum concentrations, the effectiveness and tolerability of neuropsychiatric drugs under every day conditions by a TDM competence network for child and adolescent patients [see http://www.tdm-kjp.com]. This approach could minimize the risk of exposing paediatric patients to ineffective or less tolerable psychotropic drug treatments [399].

For elderly patients, TDM should be used [1212], since ageing involves progressive impairments of the functional reserve of multiple organs [731]. Especially renal excretion and liver function may decrease significantly [628, 651]. Phase 1 reactions are more likely to be impaired than phase 2 reactions. Glomerular filtration, tubular reabsorption, and secretion change with age, and also weight and volume of distribution [1060]. Hepatic clearance can be reduced by up to 30 %, which is mainly explained by a reduced hepatic blood flow rather than by a decrease of the activity of metabolic enzymes. According to some authors [651], there are no important age-dependent changes in CYP isoenzyme activity, while others suspect a slight decrease in the activity of CYP2D6, but not of CYP2C and CYP3A [1060]. Elderly patients are frequently hypersensitive to medication, and frailty is a major problem. They are at an increased risk of homeostasis loss after stressful events and a decreased ability to recover a stable situation [164]. For example, the cholinergic system seems to be supersensitive in aged subjects [695, 908]. Many psychotropic drugs such as clozapine, tricyclic antidepressants or paroxetine display anticholinergic activity. Their use may result in the occurrence of delirium, decrease of cognitive functions and other serious adverse drug reactions [212]. As shown for nortriptyline, its anticholinergic activity increases with increasing blood concentrations, and occurs even at therapeutic nortriptyline concentrations [212]. The increased risk for adverse drug reactions has prompted many authors to develop criteria for identification of potentially inappropriate medication use in elderly patients, e. g., the Beers criteria [32], the PRISCUS list [304, 537, 1057], STOPP [393] and others [874, 875, 1022]. On the other hand, elderly patients are often undersupplied with potentially useful drugs, including antidepressants [209]. In addition, the abovementioned frailty increases the risk of comorbidities and therefore also the risk of polypharmacy, complicating pharmacotherapy in the elderly [164, 207]. Finally, the off-label prescription of psychotropic drugs seems to be frequent in the elderly patient population [561, 1140]. Clearly, there are still insufficient data available on the usefulness of TDM of psychotropic drugs in the elderly. The consequence of this situation is the relative absence of published recommendations to carry out TDM in this population, in order to optimize treatments. "Monitoring" is frequently recommended, but it does generally not explicitly include TDM [872, 1123, 1200].

In individuals with intellectual disabilities, second-generation antipsychotics are frequently used. Practical guidelines recommend TDM for these patients, at least when treated with risperidone or olanzapine [270]. For ethical and legal reasons, patients with intellectual disabilities are excluded from clinical trials, though many of them need medication. In these individuals, it may be difficult to differentiate between disease and drug induced reasons for symptom aggravation. TDM is recommended as an objective guide for the pharmacotherapy of these patients [270, 272, 494, 1062].

In patients with increased C-reactive protein (CRP) indicating inflammation or infection and under pharmacotherapy with clozapine or risperidone, TDM is recommended to minimize the risk of intoxications due to elevated drug concentrations [501].

For patients with substance use disorders and dependence syndromes, the available medications with proven efficacy are candidates for TDM [163, 396, 477, 496, 689]. Their drug concentrations are highly variable between individuals [163]. For substitution therapies with opioid agonists, overdoses may have fatal consequences [686]. Moreover, the rate of non-adherence is high. The kind of non-adherence of these patients, however, differs from other patients [685, 747, 1358]. Patients with substance use disorder usually accept their substitution medication. But they may have the impression that their dose is insufficient and therefore may consume higher doses than prescribed or add illegally acquired drugs. Other patients discontinue substituted medication. For opioid dependent patients, medical treatment was only effective when they were adherent [1291]. The opiate agonists, i. e., racemic methadone, R-(-)-methadone (levomethadone), buprenorphine with and without naloxone, and slow-release formulations of morphine are used orally for opioid maintenance treatment. In certain cases, i. v. diacetylmorphine (heroin) is administered. TDM is highly recommended for methadone or R-(-)-methadone, buprenorphine and probably also for slow-release formulations of morphine. Based on drug properties and patient characteristics, the usefulness of TDM was evaluated for treatment of alcohol addiction with drugs such

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as acamprosate, naltrexone or disulfiram and of opioid addiction with naltrexone for abstinence-oriented treatment [163]. TDM has the potential to enhance the moderate efficacy of these drugs and enable the detection of pharmacokinetic abnormalities due to gene variants of drug metabolizing enzymes or to drug-drug interactions [1183]. Because of the different kind of adherence in patients with substance related disorders one must be aware that not only decreased but also increased drug concentrations may occur.

In forensic psychiatric patients, medication is important to reduce both the risk of violence and aggressive behavior and the burden of psychiatric symptoms [41, 493, 824, 825, 1201]. To achieve these goals, adherence to medication, mostly consisting of antipsychotic drugs, is essential, since most forensic psychiatric patients disapprove of pharmacotherapy [824, 825]. Castberg and Spigset [184] analyzed data of a high security forensic unit and found higher prescribed doses in forensic patients than in a control group, whereas the dose-related concentrations were significantly lower for olanzapine but higher for quetiapine in the forensic patients. TDM is highly recommended for this group of patients especially when supervised as outpatients.

In court cases concerning the alleged adverse drug reactions of psychotropic drugs (for example, pathological gambling allegedly induced by dopamine D2/D3 receptor agonists), TDM is instrumental for the court-certified witness (i. e., expert court witness) for proving or disproving that the claimant actually took the medication and reached drug concentrations in blood that plausibly caused the alleged harm [1345]. It has been shown that 55 % of the claimants for disability pensions who had been diagnosed with depression and had been prescribed antidepressants had no detectable antidepressants in their blood [398]. A further 11 % had antidepressant levels that were close to zero and far below the lower limit of the orienting therapeutic reference range. Thus, a total of 66 % of disability pension claimants whose cases went to court could not prove that they actually took their antidepressant medication as claimed [398]. This is of great consequence, as a sick person has to contribute unambiguously to his/her reconvalescence. Only in case of treatment failure, he/she is eligible for sickness benefits or disability payments. Thus, in the sample cited above, 66 % of the claimants did not fulfil the criterion, inviting suspicion of public health insurance fraud.

For the indication "switching from an original preparation to a generic form or vice versa ", TDM should be used instead of watching and waiting if problems such as loss of efficacy or tolerability problems evolve [206, 242]. In a study which compared originator and generics in volunteers [206], the venlafaxine generic yielded 50 % higher levels during the absorption phase than the originator. Consequently, the frequency of adverse drug reactions was increased. This was not the case for the citalopram originator and a citalopram generic. Generics may be different from each other up to approximately 45 %. It is allowed for any generic to have an AUC0-24 h or AUC0-infinite AND a Cmax that is within 80 to 125 % of the originator (125 %–80 % = 45 %). There may be an even larger difference during the initial absorption phase, while the AUC0-infinite and Cmax are still within the 80–125 % limit.

Other indications for TDM are the use of over the counter (OTC) drugs and counterfeit drugs from the internet [741, 1093, 1302]. The counterfeit medications may not comply with purity and dosage standards and therefore increase the risk for adverse drug reactions.

In pharmacovigilance programs, the safety of drug use is supervised under naturalistic conditions [379, 444, 445, 450, 470, 648, 662, 946]. In case of observed adverse events, measurement of drug concentrations in blood is often essential for clarification [569].

2.7 Recommendations for measuring drug concentrations in blood

The usefulness of TDM varies with the clinical situation and the particular drug involved. In case of suspected non-adherence or incomplete adherence (compliance) to medication or intoxications, quantifying drug concentrations in blood is a generally accepted tool for all drugs and groups of patients. However, it is still a matter of debate in many countries whether TDM should be implemented in clinical routine. Based on empirical evidence, four levels of recommendation to use TDM were defined ranging from "strongly recommended" to "potentially useful" as follows:

Definitions

Level 1: Strongly recommended

Evidence: Reported therapeutic reference ranges are established. Controlled clinical trials have shown beneficial effects of TDM. Reports on decreased tolerability or intoxications exist.
Recommendation: TDM is strongly recommended for dose titration and for special indications. E.g., for lithium or carbamazepine, TDM is a standard of care.
Clinical consequences: At drug concentrations in blood within the reported therapeutic reference range, highest probability of response or remission can be expected. At subtherapeutic drug concentrations in blood, the response rate is similar to placebo under acute treatment and there is a risk of relapse under chronic treatment. At supratherapeutic drug concentrations in blood, there is an increased risk of adverse drug reactions or outright toxicity.

Level 2: Recommended

Evidence: Reported therapeutic reference ranges were obtained from drug concentrations at therapeutically effective doses and related to clinical effects; there are reports on decreased tolerability or adverse effects at "supratherapeutic" drug concentrations in blood.
Recommendation: TDM is recommended for dose titration and for special indications or problem solving.
Clinical consequences: TDM will increase the probability of response in non-responders. At subtherapeutic drug concentrations, there is a risk of poor response. At supratherapeutic drug concentrations, there is an increased risk of intolerance or intoxication.

Level 3: Useful

Evidence: Reported therapeutic reference ranges were computed from drug concentrations at approved doses. Drug concentrations related to medication effects either are not yet

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available or are based on retrospective analyses of TDM data, single case reports or non-systematic clinical experience.
Recommendation: TDM is useful for special indications or problem solving.
Clinical consequences: TDM can be used to control whether drug concentrations are in accordance with the dose-related reference range. Clinical improvement may be attained by dose increase in non-responders who display low drug concentrations.

Level 4: Potentially useful
Evidence: Drug concentrations in blood do not correlate with clinical effects due to unique pharmacology of the drug, e. g., irreversible blockade of an enzyme, or dosing can be easily guided by clinical symptoms, e. g., sleep induction by a hypnotic drug.
Recommendation: TDM is not recommended for dose titration, but may be potentially useful for special indications or problem solving.
Clinical consequences: TDM should be restricted to special indications.

According to our evidence-based evaluation, TDM was graded as "strongly recommended" for 19 of the 154 surveyed neuropsychiatric drugs, "recommended" for 39, "useful" for 61, and "potentially useful" for 35 drugs (▶ **Table 4**). TDM is strongly recommended for most tricyclic antidepressants. It reduces the risk of toxicity [168, 669, 827, 934, 959, 961, 964, 1304]. For many tricyclic antidepressants, a concentration – clinical effectiveness relationship (concentration-effect curve) has been shown. For selective serotonin reuptake inhibitors (SSRIs) a weak but significant dose dependence of clinical improvement was reported, whereas tolerability decreased at high doses [564]. Though acceptance of TDM is actually limited in clinical practice [8, 974, 1175], evidence for its usefulness is growing. For citalopram it has been shown that it is advantageous to use TDM in the early phase of treatment, i. e. one week after start of the medical treatment [896]. Another limitation to introduce TDM for SSRIs is poor methodology when analyzing drug concentrations in blood in relation to clinical effects. Using adequate methodology re-analysis of data on paroxetine concentrations and clinical improvement for which no concentration-response relationship was originally concluded [1175] found a clear-cut correlation which was almost identical with the in vivo occupancy of serotonin transporters [329]. Toxicity of SSRIs is low in comparison to most of the pre-SSRI antidepressants [79, 277, 526, 1178, 1297]. Evidence for a statistically significant relationship between drug concentration and therapeutic outcome is lacking for the tetracyclic antidepressants maprotiline, mianserin and mirtazapine and also for trazodone and reboxetine, as well as for the monoamine oxidase inhibitors moclobemide and tranylcypromine.

TDM is strongly recommended for the typical (first-generation) antipsychotic drugs haloperidol, perphenazine and fluphenazine, and for the atypical (second-generation) antipsychotics amisulpride, clozapine and olanzapine (▶ **Table 4**). Overdosing may lead to extrapyramidal symptoms. In the case of clozapine, there is a strong correlation between clozapine concentration in blood and incidence of seizures. TDM-based prevention of overdosing is, for the majority of patients treated with a typical antipsychotic, a matter of the patient's quality of life rather than of safety [237]. TDM of antipsychotics is also useful when medication is switched from the oral to the depot formulation, or vice versa.

Depot formulations of several first and second generation antipsychotics (risperidone, paliperidone, olanzapine, aripiprazole) are often recommended to address non-adherence in patients with schizophrenia. It has been assumed that stable blood levels of depot antipsychotics are associated with superior tolerability and efficacy. However, differences in effectiveness (i. e. relapse prevention) or side-effects of depot and oral antipsychotics have not been clearly evidenced and seem to depend more on the specific compound and dose or drug concentrations in blood [640, 641]. Accordingly, steady-state peak-to-trough fluctuations of drug concentrations in blood (see ▶ **Fig. 2**) are not generally lower in depot formulations (depending on tmax and t1/2) [1078], and not all studies have found a positive correlation of large blood level fluctuations and increased adverse events. For the available depot antipsychotics, pharmacokinetic studies are scarce, and recommended (therapeutic) blood levels of depot and other formulations are almost identical [28, 1113].

With regard to the mood stabilizing and/or antimanic drugs lithium, valproic acid and carbamazepine, therapeutic reference ranges and toxic levels are well defined. Therefore, TDM is strongly recommended for these drugs (▶ **Table 4**). For lithium, TDM has been established as standard of care [230, 281, 317, 463, 707, 1076, 1283, 1307]. For lithium long-term use, concentrations of 0.5–0.8 nmol/L in blood are recommended. For an acute treatment with lithium, it may be justified to increase its concentrations up to 1.2 mmol/L.

Compounds that have been shown to be effective as antidementia drugs are donepezil, rivastigmine, galantamine and memantine. TDM is rarely used for the treatment of dementia [468], although there is evidence that it can be useful. For donepezil, it has been shown that the patients' improvement was significantly greater when their concentrations in blood were above 50 ng/mL as compared to patients that showed lower donepezil concentrations [499, 1013].

Most anxiolytic and hypnotic drugs belong to the pharmacologic class of benzodiazepines. For alprazolam, TDM may be useful to suppress panic attacks [1310]. Most anxiolytic and hypnotic effects are rapid in onset. Treatment is therefore preferentially guided by immediate clinical impression rather than by TDM. Measurements, however, can be informative to identify chronic use of the drugs. In case of lack of therapeutic effects under usual doses, TDM may clarify if non-response is due to drug abuse that has led to tolerance or the result of pharmacokinetic abnormalities. Due to adaptive changes in chronic users, blood concentrations of benzodiazepines poorly correlate with driving performance [1254].

TDM is recommended for the opioid agonists racemic methadone, R-(-)-methadone (levomethadone), buprenorphine and morphine for safety reasons [163]. It must be considered that, similar to benzodiazepines, optimal drug concentrations may vary mark-

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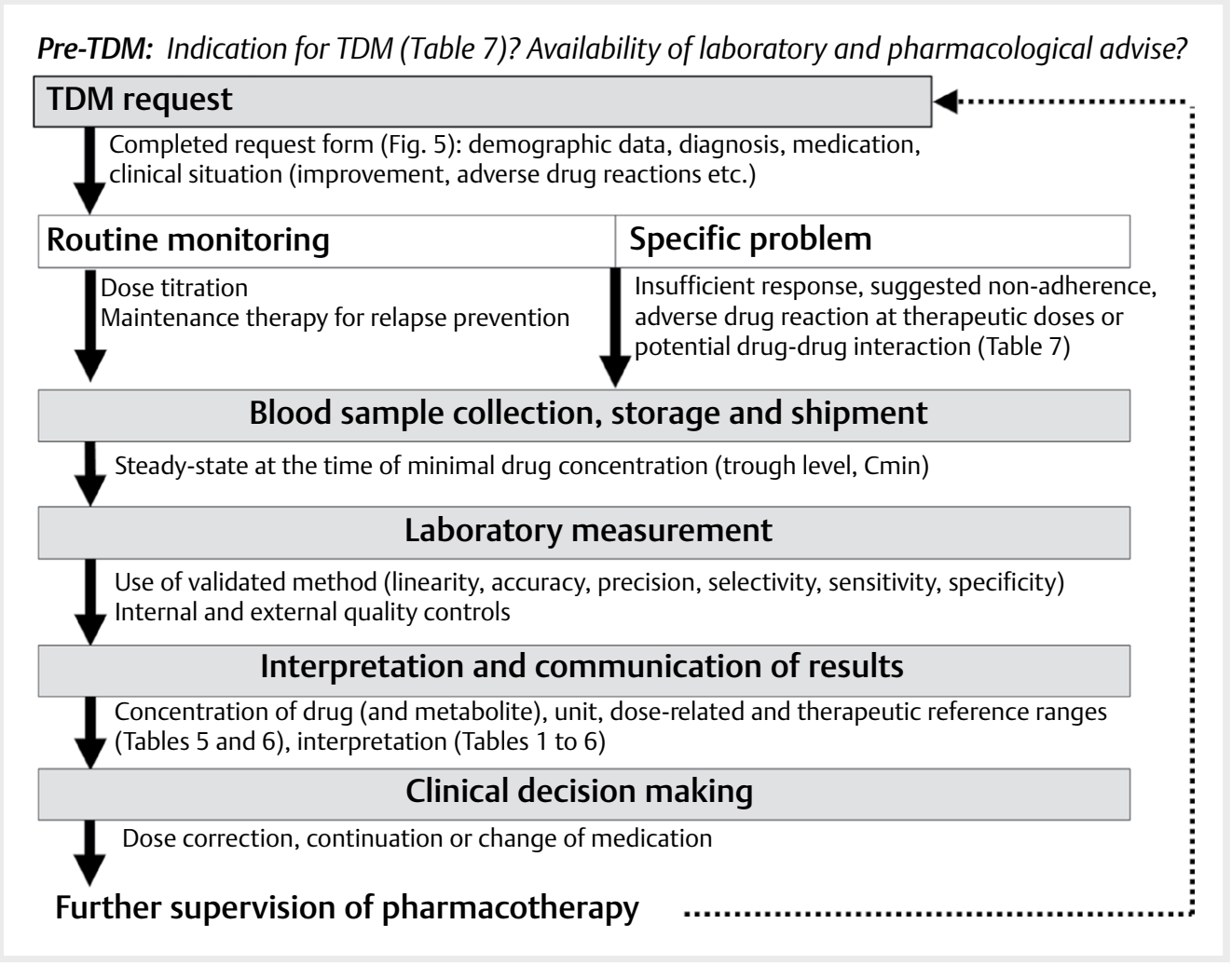

▶ **Fig. 4** The TDM process to guide neuropsychopharmacotherapy. Routine TDM is primarily applied to drugs with a narrow therapeutic index and a well-defined therapeutic reference range. However, TDM is useful for any neurologic or psychiatric drug when addressing special therapeutic problems.

edly from patient to patient due to different levels of tolerance. On the other hand, opioid dependent patients may ask for higher doses than they can tolerate because of their craving for drugs which can have fatal consequences due to toxic drug concentrations [396, 477, 496, 689]. For "anti-craving" medications such as acamprosate or naltrexone or for the use of alcohol-aversive disulfiram to treat alcohol use disorders or naltrexone in case of opioid addiction for abstinence treatment, TDM is recommended to enhance the moderate efficacy [163]. TDM of drugs to treat substance related disorders should consider preferentially expected drug concentrations (▶ **Table 5**) to clarify adherence problems, tolerance to medication or pharmacokinetic abnormalities.

For anticonvulsant drugs, TDM is well established, not only for the old drugs, which are relatively toxic [912], but also for new ones [562, 681].

For antiparkinson drugs, TDM has not been established so far. For dopamine agonists, data on reference ranges are scarce. For L-dopa, a moderate correlation between drug concentrations in blood and short-term clinical response is considered [867]. Nevertheless, the pharmacokinetic properties of these neurologic drugs have been included in the present guidelines (▶ **Tables 1–6**), because antiparkinson drugs exhibit concentration dependent sedative properties. TDM may avoid overdosing.

3. Practical Aspects of TDM in Psychiatry and Neurology

3.1 TDM request for quantification of drug concentrations in blood

Essential for an effective TDM service is the availability of appropriate analytical methods that produce results within a reasonable time, i. e., within 48 h from the arrival of the blood sample in the laboratory to send the results including advice from someone who understands pharmacokinetics and therapeutics [314]. As shown in ▶ **Fig. 4**, the TDM process starts with the request and ends with the final decision how to adjust a patient's therapeutic regimen by the health care professional.

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LABORATORY
Address
Phone
Fax

REQUESTING HOSPITAL / DOCTOR
Address
Phone in case of alert
Fax

PATIENT DETAILS	Name or code	☐ Inpatient ☐ Outpatient	Date and time of blood withdrawal
Date of birth	Sex	Diagnosis / Symptom(s)	
☐ HIV-patient	Weight (kg)	Smoker ☐ No ☐ Moderate (< 10 cig/day) ☐ Heavy (≥10 cig/day) Genotype/phenotype to be considered (e.g. CYP2D6, 2C19, 1A2):	

REASON FOR REQUEST
(tick more than one if applicable)
☐ Control of adherence
☐ Dose adaptation
☐ Insufficient improvement
☐ Adverse drug reaction (to be specified) .....
☐ Drug-drug interaction
☐ Control under maintenance therapy
☐ Other reason (to be specified) .....

SEVERITY OF ILLNESS *(CGI-S)*
How mentally ill is the patient at this time?
☐ Not at all ill (1)
☐ Borderline mentally ill (2)
☐ Mildly ill (3)
☐ Moderately ill (4)
☐ Markedly ill (5)
☐ Severely ill (6)
☐ Extremely ill (7)

IMPROVEMENT *(CGI-I)*
Change compared to condition at admission?
☐ Very much improved (1)
☐ Much improved (2)
☐ Minimally improved (3)
☐ No change (4)
☐ Minimally worse (5)
☐ Much worse (6)
☐ Very much worse (7)

ADVERSE DRUG REACTION *(UKU)*
☐ not at all (0) ☐ a little (1) ☐ moderate (2) ☐ severe (3)

☐ Concentration difficulties ☐ Asthenia ☐ Sleepiness/Sedation
☐ Tension/inner unrest ☐ Sleep disturbances ☐ Emotional indifference
☐ Dystonia ☐ Rigidity ☐ Akinesia ☐ Hypokinesia ☐ Tremor
☐ Akathisia ☐ Epileptic seizures ☐ Paresthesias ☐ Headache
☐ Accomodation disturbance ☐ Increased salivation ☐ Dry mouth
☐ Nausea/Vomiting ☐ Diarrhoea ☐ Constipation ☐ Micturation disturbance
☐ Polyuria/Polydypsia ☐ Increased sweating ☐ Galactorrhoea ☐ Weight gain
☐ Sexual dysfunction ☐ Other (to be specified)
Causal relationship: ☐ improbable ☐ possible ☐ probable

Drug(s) to be assayed	Formulation	Daily dose / dosing schedule	Date started	Time of last dose

Other medications (include herbals, over the counter drugs etc.)

TDM request: *Blood should be withdrawn under steady-state conditions, preferably in the morning BEFORE taking the morning dose.*
Return the completed form, together with a minimum of 1 mL serum or plasma.

Date of sample receipt:

Signature:

▶ **Fig. 5** Example of a request form recommended for therapeutic drug monitoring of neuropsychiatric drugs.

As mentioned above, TDM should only be requested when there is evidence that the result will provide an answer to a specific question. Typical indications are listed in ▶ **Table 7**. A single measurement is often insufficient for problem solving. For example, a series of measurements may be required at appropriate intervals to clarify if a low drug concentration in blood is either due to poor adherence, reduced bioavailability or abnormally rapid elimination.

TDM requests must include a completed request form (▶ **Fig. 5**), which is essential for effective drug concentration measurements and an adequate interpretation of the results [923, 1159]. The form should contain the patient's name or code, demographic data, diagnosis, medication, reason for the request, the commercial and the generic name of the drug and its dose, the galenic formulation, the time of the last change of the dose, time of drug intake, time of blood withdrawal. A brief comment on the clinical situation should be given for interpretation of the results. As indicated in ▶ **Fig. 5**, we recommend to use symptom rating scales, e. g., the clinical global impression (CGI) [467], to measure the severity of illness (CGI-S) and document any therapeutic improvement or worsening (CGI-I). The summary form of the UKU scale is useful to evaluate the occurrence and severity of adverse drug reactions [717]. However, documented feedback to questionnaires indicates that clinicians often do NOT want to write that much information on the form. Moreover, the filled-in information is often not accurate. On the other hand, the completed request form is a case document for the physician to review the pharmacotherapy and a suitable training device to learn TDM. As an alternative, feedback by phone may be offered for interested physicians. Adding the website address of the lab will facilitate the download of request forms and other documents by the client.

When interpretation of the results is requested from the laboratory, it is necessary to fill out the request forms adequately. Computerized ordering of TDM has advantages. It is inexpensive and it guides the ordering physician to give the relevant information required for interpretation in a comfortable way.

3.2 Specimen collection

3.2.1 Blood sample collection

Generally, TDM is carried out in plasma or serum samples. There is no consensus whether plasma or serum should be preferred. Definite experimental data that unequivocally demonstrate differences in the drug concentrations using either plasma or serum are still lacking. The few available comparisons indicate that values obtained from serum or plasma can be used interchangeably [513]. For most laboratories the collection tubes should not contain EDTA,

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citrate, heparin or other additives. An amount of one mL plasma or serum is sufficient for most laboratories. Concentrations of neuropsychiatric drugs reported in this guideline refer to the total drug fraction in accordance with the literature. There is no experimental evidence for the hypothesis, that the assay of unbound ("free") drug concentrations in blood would be advantageous. Moreover, the assay of the free fraction represents an analytical challenge [87]. For imipramine, it has been shown that the drug is rapidly and almost totally cleared by the brain through a single passage in the microvasculature [994]. The extraction was not significantly affected in the presence of albumin, lipoproteins or erythrocytes. For nortriptyline, statistical relationships between free levels of drug and clinical response were found to be insignificant [929]. Therefore, at least for psychiatric drugs, it seems likely that the clinical response depends on the total drug fraction. With the exception of saliva, analysis of neuropsychiatric drugs in other materials such as urine, spinal fluid, tears, hairs or maternal milk have not been introduced for TDM purposes, and no validated data are available which deal with therapeutic concentrations.

Blood collection via dried blood spots can be an alternative to the common venous blood withdrawal. The minimally invasive sampling, low blood volume requirements, easy transport and storage and good analyte stability are key advantages of this sampling method. The high sensitivity of modern analytical techniques such as liquid chromatography-tandem mass spectrometry (LC-MS/MS) or ultra-high performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) allows the use of dried blood samples for TDM [810, 913, 916, 1303]. Thereby, several points need to be taken into consideration: dried blood sample concentrations must be corrected for plasma/serum concentrations, the influence of haematocrit, the influence of the collected blood volume and various types of filter paper. Volume defining dried blood sampling techniques and automated techniques such as online desorption, paper spray analysis and fully automated extraction of dried blood samples are already available. However, they require further clinical validation in order to make dried blood spots sampling a suitable and cost-effective alternative to whole blood sampling in a clinical routine laboratory providing TDM [1303].

With regard to the timing of blood collection, it must be considered that TDM guided neuropsychopharmacotherapy mostly relies on minimal drug concentrations (Cmin) at steady-state. Steady-state is reached under constant doses after at least 4 to 6 elimination half-lives (see ▶ **Table 4**) and Cmin at the end of the longest dosing interval. For practicability, most blood samples taken for determination of Cmin are withdrawn in the morning before the first dose of the day, which is mostly the time of minimal drug concentrations (tmin). A frequent problem, however, is blood sampling at different time points throughout the dosing interval. This leads to concentrations that may be misinterpreted when in reality true trough levels are lower or higher. For antibiotics, it has been reported that up to 55 % of inappropriate levels were due to improper timing of sample collections [1205].

For antiparkinson drugs and drugs like methylphenidate for the treatment of attention-deficit hyperactivity disorder blood is withdrawn at tmax, the time of maximal drug concentrations (Cmax). Most of these drugs have a short elimination half-life and clinical effects correlate with Cmax.

Blood sampling under treatment with depot or extended release formulations

In patients treated with a depot formulation of an antipsychotic drug, blood should be sampled immediately before the next injection. The drug concentration in blood depends on the release from the depot and the elimination. TDM may of course be carried out at any time if unexpected adverse drug reactions are observed. It is not necessary to measure trough levels, but the dosing schedule should be reported for interpretation.

Long acting formulations of antipsychotic drugs such as haloperidol decanoate or risperidone and aripiprazole are characterised by a slow absorption after intramuscular administration. Maximum concentrations in blood of first generation depot antipsychotics are reached 1–14 days after injection, and the apparent elimination half-life of the depot is 2–3 weeks [1179]. Paliperidone palmitate exhibits similar properties [1113] with an apparent elimination half-life ranging between 25 and 49 days [976]. For risperidone microspheres, the mean time to peak concentrations is 4 weeks and its apparent elimination half-life 4–6 days [1179]. Long-acting olanzapine pamoate [714] slowly releases olanzapine from the injection site into the muscle tissue. However, it dissolves rapidly when it is in contact with blood or plasma. The latter results in high concentrations in blood and may lead to marked sedation and delirium, the so-called post-injection syndrome [714, 1179]. Due to the low solubility, the absorption of aripiprazole depot (once monthly) is slow and prolonged with an apparent average absorption half-life of 4 weeks. Maximal drug concentrations are reached in blood 5–7 days after injection; the mean apparent terminal elimination half-life after 400 or 300mg aripiprazole monthly is 47 and 30 days, respectively [365, 751].

For oral drugs delivered in extended release formulations like venlafaxine, methylphenidate, paliperidone [110] or quetiapine [356], special attention has to be given to the time of drug intake for correct interpretation (see ▶ **Table 4**). In these formulations, the time of maximal drug concentration in blood is delayed too, whereas the terminal elimination half-life of the drugs is essentially unchanged.

3.2.2 Oral fluid for TDM

Oral fluid offers the advantage of non-invasive collection [30, 39, 613]. It has been applied to optimize the treatment with a few antiepileptic drugs [911] for confirmatory purposes [683] and qualitative interpretations of results [914]. It has been long assumed that drug concentrations in oral fluid reflect the free fraction (i. e., non-protein-bound) that circulates in blood and which for most psychopharmacological drugs is only 10 % or less of their total concentration. Detection problems were therefore a major problem in the past when using saliva instead of blood plasma or serum. Improved methods are now available to analyse saliva with sufficient precision and accuracy [913, 914]. Using such techniques it was found that the ratio of concentrations in blood to saliva differed a lot and did not fully support the assumption that saliva contains the free fraction of the drug in blood. Comparisons of drug concentrations in blood and oral fluid revealed that oral fluid will actually not replace blood as matrix for TDM [914]. There was an apparent positive correlation between the concentration of monohydroxyoxcarbazepine (MHD, the major metabolite of oxcarbazepine) in blood plasma and saliva [706]. For carbamazepine, pheny-

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toin and phenobarbital the correlation was poor but still significant [316]. For valproic acid, however, the correlation was not significant [315]. It was reported that saliva cannot replace blood for monitoring of methadone [1084].

For amitriptyline and nortriptyline, no significant relationship was found between concentrations in saliva and plasma [87]. Many neuropsychiatric drugs are bases, with a pKa value >9. The distribution of drugs between blood and saliva depends on the pH. The pH of saliva increases when the secretion is stimulated. For methylphenidate, an inverse correlation was found for the ratio of drug concentration in oral fluid to serum and pH value of oral fluid samples [1133]. Standardization and optimizing of sampling [682] is needed. In any case, more data are required for measurement of drug concentrations in saliva as a matrix.

3.3 Storage and shipment of blood samples

With few exceptions, serum or plasma samples can be stored in the dark at 4°C for at least 24 h, and most drug samples can be sent without freezing [506]. Exceptions are light and/or oxygen sensitive substances like bupropion or methylphenidate. For their determination, samples must be stabilized by freezing or extraction immediately after blood withdrawal and centrifugation (see ▶ **Table 4**). For determination of olanzapine, serum or plasma samples must be stored frozen (−20°C) if not analysed within 72 h [506]. When samples must be stored and sent frozen, it is required to prepare serum or plasma before freezing, since it is not possible to prepare serum or plasma from frozen blood. The laboratory should give instructions on its web site or the request form how to collect (plasma volume, labelling of the samples), store and mail the sample.

3.4 Laboratory measurements

Selective and sensitive analytical methods for the quantitative evaluations of the analytes, i. e., the drugs and their metabolites, are essential for the successful application of TDM. Methods have to be validated [185, 715]. The validation includes all procedures demonstrating that a particular method used for quantitative measurement of analytes in a given biological matrix is reliable and reproducible for its intended use. The fundamental parameters for this validation comprise (1) accuracy, (2) precision, (3) selectivity, (4) sensitivity, (5) reproducibility and (6) stability. Validation involves documenting that the performance characteristics of the method are suitable and reliable for the intended analytical procedure. The acceptability of analytical data corresponds directly to the criteria used to validate the method [185, 370 and see: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf].

For neuropsychiatric compounds, chromatographic techniques (preferentially high-performance liquid chromatography, HPLC), in combination with suitable detection methods, are preferred [318]. They are sufficiently precise, accurate and robust and can be adapted to the analysis of almost every neurologic or psychiatric drug. A disadvantage is the need for sample preparation before chromatographic separation and hence a limited sample throughput. Throughput can be enhanced by automated sample preparation prior to HPLC. Some laboratories have introduced HPLC with column switching which allows direct injection of plasma or serum into the HPLC system. Such procedures are available for a number of antidepressant [446, 486, 487, 490, 491, 1274, 1288] and antipsychotic drugs [638, 639, 1026–1028, 1287, 1289]. Another high-throughput chromatographic method is liquid chromatography coupled with mass spectroscopy (LC-MS), especially tandem MS (LC-MS/MS) [1032]. LC-MS/MS is most sensitive and selective. Additionally, this technique can be applied with minimal sample preparation such as protein precipitation and dilution. Many compounds can be analysed simultaneously. An excellent example is the LC-MS/MS method described by Kirchherr and Kühn-Velten [635] that was validated for over 50 psychoactive drugs. Major disadvantages of LC-MS/MS methods are high equipment costs and the need for well trained personnel. Moreover, quantification can be jeopardized due to matrix effects and ion suppression. These effects can be minimized by good chromatographic separation of matrix and the analyte of interest and the use of stable isotopically labelled standards for internal calibration, preferentially deuterated analogues [1047]. During the last years, therefore, LC-MS/MS methods are used with increasing frequency [37, 914, 915, 917]. Their big advantage is flexibility. Their disadvantage of high costs was gradually reduced to acceptable prices. LC-MS/MS is nowadays the preferred analytic method for TDM of neuropsychiatric drugs in many specialized laboratories. HPLC with UV- or fluorescence detection is, however, still the established method of choice in many laboratories of low to medium throughput due to its cost effectiveness and robustness.

In case of suspected intoxications, TDM methods should allow drug analysis within 1–2 h [364]. For this purpose, automated methods are advantageous. The use of LC-MS/MS in this special application is advantageous due to the high selectivity of mass spectrometry for identification.

The assay of enantiomers of chiral compounds requires either stereoselective derivatisation of the drugs prior to their quantification, or their separation by chiral chromatographic columns. For detection tandem mass spectrometry is the method of choice. As an example, the TDM of the enantiomers of methadone using a classical detection method such as fluorescence or ultraviolet light absorption is often jeopardized by co-medication or by co-consumption of drugs of abuse. These problems may be circumvented by use of a mass detector, preferably a tandem mass spectrometer.

Within the therapeutic reference range, intraday- and interday precision should not exceed 15 % (coefficient of variation) and accuracy should not deviate more than 15 % from the nominal value [185, 370].

To ensure quality and reliability of drug assays, internal and external quality control procedures are mandatory. Samples must contain suitable internal standards, and each series of samples must include internal control samples. If standards are not available commercially, they should be prepared by personnel other than that performing the assays and by separate weighing of reference material. Commercial quality control samples are increasingly available spanning a wide range of psychoactive drugs today. Reporting of results requires that the results of the quality controls are within the expected ranges. If quality controls are outside the expected range, the reason underlying the outlier needs to be clarified and documented.

The laboratory has to participate in an external quality assessment scheme, although this is not a legal requirement in all countries. For neuropsychiatric drugs, the first external quality program

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was introduced by Cardiff Bioanalytical Services Ltd in 1972 [1306]. The service was taken over by other providers of external quality control schemes like LGC (www.lgcstandards.com) or Instand e. V. (www.instand-ev.de). Moreover, reference materials are also available from the Task Force of Clinical Toxicology of the Society of Toxicological and Forensic Chemistry (www.gtfch.org).

3.5 Computing of trough steady-state concentrations

When comparing drug concentrations measured by TDM and expected steady-state Cmin, it is assumed that blood was withdrawn at the time of minimal drug concentrations (tmin). To measure steady-state Cmin, blood should be collected after at least 4 drug elimination half-lives after the start of medication or a change in dosage and during the terminal ß-elimination phase. For most psychiatric and neurologic drugs, elimination half-lives vary between 12 and 36 h (▶ **Table 4**). Notable exceptions are quetiapine, venlafaxine or trazodone which display elimination half-lives around 6 h. Fluoxetine, donepezil and aripiprazole have longer elimination half-lives. In clinical practice, the appropriate sampling time for most neurologic and psychiatric drugs is one week after stable daily dosing and immediately before ingestion of the morning dose, which usually is 12–16 h (or 24 h when the drug is given once daily in the morning) after the last medication. If, for logistic reasons, blood can only be collected late in the morning, the patient should not be medicated before blood withdrawal. In an outpatient setting, it is important to indicate exactly the time of administration of the last dose to be able to calculate expected trough levels. This can be done by the following Eq. (5).

$$Cmin = Ct \times e^{-ke \cdot (tmin - t)} \quad (5)$$

where Ct is the drug concentration measured at time t, tmin the time at Cmin and ke the elimination rate constant ($ke = \ln 2 / t_{1/2}$).

As an example it is given that amisulpride, which has an average elimination half-life of 16 h (see ▶ **Table 5**, $ke = 0.0433\ h^{-1}$), was applied daily as single dose per day (at 08:00 h). On the day of blood withdrawal, the patient did not take the medication, since he was instructed to take it after blood withdrawal for TDM. Because of organizational reasons, blood was finally withdrawn at 11:00 h in the morning. When the measured drug concentration (Ct) was 351 ng/mL, Cmin at time 24 h (= tmin) should amount to

$$351 \cdot e^{-0.0433\ (24-27)} = 399\ ng/mL$$

Eq. (5) can also be used for estimation of Cmin when blood was withdrawn in the postabsorptive phase before tmin was reached.

Given e. g., that lithium, which has an elimination half-life of 24 h (see ▶ **Table 5**), was applied as single dose per day in the evening at 20:00 h, blood was withdrawn at 08:00 h in the morning (t = 12 h) and the measured drug concentration (Ct) was 1.0 mmol/l, then Cmin at time 24 h (= tmin) should amount to

$$1.0 \cdot e^{-ke\ (24-12)} = 0.71\ mmol/l$$

3.6 Interpretation and communication of results and recommendations

The concentration of the neuropsychiatric drug as well as that of its active metabolites contributing to the therapeutic action should be reported together with reference ranges (▶ **Table 4**), either in mass or molar units. We recommend the use of mass units instead of molar units to relate concentration to dose. Laboratories vary in the presentation of their results. The clinician should take note of the units (i. e., ng/mL, µg/L, µmol/L, or nmol/L) in which the results of the analysis are expressed. This is especially recommended for comparisons of values obtained from different laboratories or with those in the literature. To transform molar units into mass units and vice versa conversion factors are given in ▶ **Table 4**.

When drug concentrations are below the lower limit of quantification, which refers to the lowest concentration of the standard curve that can be measured with at least 80–120 % accuracy and 20 % precision, this limit should be indicated [370].

The results should be available for decision making within a clinically meaningful time. A 24 h TDM service is desirable, however, a 48 h turnaround time is sufficient in most cases. In case of suspected intoxications, a few hours service is necessary [364]. To assist rapid intervention in patients at risk for toxicity or loss of tolerability, prompt information of the treating physician (i. e., a phone call) is required when the laboratory measures drug concentrations above the laboratory alert level (▶ **Table 4**).

We highly recommend that interpretation and pharmacologic advice are provided with every assessment of a drug concentration. Expert interpretation and the adequate use of the information are essential to ensure the full clinical benefit of TDM report [82, 314, 469, 471, 519, 979, 1159]. Reporting of results with inclusion of dose recommendations and other comments must be guided by the best available evidence. Expert knowledge may be necessary to calculate dose corrections or to analyse drug-drug interactions. It is advantageous for the clinician to choose a laboratory that offers this service. Otherwise, the treating physician, a clinical pharmacologist or a trained expert of the clinic has to interpret the results. Access to specialist advice is also necessary if TDM results suggest that genotyping may be advisable.

It may even be legally required to include collaboration with a clinical pharmacologist. In Switzerland, a psychiatrist may prescribe CYP genotyping, but it will only be reimbursed by insurances, when the test is prescribed by a physician specialized in clinical pharmacology.

Diagnosis and drug dose are important for interpretation, since they permit a judgment on whether a result is plausible or not. Moreover, it must be checked whether blood samples were collected under recommended conditions, especially when the drug concentration in blood is unexpectedly high in an outpatient. When the drug was taken only a few hours before blood sampling, the drug concentration can be several-fold higher than the trough level (▶ **Fig. 2**). The trough steady-state concentration can be easily calculated by Eq. (5) when blood was withdrawn in the postabsorptive phase.

For interpretation of the results, it must be checked whether the concentration of the drug in blood is within the therapeutic reference range (▶ **Table 4**) and fits to the dosage (▶ **Table 5**). When a drug concentration is outside the therapeutic reference range, it is wise to take into account the level of recommendation underlying the therapeutic reference range of the particular drug (▶ **Table 4**). Any drug concentration outside its dose-related reference range (▶ **Table 5**) should alert the TDM laboratory to actively look for drug-drug-interactions or gene polymorphisms that give rise to poor or ultrarapid metabolism, altered function of the excretion organs liver and kidneys, age and/or disease-related changes in the

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patient's pharmacokinetics, adherence problems, a non-steady-state and even signal interference from other medications that the patient may not have declared to the prescribing physician (e. g., St. John's wort). It should also be considered whether the daily drug dose was given as a single or a multiple dose regimen.

Often it is necessary to deal with metabolic pathways, enzymes involved and substrate and inhibitor properties of all drugs taken by the patient for interpretation of the results. Supportive information is therefore given in the present updated guidelines showing literature based substrate (▶ **Table 1**) and inhibitor or inducer properties of drugs (▶ **Tables 2**, **3**) as causes of possible drug-drug interactions.

For the treatment of pain, relatively low concentrations of tricyclic antidepressants may be sufficient. They may be within the dose-related reference range (▶ **Table 5**) but outside the therapeutic reference range of ▶ **Table 4**, which was established for the indication of depression.

A laboratory may recommend that an additional sample should be taken after a certain period, because in cases with unusually low or high drug concentrations, repeated measurements may help to decide whether the patient's adherence is inconstant (irregular intake of the drug) or whether the patient is an ultrarapid or poor metabolizer.

Recommendations must be given with the clinical presentation in mind as explained for the cases below. Dosage changes constitute the most frequent advice.

3.6.1 How to use the TDM guidelines for interpretation of results – cases

To demonstrate how to use information of the consensus guidelines for interpretation of laboratory results, three representative cases are shown below.

Case 1

Patient:	51 years/male/inpatient/ smoker (> 10 cig./day)
Diagnosis:	Paranoid schizophrenia
Reason for request:	Uncertain adherence
Severity of illness:	Severely ill (CGI-S score 6)
Improvement:	No change (CGI-I score 4)
Adverse drug reactions:	Not reported
Drugs to be assayed/dose:	Clozapine/250 mg/d
Start of medication:	5 weeks before
Last change of dose:	2 weeks before
Last drug intake:	12 h before
Co-medication:	Acetylsalicylic acid, simvastatin, sertraline

Laboratory results

- Clozapine: 224 ng/mL (Therapeutic reference range 350–600 ng/mL, see ▶ **Table 4**)
- N-Desmethylclozapine: 175 ng/mL

Interpretation

TDM was indicated in accordance with the consensus guidelines (▶ **Table 7**). Under a therapeutic dose of 250 mg, the patient did not improve according to the assessment by the Clinical Global Impressions (CGI-I) scale (see ▶ **Fig. 5**). TDM had to clarify whether the patient was non-adherent or whether the dose should be increased to improve therapeutic efficacy.

Determination of clozapine revealed a concentration of 224 ng/mL, which is below the therapeutic reference range of 350 to 600 ng/mL (see ▶ **Table 4**) but within the dose-related reference range for clozapine and its metabolite (▶ **Table 5**). At a dose of 250 mg/day the expected dose-related reference ranges (for calculation see DRC factors low and high in ▶ **Table 5**) are 250 × 0.43 = 108 to 250 × 1.59 = 398 ng/mL for clozapine, and 250 × 0.50 = 125 to 250 × 1.25 = 313 ng/mL for N-desmethylclozapine. The ratio of concentrations for N-desmethylclozapine to clozapine was 0.78 and thus as expected for the metabolite to parent compound ratio (MPR) of 0.45 to 0.78 (see ▶ **Table 6**). The patient was a smoker. ▶ **Table 2** does not indicate an inhibitor within the list of comedications, but ▶ **Table 3** indicates that smoking induces CYP1A2 which is involved in the metabolism of clozapine (▶ **Table 1**).

Recommendation

Dose increase is recommended to improve efficacy. From the concentration to dose ratio of 0.9 ng/mL/mg it can be assumed that 400 mg/day are required to attain therapeutically recommended concentrations (350–600 ng/mL).

Case 2

Patient:	70 years/female/inpatient/ smoker (> 10 cig./day)
Diagnosis:	Major depressive episode
Reason for request:	Adverse drug reaction and clinical improvement
Severity of illness:	Moderately ill (CGI-S score 4)
Improvement:	Much improved (CGI-I score 2)
Adverse drug reactions:	Gastrointestinal disturbance
Drugs to be assayed/dose:	Venlafaxine XR/225 mg/d
Start of medication:	3 weeks before
Last change of dose:	1 week before
Last drug intake:	24 h before
Co-medication:	Levomepromazine

Laboratory results

- Venlafaxine: 168 ng/mL
- O-Desmethylvenlafaxine: 251 ng/mL
- Active moiety: 419 ng/mL (Therapeutic reference range 100–400 ng/mL, see ▶ **Table 4**)
- N-Desmethylvenlafaxine: 143 ng/mL

Interpretation

TDM was indicated in accordance with the consensus guidelines. Under a therapeutic dose of 225 mg, the 70 years old

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patient had adverse drug reactions but was much improved according to the assessment by the Clinical Global Impressions (CGI-I) scale (see ▶ **Fig. 5**). TDM had to clarify whether adverse drug reactions were associated with high concentrations of venlafaxine active moiety and whether the dose could be lowered without risking loss of therapeutic efficacy.

Determination of drug and metabolite concentrations revealed an active moiety concentration of venlafaxine plus O-desmethylvenlafaxine of 419 ng/mL, which is slightly above the therapeutic reference range of 100 to 400 ng/mL (see ▶ **Table 4**) and above the dose-related reference range. At a dose of 225 mg/day the expected dose-related reference ranges (for calculation see DRC factors in ▶ **Table 5**) are 225 × 0.12 = 27 to 225 × 0.36 = 81 ng/mL for venlafaxine, 225 × 0.78 = 176 to 225 × 1.30 = 293 ng/mL for O-desmethylvenlafaxine. The expected active moiety concentration should amount to 203–376 ng/mL. ▶ **Table 1** indicates that venlafaxine is a substrate of CYP2D6 and CYP2C19. The ratio of concentrations for O-desmethylvenlafaxine to venlafaxine was 1.49 and thus below the expected metabolite to parent compound ratio (MPR) of 2.7 to 7.7 (see ▶ **Table 6**). This points to a PM phenotype of CYP2D6. The ratio of concentrations for N-desmethylvenlafaxine to venlafaxine was 0.85, which is consistent with a normal CYP2C19 phenotype (see ▶ **Table 6**). Co-medication was levomepromazine, and the patient was a smoker. ▶ **Table 2** indicates that levomepromazine is an inhibitor of CYP2D6, which catalyzes the formation of O-desmethylvenlafaxine and ▶ **Table 3** shows that smoking induces CYP1A2 which is not involved in the metabolism of venlafaxine (▶ **Table 1**). It thus seemed likely that adverse effects were related to the high drug concentrations possibly due to inhibition of CYP2D6 by levomepromazine. The PM phenotype of CYP2D6 is further confirmed by the higher than expected concentration of N-desmethylvenlafaxine of 143 ng/mL (expected concentration 34 to 74 ng/mL). Since levomepromazine is a substrate of CYP2D6, its concentrations may also be high, especially in a PM genotype, and then contribute to the adverse effects.

Recommendation

Reported adverse drug reactions can be explained by high concentrations of venlafaxine and O-desmethylvenlafaxine most probably due to a drug-drug interaction and old age. The patient may be a PM phenotype of CYP2D6 because of inhibition by levomepromazine. Dose reduction can be helpful and possibly improve tolerability without risking loss of efficacy. Alternatively, levomepromazine may be replaced by a non CYP inhibiting drug, e. g., pipamperone, since reported gastrointestinal disturbances could also be due to levomepromazine.

Case 3

Patient:	51 years/male/inpatient/smoker (< 10 cig./day)
Diagnosis:	Bipolar disorder, currently manic
Reason for request:	Poor clinical improvement/uncertain adherence
Severity of illness:	Markedly ill (CGI-S score 5)
Improvement:	No change (CGI-I score 4)
Adverse drug reactions:	No
Drugs to be assayed/dose:	Valproic acid/900 mg/d Olanzapine/10 mg/d
Start of medication:	> 6 weeks before
Last change of doses:	2 weeks before
Last drug intake:	12 h before
Co-medication:	None

Laboratory results

▪ Valproic acid:	37 µg/mL (Therapeutic range 50–100 µg/mL, see ▶ **Table 4**)
▪ Olanzapine:	7 ng/mL (The therapeutic reference range for bipolar disorders is unclear. Considering the dose of 10 mg which is recommended for combination therapies, 8 to 23 ng/mL may be suggested as an orienting therapeutic range)
▪ N-Desmethylolanzapine:	2 ng/mL

Interpretation

TDM was indicated in accordance with the consensus guidelines. According to the CGI-I score of 4, the patient had not improved (see ▶ **Fig. 5**). TDM could clarify if the patient has taken his medication as prescribed and if dose escalation could be helpful.

Determination of valproic acid (valproate) revealed a concentration of 37 µg/mL which is below the therapeutic reference range (▶ **Table 4**) and also lower than the expected dose-related concentration. Calculation of the dose-related reference range (see DRC factors in ▶ **Table 5)** leads to 55,980 to 121,320 ng/mL (i. e. 56–121 µg/mL) for a dose of 900 mg valproic acid. For olanzapine and its metabolite the concentrations were 7 ng/mL and 2 ng/mL, respectively. These concentrations cannot be related to therapeutic effects, since a therapeutic reference range has not been established for the indication bipolar disorder. At a dose of 10 mg/day, however, the expected concentration can be calculated (see ▶ **Table 5).** They should amount to 12 to 25 ng/mL for olanzapine. The 7 ng/mL reported for olanzapine were thus lower than expected Cmin. On the other hand, the metabolite to parent compound ratio was 0.29 and thus as expected (see ▶ **Table 6**). The

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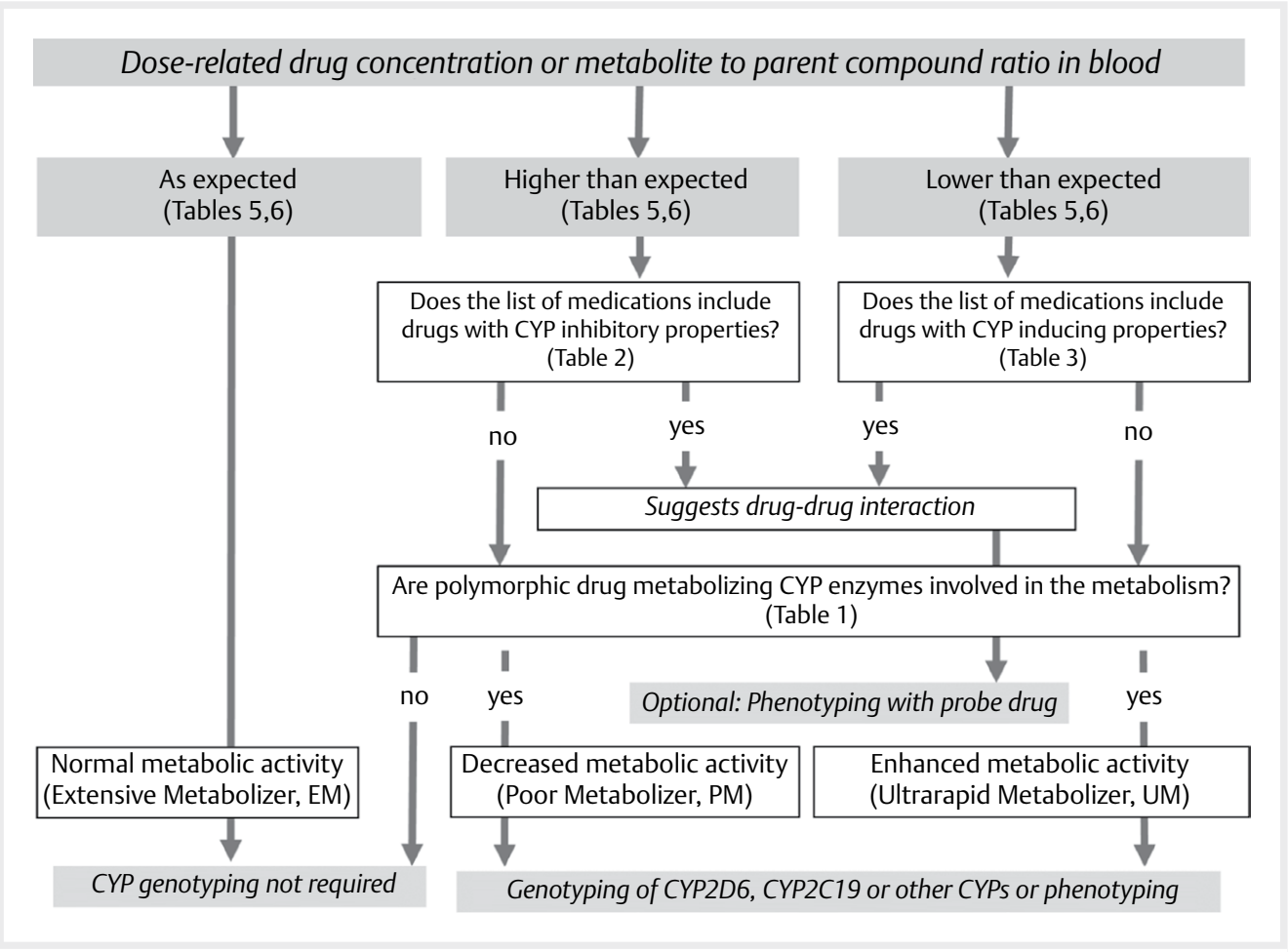

▶ **Fig. 6** Algorithm for using genotyping of cytochrome P450 (CYP) enzymes and phenotyping with a probe drug in combination with TDM.

patient was a moderate smoker. ▶ **Table 3** indicates that smoking induces CYP1A2 and ▶ **Table 1** shows that olanzapine is a substrate of CYP1A2. Lower-than-expected concentrations of olanzapine and normal metabolite to parent compound ratios can be best explained by adherence problems. However, the effect of enhanced olanzapine degradation by smoking is another possible explanation.

Recommendation

Poor response is plausible due to the low drug concentration in blood. Patient adherence has to be addressed and verified. In case of complete adherence, a dose increase can be helpful.

The three cases demonstrate how information given in the ▶ **Tables 1–6** can be used for interpretation of laboratory data to draw valid conclusions and give substantial recommendations for rational pharmacotherapy. Nevertheless, interpretation of TDM results relies on complex quantitative relationships. Therefore, training in clinical neuropsychopharmacology, pharmacokinetics and the application of TDM information is essential. Regular conferences with discussion of the interpretation of real cases are most helpful for learning. It is also recommended that junior psychiatrists interpret the results under supervision of an expert.

3.7 Pharmacogenetic tests in addition to TDM

When a pharmacogenetic test is carried out prior to prescribing a particular drug under defined circumstances [247, 248, 332, 568, 569, 632–634, 658, 1135, 1229] concentrations outside the therapeutic or dose-related reference range may be avoided when this is due to gene polymorphisms that give rise to poor/ultrarapid metabolizers (pharmacokinetic level). Situations and cases where pharmacogenetic tests could be combined with TDM are explained in ▶ **Fig. 6**. In agreement with recommendations of the German Commission Genetic Testing (GeKO) and the Clinical Pharmacogenetics Implementation Consortium [515, 517, 1229] as well as regulatory administrations such as the FDA and EMA the most important indications for genotyping of drug metabolizing enzymes in combination with TDM are the following:

- A priori genotyping when a drug is characterized by a small therapeutic index with a risk of toxicity in the case of a genetically impaired metabolism.

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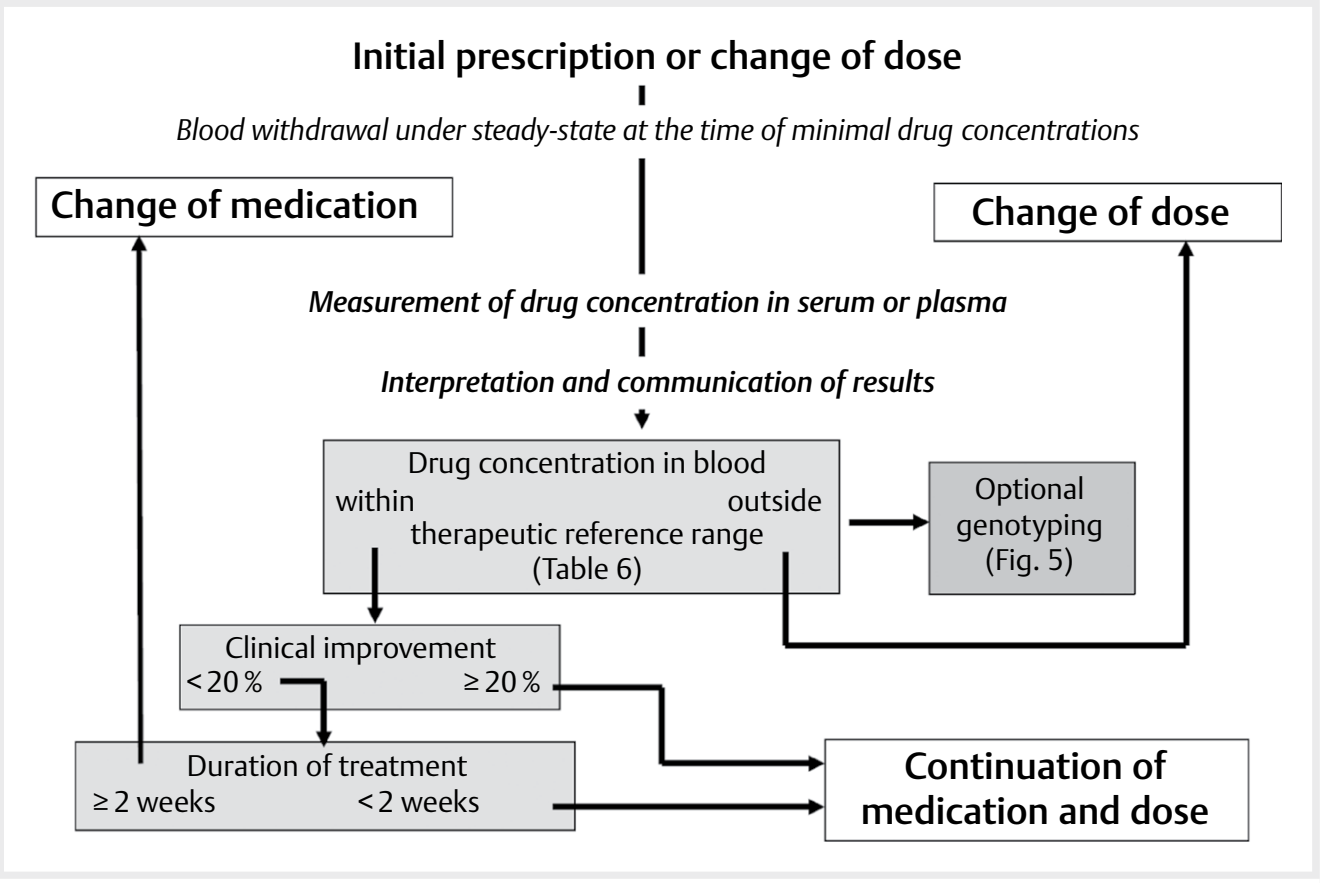

▶ **Fig. 7** TDM-guided dose titration for treatment with mood stabilizing, antidepressant, antipsychotic or antiepileptic drugs. Clinical decision making has to consider steady-state concentration of the drug in blood, clinical improvement and duration of treatment. 94 % of the steady-state is reached after four elimination half-lives of the drug or active metabolite. Decisons to change the dose or the medication can be necessary in case of adverse drug reactions. This was not considered in this scheme.

- A priori genotyping when the patient is treated with a substrate with a wide interindividual variability in metabolism and considerable risk of toxicity in case of overdosing, e. g., tricyclic antidepressants.
- Post hoc genotyping when the patient presents unusual plasma concentrations of the drug or its metabolite(s) to define metabolic status prior to administering other drugs e. g., codeine in the case of ultrarapid metabolizers (see warnings in the drug labels for codeine for ultrarapid metabolizers [331]).

In a patient who is genotyped as a PM or UM, the medication needs not automatically be replaced, but the dose may be adapted, using TDM and clinical judgement.

Pharmacogenetic testing on a pharmacodynamic level is not recommended yet in clinical practice, except for carbamazepine [354].

Commercially available test batteries for detection of pharmacokinetic and pharmacodynamic gene variants are currently marketed, but evidence at present does not allow recommending their uncritical integration into everyday clinical practice.

There is a definite need for further research in large multi-centre trials.

3.8 Clinical decision making

A TDM result is a guide to proper dosing of the individual patient (▶ **Fig. 7**). The physician has to be aware that, under optimal conditions, reporting of results with inclusion of dose recommendations and other comments by the laboratory is based on the best available evidence [518, 520]. The laboratory, however, has only restricted knowledge of the clinical situation. On the other hand, most treating physicians have limited pharmacokinetic knowledge. Therefore, it is essential to acknowledge that optimal TDM is an interdisciplinary task requiring close communication between laboratory and clinical experts.

If the measured drug concentration is within the therapeutic reference range, a change of the dose is, of course, only recommended if clinical reasons, such as adverse drug reactions or non-response, clearly justify such a decision. The treating physician has to decide whether the treatment strategy is to be changed or not. On the other hand, when the advice given on the TDM report is not followed, the reason must be substantiated to allow evaluation of the treating physician's decision should the patient come to harm. Recommendations for such an evaluation in a court of law have been published by the TDM-AGNP group [1345].

In patients with known abnormally rapid elimination it may be useful to prescribe a dose above the maximal recommended dose,

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since such patients can exhibit drug concentrations below the reference range under standard doses. However, the medication should be changed if the patient exhibited sufficiently high drug concentrations for a sufficiently long treatment period, i. e., for at least 2 weeks, and did not improve by at least 20 %. Another option can be the use of a drug that is not metabolized via CYP, like the antidepressant drug milnacipran or the antipsychotic drug amisulpride.

When adverse drug reactions are associated with clinical improvement under recommended doses, measurement of the drug concentrations in blood may clarify if adverse drug reactions are related to exceedingly high drug levels in the blood. In this situation, the dose can be decreased, normally without risk of loss of action.

For the treatment with antidepressant, antipsychotic or mood stabilizing drugs, there is good evidence that clinical non-improvement at week 2 is highly predictive for later treatment failure [196, 239, 615, 696, 1130, 1131, 1162]. For dose titration with antidepressant or antipsychotic drugs we therefore recommend to include symptom rating by the treating physician [239] at baseline and at week 2 in addition to drug concentration measurements. ▶ **Fig. 7** summarizes the above recommendations in a flow chart.

When further drug concentration measurements in blood are recommended after a modification of the dose or after prescription of a comedication that is known to inhibit or enhance the metabolism of the drug to be measured, the next TDM should be delayed until steady-state conditions are reached again. For this, the terminal elimination half-life (t1/2) of the drug has to be considered (▶ **Table 4**). Finally, if the patient has improved under a drug concentration below the reference range, (gradual) termination of the medication should be considered, because the medication may serve as a placebo only while still carrying the risk of adverse drug reactions and being costly.

3.9 Cost-effectiveness of TDM

TDM has been shown to be cost-effective (for review see [1204]). For tricyclic antidepressant drugs, this was evidenced as a reduction of the intoxication risk [168, 961, 962]. When patients were pre-monitored by administration of test doses of amitriptyline or nortriptyline for an estimation of the elimination rate and the elimination half-life to calculate the dose required to attain therapeutically effective steady-state concentrations of the drug in blood [159], the pharmacokinetic dosing decreased costs markedly [1089]. The pharmacokinetically dosed patients were discharged from hospital six days earlier and returned to work 55 days earlier than the empirically dosed patients. For SSRI, Lundmark and coworkers [734] observed in a sample of 127 elderly outpatients that the introduction of TDM led to dose reduction in 38 cases resulting in a reduction of drug costs by 16 %. A large cost reduction was reported for citalopram: TDM markedly decreased the duration of hospitalization [894]. In this study on inpatients, TDM-guided pharmacotherapy, yielding sufficiently high citalopram serum concentrations (> 50 ng/ml), decreased the stay in the hospital by 23 days compared to a patient group with subtherapeutic citalopram concentrations. Drug concentrations below 50 ng/mL on day 7 of treatment were highly predictive for later treatment failure [895]. Similar findings have been reported for depressed patients treated with venlafaxine [1129]. Moreover, it can be assumed that TDM has the potential to reduce relapse rates. Given that TDM detects non-adherence to medication before re-hospitalization, TDM is highly cost-effective. One day in the hospital is 4–16 times more expensive than a single drug concentration measurement in the laboratory. In summary, due to the potential of improving adherence, acceleration of clinical improvement or decrease of hospitalisation length by TDM, a marked cost effect can be expected by TDM. More studies on the cost effectiveness of TDM, however, are required.

4. Conclusions and Perspectives

This second update of the AGNP guidelines describes the practice of TDM to promote the appropriate use of TDM in psychiatry and neurology. When applied adequately, TDM is an excellent tool of precision medicine to optimize the pharmacotherapy of individual patients. During the past decades, knowledge on the metabolic fate and actions of drugs in the human body has markedly advanced. However, there is a gap between the availability of knowledge in pharmacology and its utilization in health care [518, 1094]. TDM bridges this gap. For this update, special attention was given to methods that enable pharmacokinetic characterization of the patient. Combining information related to therapeutic reference ranges, dose-related reference ranges, metabolite to parent compound ratios as well as properties of administered drugs like CYP substrate, inhibitor and inducer specificities and finally genotypes of CYP enzymes and drug transporters allows to recognize and document individual characteristics in the pharmacodynamics and -kinetics of neuropsychiatric drugs. The information can be used for rational dose corrections to optimize efficacy and tolerability of these medications as well as treatment costs. In spite of objective advances with respect to the use of TDM in everyday clinical practice, quality improvement of TDM must still be continuously addressed. There is also a need for inclusion of pharmacokinetic measurements during clinical trials of drug development. It is a major shortcoming that data on drug concentrations in blood that are optimal for attaining the highest probability of clinical response are not legally required for the registration of medications. Product information should be supplemented with TDM-related data. Last not least, teaching of these issues at a postgraduate level is necessary for psychiatry residents [86].

Conflicts of Interest

Christoph Hiemke has received speaker's and consultancy fees from Janssen, Stada, Servier. He is managing director of the psiac GmbH (www.psiac.de) which provides an internet based drug-drug interaction program. Pierre Baumann has received speaker's or consultancy fees from almost all pharmaceutical companies selling psychotropic drugs in Switzerland. Niels Bergemann received speaker's or consultancy fees and/or educational grants from AstraZeneca, Bristol-Myers Squibb, Janssen, Lilly, Otsuka, Pfizer, Servier. Andreas Conca has served as a consultant for Lilly, Bristol-Myers Squibb, Pfizer. He has served on the speakers' bureau of Lilly, BMS, Astra Zeneca, Lundbeck, Italfarma, Janssen. Gabriel Eckermann has received speaker's fees from almost all pharmaceutical companies selling psychotropic drugs in Germany. He is shareholder of the psiac GmbH (www.psiac.de), which provides an internet based drug-drug interaction program. Karin Egberts participated in performing clinical trials for AstraZeneca, Janssen-Cilag, Lilly, Shire and has received research grants pertaining to pharmacovigilance in children and

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adolescents from the German Federal Institute for Drugs and Medical Devices. Ursula Havemann-Reinecke has received speaker's and consultancy fees and unrestricted educational grants from AstraZeneca, Bristol-Myers Squibb, Cephalon, Essex, Janssen Cilag, Lundbeck, Pfizer, Schering-Plough, Wyeth. Ekkehard Haen is chairman and managing director of the AGATE (www.amuep-agate.de) that supports reasonable and economic drug therapy. He is shareholder of the psiac GmbH (www.psiac.de), which provides an internet based drug-drug interaction program. Manfred Gerlach has received research grants pertaining to pharmacovigilance in children and adolescents from the German Federal Institute for Drugs and Medical Devices. He has also received royalties from Springer Vienna for editing a German and English textbook on child and adolescent psychiatry. Gerhard Gründer has served as a consultant for Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, Otsuka. He has served on the speakers' bureau of Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, Janssen Cilag, Otsuka, Pfizer, Servier, Wyeth. He has received grant support from Alkermes, Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson. He is co-founder of Pharma-Image – Molecular Imaging Technologies GmbH. Eveline Jaquenoud is a member of mediQ (www.mediq.ch) which provides an internet based drug-drug interaction program for psychiatry. Gerd Laux has received speaker's or consultancy fees or unrestricted educational grants from AstraZeneca, Bayer, Eli Lilly, Lundbeck, Merz, Pfizer, Servier, Wyeth. Thomas Messer has received speaker's or consultancy fees or unrestricted educational grants from Eli Lilly, Bristol-Myers Squibb, Janssen, Servier, Pfizer, Lundbeck, Bayer Vital Health Care. Matthias J. Müller has received speaker's or consultancy fees from Janssen, Lundbeck, Servier. Bruno Pfuhlmann has received speaker's or consultancy fees from AstraZeneca, Janssen, Pfizer. Sven Ulrich is an employee of Ariston Pharma GmbH, Berlin, Germany. Gerald Zernig has received speaker's or consultancy fees or educational grants from AlcaSynn, AstraZeneca, Bio-Rad, Bristol-Myers Squibb, Eli Lilly, Lundbeck, Mundipharma, Novartis, Pfizer, Wyeth. Hans Willi Clement, Jürgen Deckert, Katharina Domschke, Christine Greiner, Gudrun Hefner, Renate Helmer, Ger Janssen, Rainold Mössner, Michael Paulzen, Peter Riederer, Alois Saria, Bernd Schoppek, Georgios Schoretsanitis, Markus Schwarz, Margarete Silva Gracia, Benedikt Stegmann, Werner Steimer, Julia C. Stingl, Manfred Uhr, Stefan Unterecker and Roland Waschgler were not supported by pharmaceutical industry.

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Erratum

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