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AGNP Consensus Guidelines for Therapeutic Drug Monitoring in Psychiatry: Update 2011

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- reference ranges
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- therapeutic window

Abstract

Therapeutic drug monitoring (TDM), i.e., the quantification of serum or plasma concentrations of medications for dose optimization, has proven a valuable tool for the patient-matched psychopharmacotherapy. Uncertain drug adherence, suboptimal tolerability, non-response at therapeutic doses, or pharmacokinetic drug-drug interactions are typical situations when measurement of medication concentrations is helpful. Patient populations that may predominantly benefit from TDM in psychiatry are children, pregnant women, elderly patients, individuals with intelligence disabilities, forensic patients, patients with known or suspected genetically determined pharmacokinetic abnormalities or individuals with pharmacokinetically relevant comorbidities. However, the potential benefits of TDM for optimization of pharmacotherapy can only be obtained if the method is adequately integrated into the clinical treatment process. To promote an appropriate use of TDM, the TDM expert group of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) issued guidelines for TDM in psychiatry in 2004. Since then, knowledge has advanced significantly, and new psychopharmacologic agents have been introduced that are also candidates for TDM. Therefore the TDM consensus guidelines were updated and extended to 128 neuropsychiatric drugs. 4 levels of recommendation for using TDM were defined ranging from "strongly recommended" to "potentially useful". Evidence-based "therapeutic reference ranges" and "dose related reference ranges" were elaborated after an extensive literature search and a structured internal review process. A "laboratory alert level" was introduced, i.e., a plasma level at or above which the laboratory should immediately inform the treating physician. Supportive information such as cytochrome P450 substrate- and inhibitor properties of medications, normal ranges of ratios of concentrations of drug metabolite to parent drug and recommendations for the interpretative services are given. Recommendations when to combine TDM with pharmacogenetic tests are also provided. Following the guidelines will help to improve the outcomes of psychopharmacotherapy of many patients especially in case of pharmacokinetic problems. Thereby, one should never forget that TDM is an interdisciplinary task that sometimes requires the respectful discussion of apparently discrepant data so that, ultimately, the patient can profit from such a joint effort.

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Introduction

In psychiatry, around 130 drugs are now available which have been detected and developed during the last 60 years [54]. These drugs are effective and essential for the treatment of many psychiatric disorders and symptoms. Despite enormous medical and economic benefits, however, therapeutic outcomes are still far from satisfactory for many patients [5,6,396,661]. Therefore, after having focused clinical research on the development of new drugs during more than 5 decades [521,522], growing evidence suggests that improving the way the available medications are administered may bring substantial benefit to patients [45]. Evidence-based guidelines for optimum treatment have been published during the last decade [23,46,101,204,205,221,234,254,276,284,582,585,748].

A valuable tool for tailoring the dosage of the prescribed medication(s) to the individual characteristics of a patient is therapeutic drug monitoring (TDM). The major reason to use TDM for the guidance of psychopharmacotherapy is the

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considerable interindividual variability in the pharmacokinetic properties of the patient [524,526]. At the very same dose, a more than 20-fold interindividual variation in the medication'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 peculiarities [61,94,310,311,334,335,374]. Different formulations of the same medication may also influence the degree and temporal pattern of absorption and, hence, medication concentrations in the body. TDM uses the quantification of drug concentrations in blood plasma or serum to titrate the dose of individual patients so that a drug concentration associated with highest possible probability of response and tolerability and a low risk of toxicity can be obtained. Moreover, TDM has the possible and widely unexploited potential to improve cost-effectiveness of psychopharmacotherapy [527,660]. For a considerable number of psychopharmacologic compounds, the quantification of the medications' plasma concentration has become clinical routine for dose adjustment. Clear evidence of the benefits of TDM has been given for tricyclic antidepressants, a number of old and new antipsychotic drugs and for conventional mood stabilizing drugs [51,459,505]. For lithium, TDM has become a standard of care due to its narrow therapeutic range [133,395].

The benefits of TDM regarding the optimization of pharmacotherapy, however, can only be obtained if the method is adequately integrated into the clinical treatment process. Current TDM use in psychiatric care is obviously suboptimal [134,700,742]. Similar to other medical disciplines, systematic studies have demonstrated that the inappropiate use of TDM is widespread. Inappropriate TDM testing wastes laboratory resources and also bears the risk that misleading results will adversely influence clinical decision making [122]. A study on the clinical use of TDM for tricyclic antidepressants in psychiatric university hospital settings showed that between 25 and 40% of the requests for TDM were inappropriate and the interpretation of the results led to about 20% of inappropriate therapeutic adjustments [700,742]. Other typical errors were absence of steady-state conditions and transcription errors on the request form [700,743]. Studies on TDM for antidepressant and mood stabilizing drugs further specified the information on the inappropriate use of TDM [420,421].

Against this background, the TDM group of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) issued best practice guidelines for TDM in psychiatry in 2004 [51]. These guidelines were widely accepted by many laboratories and practicing clinicians. They have been cited more than 200 times in the literature and were translated into German [312] and French [50]. Moreover, they were summarized for depression [52]. The AGNP-TDM consensus guidelines have also been implemented in recent international guidelines on the treatment of mental diseases [582]. Since 2004, knowledge on TDM has advanced significantly. New psychotropic medications have been introduced which are also candidates for TDM. The TDM group of the AGNP therefore decided to prepare an updated version of their guidelines.

Objectives of this Consensus Document

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

Aiming to optimise the practice of TDM the following topics were addressed:

- definition of indications to utilize TDM in psychiatry
- definition of graded levels of recommendations to use TDM
- definition of therapeutic reference ranges ("therapeutic windows") and dose-related reference ranges that laboratories can quote and clinicians can use to guide the psychopharmacotherapy
- definition of alert levels for laboratories to warn the treating physician when plasma concentrations are considered to be too high and potentially harmful
- recommendations and help for interpretative services
- recommendations concerning the combination of TDM with pharmacogenetic tests

Preparation of the Consensus Document

The updated consensus guidelines were prepared by the interdisciplinary TDM group of the AGNP consisting of clinical psychiatrists, pharmacologists, biochemists, pharmacists and chemists from academic and non academic hospitals and institutions of Germany, Switzerland, Austria and Italy, who have been involved for many years in the development and implementation of TDM for psychotropic medications in everyday clinical practice. The experts compiled information from the literature and worked out the present best practice guidelines aiming at promoting the appropriate use of TDM in psychiatry. Because TDM is widely used in daily clinical practice for antidepressant, antipsychotic and mood stabilizing drugs, these 3 pharmacologic classes are extensively represented in the present guidelines. Anxiolytic and hypnotic drugs, antidementia drugs, drugs for treatment of substance abuse related disorders and other psychotropic drugs are also candidates for TDM and are thus covered in the present guidelines. In special situations, the measurement of drug plasma concentrations can be helpful for any drug. Many patients are simultaneously treated for neurologic and psychiatric disorders. Therefore, the updated guidelines also contain information on anticonvulsant and antiparkinson drugs which are also more or less well established candidates for TDM [481,499] and were thus extended from 65 psychiatric drugs in 2004 [51] to 128 neuropsychiatric drugs at present.

Data published in the AGNP consensus guidelines 2004 [51] and other guidelines and recommendations for TDM of primarily antidepressant and antipsychotic drugs [317,400,488–490, 504,505] were initially used as the basis for this update. An extensive literature search was conducted, primarily in MEDLINE, to identify TDM-related information for the surveyed 128 neuropsychiatric drugs. The search concentrated on reports on "optimum plasma concentrations", "dose related drug plasma concentrations", "cytochrome P450 substrate, inducer and inhibitor properties" and on "ratios of concentrations of drug metabolites to parent drugs". Relevant reports were also searched by hand in pharmacologic and clinical chemical journals dealing with TDM. Over 1000 articles were assessed and

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analysed. Extracted data on reference ranges were listed in tables by 7 authors (CH, EH, CG, BR, PR, HK). Results of the literature search and analyses were sent out for review to 20 members of the TDM group with inclusion of a checklist how to extract and analyse the data. An internet based and password-protected platform was built up for the reviewers to have access to relevant articles. The reviewers' protocols and commentaries were distributed to all authors of these guidelines. Final decisions on data reported in this document were made during 2 consensus conferences and by e-mail communication. Consensus making also included definitions of reference ranges, alert levels and graded levels of recommendations to utilize TDM.

Theoretical Aspects of TDM in Psychiatry

Pharmacokinetics, metabolism and pharmacogenetics of neuropsychiatric drugs

Most psychotropic drugs share a number of pharmacokinetic characteristics

- good absorption from the gastrointestinal tract within plasma concentrations reaching a maximum within 1–6 h
- highly variable first-pass metabolism (systemic bioavailability ranging 5–90 %)
- fast distribution from plasma to the central nervous system with 2- to 40-fold higher levels in brain than in blood
- high apparent volume of distribution (about 10–50 L/kg)
- low trough plasma concentrations under steady-state (about 0.1–500 ng/mL for psychoactive drugs and up to 20 µg/mL for neurological drugs)
- slow elimination from plasma (half-life 12–36 h) mainly by hepatic metabolism
- linear pharmacokinetics at therapeutic doses which has the consequence that doubling the daily dose will result in a doubling of the plasma level
- low renal excretion with small effect of renal insufficiency on the plasma concentrations of parent drug and active metabolites
- cytochrome P450 (CYP) and UDP-glucuronosyltranferases as major metabolic enzyme systems

There are, however, numerous exceptions. For example, venlafaxine, nefazodone, trazodone, tranylcypromine, moclobemide, quetiapine, rivastigmine and 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 not or only poorly metabolised in the liver but also mainly excreted renally. Paroxetine exhibits non-linear pharmacokinetics, due to the inhibition of its own metabolism by a metabolite which is irreversibly bound to the enzyme (mechanism based inhibition) resulting in its inactivation [69].

Many psychotropic drugs are used as racemic compounds, and their enantiomers differ markedly in their pharmacology, metabolism and pharmacokinetics [53,605]. So far however, methadone, methylphenidate and flupentixol are at present the only racemic psychotropic compounds for which TDM of the enantiomers has been introduced [39,189]. The active principles of racemic methadone and fluoxetine are (R)-methadone and cis-(Z)-flupentixol, respectively. For research projects and other special situations, stereoselective analysis should be considered, e.g., for citalopram, fluoxetine, reboxetine, venlafaxine, paliperidone or amitriptyline metabolites.

Most psychotropic drugs undergo phase-I 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, dealkylation, oxidation to N-oxides, carbonyl reduction to secondary alcohols or S-oxidation to sulfoxides or sulfones. The phase-I reactions are predominantly catalysed by cytochrome P450 (CYP) enzymes which comprise more than 200 isoenzymes. The most important isoenzymes for psychotropic medications are CYP1A2, CYP2B6, CYP2D6, CYP2C9, CYP2C19 and CYP3A4/5 (**Table 1**) [745–747]. In general, phase-I reactions introduce a polar functional group that enables a phase-II conjugation reaction with highly polar molecules such as glucuronic or sulphuric acid. For psychotropic compounds possessing functional groups in the parent compound, glucuronidation of a hydroxyl group (for example oxazepam or lorazepam) or an N-H group (for example olanzapine) may represent the essential metabolic pathway. In addition, tertiary amine groups can be conjugated with the formation of quaternary ammonium glucuronides. Actually, phase II enzymes are poorly characterised with regard to substrate specificity, and there is much overlap between the isozymes regarding affinity for substrates [143].

Other enzymatic systems may also be involved, such as ketoaldehyde oxidases [43], which have been shown to reduce ziprasidone to its dihydro-derivative [58] or naltrexone to naltrexol [92], or MAO-A and MAO-B, which deaminate citalopram stereoselectively to an apparently inactive acidic metabolite [562].

Drugs are metabolised mainly in the liver and, to a minor degree, in extrahepatic tissues such as the intestinal mucosa or the brain [59,238,444]. Inter- and intra-individual differences in plasma concentrations of psychotropic drugs (i.e., the pharmacokinetic variability) are caused by different activities of drug-metabolising enzymes. The enzyme activity may decrease with age [374] and can be modified by renal and hepatic diseases. Gender differences have been reported for psychotropic drugs, but the findings are inconsistent and the clinical relevance is not clear [7–9,608].

For a number of psychoactive drugs, metabolites actively contribute to the overall clinical effect of the parent compound. For this reason, TDM must include the quantification of active metabolites, e.g., in the case of clomipramine (norclomipramine), doxepin (nordoxepin), fluoxetine (norfluoxetine) or risperidone (9-hydroxyrisperidone). For drugs like sertraline or clozapine, the clinical relevance of their metabolites norsertraline and norclozapine, respectively, is still a matter of debate. The analysis of pharmacologically inactive metabolites, however, may give useful information on the metabolic state of the patient or on his/her compliance [105,569]. **Table 2** shows the "normal" ratios of concentrations of metabolites to parent drugs. Calculated ranges contain 68 % of the ratios expected under standard dosages, i.e., ratios within the range of the mean ± 1 SD assuming normal distribution. A ratio above or below the "normal ratio" (**Table 2**) can indicate problems of drug adherence [546] or metabolic abnormalities due to a genetic variation [157,159,350,592] or a drug-drug interaction. Spina and coworkers [618] have shown this for the conversion of 2-hydroxydesipramine to desipramine. With regard to drug-drug interactions, ratios increase if the enzymatic conversion of the parent medication is induced by concurrent psychotropic or non-psychotropic medications or pharmacokinetically relevant activities such as smoking (**Table 3**). Other co-medications and food

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Table 1 Psychopharmacologic medications and enzymes involved in their metabolism.

Drug (active metabolite)	Enzymes	Reference
Acamprosate	not involved (not metabolized)	[578]
Agomelatine	**CYP1A2**, CYP2C19	[78]
Amantadine	merely involved (90 % excreted unmetabolized)	[24]
Alprazolam	**CYP3A4/5**	[17, 496]
Amisulpride	merely involved (more than 90 % is excreted unmetabolized via the kidney)	[566]
Amitriptyline and amitriptyline oxide (amitriptyline, nortriptyline)	CYP1A2, CYP2C9, **CYP2C19, CYP2D6**, CYP3A4	[90, 650, 713]
Aripiprazole (dehydroaripiprazole)	**CYP2D6, CYP3A4**	[306, 701]
Asenapine	Glucuronosyltransferase and CYP1A2	[707]
Atomoxetine	**CYP2D6**	[446]
Benperidol	**unclear**	[589]
Benserazide	**hydroxylation,** COMT	[347]
Biperiden	**hydroxylation**	[628]
Bromocriptine	**CYP3A4**	[513]
Bromperidol	**CYP3A4**	[230, 633, 645, 736]
Brotizolam	**CYP3A4**	[655]
Buprenorphine (norbuprenorphine)	CYP2C8, **CYP3A4**	[79, 454]
Bupropion (hydroxybupropion)	**CYP2B6**	[309]
Buspirone	**CYP3A4**	[416]
Cabergoline	**hydrolysis,** CYP3A4	[167]
Carbidopa	unknown metabolic pathways 1/3 unmetabolized	[575]
Carbamazepine, CBZ (CBZ-10,11-epoxide)*	CYP1A2, CYP2B6, CYP2C8, **CYP3A4/5**	[360, 497]
Chlorpromazine	**CYP1A2, CYP2D6**	[724]
Citalopram	**CYP2C19,** CYP2D6, CYP3A4	[97, 227, 739]
Clomipramine (norclomipramine)	CYP1A2, **CYP2C19, CYP2D6,** CYP3A4	[244]
Clomethiazol	CYP2A6, CYP2B6, CYP3A4	[116]
Clozapine	**CYP1A2, CYP2C19,** CYP3A4	[334, 487]
Desipramine	**CYP2D6**	[244]
Diazepam (nordazepam, oxazepam, temazepam)	CYP2B6, **CYP2C19,** CYP3A4	[228, 704]
Dihydroergocryptine	**CYP3A4**	[19, 162]
Diphenhydramine	**CYP2D6**	[13]
Disulfiram	CYP1A2, CYP2B6, CYP2E1, CYP3A4	[412]
Donepezil	**CYP2D6,** CYP3A4	[681]
Dothiepin = Dosulepin	**CYP2C19,** CYP2D6	[740]
Doxepin (nordoxepin)	**CYP2C9, CYP2C19, CYP2D6**	[295, 365]
Duloxetine	**CYP1A2,** CYP2D6	[405]
Entacapone	**Glucuronosyltransferase**	[387]
Escitalopram	**CYP2C19,** CYP2D6, CYP3A4	[662, 697]
Fluoxetine (norfluoxetine)	CYP2B6, **CYP2C9, CYP2C19, CYP2D6**	[404, 588]
Flupenthixol	**CYP2D6**	[148, 365]
Fluphenazine	**CYP2D6**	[746]
Fluvoxamine	**CYP2D6, CYP1A2**	[354, 450]
Galantamine	CYP2D6, CYP3A4	[34]
Gabapentin	unmetabolized renal excretion	[77]
Haloperidol	CYP2D6, **CYP3A4**	[93, 645]
Iloperidone	**CYP2D6,** CYP3A4	[106]
Imipramine (desipramine)	**CYP1A2, CYP2C19, CYP2D6,** CYP3A4	[244, 413]
Lamotrigine	Glucuronosyltransferase, CYP2A6	[121]
Levodopa	**Dopadecarboxylase,** COMT, MAO	[575]
Levomepromazine	CYP1A2, CYP2D6	[36]
Levomethadon	CYPC19, CYP2B6, **CYP3A4,** CYP2D6	[145]
Lisuride	CYP3A4, CYP2D6	[539]
Lithium	no metabolism, renal clearance	[256, 619]
Lorazepam	Glucuronosyltransferase	[164, 196]
Maprotiline	**CYP2D6**, CYP1A2	[86]
Melatonin	CYP1A2	[296]
Memantine	merely metabolized	[251]
Methadone	**CYP2B6,** CYP2C19, CYP3A4, CYP2D6	[145]
Methylphenidate	Carboxylesterase 1	[468]
Mianserine	**CYP2D6,** CYP1A2, CYP3A4	[379]
Midazolam	**CYP3A4**	[220]
Milnacipran	no CYP related metabolism	[495, 533]

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Table 1 Continued.

Drug (active metabolite)	Enzymes	Reference
Mirtazapine	CYP3A4, CYP1A2, CYP2B6, CYP2D6	[397,630]
Moclobemide	**CYP2C19,** CYP2D6	[255]
Modafinil	Amide hydrolysis, CYP3A4	[561]
Naltrexone	Aldoketoreductase AKR1C4	[92]
Nortriptyline	**CYP2D6**	[385,485,687]
Olanzapine	N-Glucuronosyltransferase, Flavin monoxigenase, **CYP1A2**, CYP2D6	[107]
Opipramol	unclear	
Paliperidone (= 9-Hydroxyrisperidone)	60 % excreted unmetabolized, different pathways	[161]
Paroxetine	CYP1A2, **CYP2D6**, CYP3A4	[209,349,691]
Perazine	CYP1A2, **CYP2C19**, CYP3A4, Flavin monoxigenase	[629,725]
Pergolide	CYP3A4	[731]
Perphenazine	CYP1A2, CYP2C19, **CYP2D6,** CYP3A4	[12,77,168,486]
Pregabalin	unmetabolized renal excretion	[77]
Piripedil	demethylation, p-hydroxylation, and N-oxidation	[168]
Pimozide	CYP1A2, **CYP3A4**	[171]
Pramipexole	not metabolized	[62]
Promazine	CYP1A2, CYP2C19, CYP3A4	[726]
Promethazine	**CYP2D6**	[465]
Quetiapine	**CYP3A4,** CYP2D6	[38]
Rasagiline	**CYP1A2**	[277]
Reboxetine	CYP3A4	[307,716]
Risperidone (9-Hydroxyrisperidone)	**CYP2D6,** CYP3A4	[732]
Ropinirole	**CYP1A2**	[357]
Rotigotine	Glucuronosyltransferase, several other unknown pathways	[115]
Selegiline	**CYP2B6**	[60]
Sertindole	**CYP3A4, CYP2D6**	[729]
Sertraline	**CYP2B6, CYP2C19,** CYP2C9, CYP2D6	[482,705]
Thioridazine	**CYP1A2,** CYP2C19, **CYP2D6,** CYP3A4	[648,714]
Tiapride	**mainly not metabolized**	[477]
Tolcapone	**Glucuronosyltransferase**	[387]
Trimipramine (nortrimipramine)	**CYP2C19, CYP2D6,** CYP2C9	[187]
Tranylcypromine	monoamine oxidase, unclear	[37]
Trazodone	**CYP3A4,** CYP2D6	[268,567]
Valproic acid	**Glucuronosyltransferase,** CYP2A6, CYP2B6, CYP2C9, **beta-oxidation**	[641]
Venlafaxine (O-desmethylvenlafaxine)	CYP2C19, **CYP2D6,** CYP3A4	[217,434]
Zaleplone	**Aldehyde oxidase, CYP3A4**	[554]
Ziprasidone	CYP3A4, Aldehyde oxidase	[58,519]
Zolpidem	CYP1A2, CYP2C9, **CYP3A4**	[698]
Zopiclone	CYP2C8, **CYP3A4**	[57,659]
Zotepine	CYP1A2, CYP2D6, **CYP3A4**	[596]
Zuclopenthixol	**CYP2D6**	[330]

Inhibition of enzymes indicated in bold will significantly increase the plasma concentrations of the drug, induction (CYP1A2, CYP3A4) will lead to decreased plasma concentrations (See **Table 2**). Prepared by CH, reviewed and supplemented by EJS

which inhibit metabolic enzymes may decrease the ratio. **Table 3** summarizes drugs that are inhibitors or inducers of CYP enzymes and thus may lead to clinically relevant pharmacokinetic drug-drug interactions.

Pharmacogenetic aspects

The clinical importance of pharmacogenetic factors in the pharmacokinetics and pharmacodynamics of psychoptropic drugs is increasingly recognised [156,199,457]. Drug-metabolising enzymes, especially CYP isoenzymes, exhibit genetic variability [745–747]. When the frequency of a deviation in the alleles is at least 1 % of the population, it is considered a genetic polymorphism. The number of active alleles in a gene determines how much of the enzyme is expressed (phenotype). Poor metabolisers (PM) lack functional alleles. Intermediate metabolisers (IM) are either genetically heterozygous, carrying an active and an inactive allele (or an allele with reduced activity) or have 2 alleles with reduced activity. Extensive metabolisers (EM) are wild-type with 2 active alleles, and ultra-rapid metabolisers (UM) have an amplification of functional alleles [66]. Genetic polymorphisms of drug-metabolising enzymes may be clinically important, because unexpected adverse reactions and toxicity may occur in PM due to increased plasma concentrations and non-response may occur in UM due to subtherapeutic plasma concentrations [160]. Prodrugs are activated by metabolism such as codeine by CYP2D6 to morphine or clopidogrel by CYP2C19 to 2-oxoclopidogrel. PM patients will not be able to produce pharmacologically active metabolites. Other enzyme systems such as UDP-glucuronosyltransferases also display genetic polymorphism [155], but their clinical relevance in pharmacopsychiatry is unclear.

CYP genotyping methods are becoming more and more available, and guidelines have been published for their use in clinical practice [675]. The functional significance of many genotypes,

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Table 2 Ranges of metabolite-to-parent concentration ratios for psychopharmacologic medications. Reported ranges contain 68 % of ratios determined under "normal" conditions in the blood of patients or healthy subjects.

Drug	Metabolite	Ratios of concentrations metabolite: parent drug (Mean – SD – Mean + SD)	Reference
Amitriptyline	Nortriptyline*	0.2–1.8 (n = 83)	[545]
Aripiprazole	Dehydroaripirazole(*)	0.3–0.5 PM of CYP2D6: 0.2	[306, 368, 452]
Bromperidol	Reduced bromperidol	0.11–0.51 (n = 31)	[609, 633]
Buprenorphine	Norbuprenorphine	0.8–2.0 (n = 5)	[383]
Bupropion	Hydroxybupropion	5–47 (24 h, n = 9) 6–30 (12 h, n = 9)	[152, 253, 336]
Buspirone	6-Hydroxybuspirone	25–53 (n = 20)	[178]
Carbamazepine	Carbamazepine-10,11-epoxide	0.07–0.25 (n = 14)	[338]
Citalopram	N-Desmethylcitalopram	0.31–0.60 (n = 2 330)	[549]
Clomipramine	Norclomipramine*	0.8–2.6 (n = 115)	[545]
Clozapine	Norclozapine(*)	nonsmokers (n = 98) 0.5–0.6 smokers (n = 198) 0.4–0.7	[140, 308, 500]
Dothiepin	Nordothiepin	0–1.4 (n = 50)	[325]
Doxepin	Nordoxepin	0.6–1.6 (n = 12) PM CYP2C19: 1.8 (n = 4) PM CYP2D6: 0.8 (n = 6)	[172, 363]
Escitalopram	N-Demethylescitalopram	0.3–1.0 (n = 243)	[548]
Fluoxetine	Norfluoxetine*	0.7–1.9 (n = 334)	[545]
Fluvoxamine	Fluvoxamino acid	0–1.2 (n = 49)	[237]
Haloperidol	Reduced haloperidol	mean 0.6	[673]
Imipramine	Desipramine	0.6–3.2 (n = 14) PM CYP2D6 4.1 (n = 2)	[95, 96, 632]
Maprotiline	Desmethylmaprotiline	1.1–3.7 (n = 76) PM CYP2D6 4.9	[699]
Mianserin	N-Desmethylmianserin	0.5–0.8 (n = 182)	[545]
Mirtazapine	N-Desmethylmirtazapine	0.2–1.2 (n = 100)	[591]
Moclobemide	Moclobemide N-oxide	0.8–2.5 (n = 6)	[291]
Olanzapine	N-Demethylolanzapine	non smokers: 0.1–0.3 (n = 76) smokers: 0.2–0.4 (n = 69)	[602]
Perazine	Desmethylperazine	1.1–3.3 (n = 27)	[91]
Perphenazine	N-Dealkylperphenazine	0.6–2.8 (n = 54)	[637]
Quetiapine	Norquetiapine	0.1–3.8 (n = 25) (calculated for 400 mg)	[723]
Reboxetine	O-Desethylreboxetine	< 0.1	[484]
Risperidone	9-Hydroxyrisperidone*	EM or IM CYP2D6: 1.5–10.0 PM CYP2D6: ≤ 1	[159, 677]
Risperidone depot	9-Hydroxyrisperidone*	EM: 1.2–4.3	[469]
Sertindole	Dehydrosertindole	1.1–2.7 (n = 6) 1.0 in PM of CYP2D6	[729]
Sertraline	Norsertraline	1.7–3.4 (n = 348)	[546]
Trazodone	m-Chlorophenylpiperazine (mCPP)	0.04–0.22 (total range)	[328]
Trimipramine	Nortrimipramine*	0–12.0 (n = 17)	[142]
Venlafaxine	O-Desmethylvenlafaxine* N-Desmethylvenlafaxine	EM or IM CYPD26: 0.3–5.2 PM CYP2D6: ≤ 0.3 UM CYP2D6: > 5.2 0.46–1.48	[592]

*pharmacologically active metabolite, (*) active metabolite in vitro but unclear under in vivo conditions

When SD values of ranges of ratios (SD ratio) were not reported in the literature, SD ratios were calculated in accordance with Gaussian's law for the propagation of errors: SD ratio = [(SD parent drug x mean metabolite)+(SD metabolite x mean parent drug)]/(mean metabolite)^2

Prepared by CH, reviewed by Sonja Brünen, Christiane Knoth, Elnaz Ostad Haji and Viktoria Stieffenhofer

however, is unclear. For some enzymes, a genetic polymorphism is not clearly demonstrated despite the fact that they display a wide interindividual variability in their activity. Therefore it may be advantageous to use phenotyping methods with probe drugs such as caffeine for CYP1A2, omeprazole for CYP2C19, dextromethorphan for CYP2D6, or midazolam for CYP3A4/5 [403, 643]. Phenotyping measures the metabolic situation of the patient at the moment of the test, and allows to follow its evolution. The measurement, however, may be influenced by environmental factors such as smoking or comedications [201, 601, 749]. 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.

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Table 3 Inhibitors and inducers of enzymes involved in the metabolism of drug.

Inhibiting drugs	Inhibited enzymes	Inducing drugs	Induced enzymes
Amiodarone	CYP2C9, CYP2D6, CYP3A4	Carbamazepine	CYP1A2, CYP2B6, CYP2C9, CYP3A4
Bupropion	CYP2D6	Dexamethason	CYP2C9, CYP3A4
Bromocriptine	CYP3A4	Efavirenz	CYP2B6, CYP3A4
Chinidine	CYP2D6	Ethanol	CYP2E1
Cimetidin	CYP1A2, CYP2D6, CYP3A4	Ginkgo biloba	CYP2C19
Ciprofloxacin	CYP1A2	Isoniazide	CYP2E1
Clarithromycin	CYP3A4	St. John's wort	CYP2C19, CYP3A4
Clopidogrel	CYP2B6	Oxybutynin	CYP3A4
Disulfiram	CYP2E1	Phenobarbital	CYP2C9, CYP2C19, CYP3A4
Duloxetine	CYP2D6	Phenytoin	CYP2B6, CYP2C9, CYP2C19, CYP3A4
Enoxacin	CYP1A2	Primidon	CYP2C9, CYP2C19, CYP3A4
Erythromycin	CYP3A4	Smoke	CYP1A2
Esomeprazole	CYP2C19	Rifabutin	CYP3A4
Felbamate	CYP2C19	Rifampicin	CYP1A2, CYP2B6, CYP2C9, CYP2C19
Fluconazole	CYP2C19, CYP2C9, CYP3A4	Ritonavir	CYP3A4, CYP2C9, CYP3A4 (high dose)
Fluoxetine and norfluoxetine	CYP2D6, CYP2C19		
Fluvoxamine	CYP1A2, CYP2C9, CYP2C19, CYP3A4		
Indinavir	CYP3A4		
Isoniazid	CYP1A2, CYP2A6, CYP2C19, CYP3A4		
Itraconazol	CYP2B6, CYP3A4		
Ketoconazol	CYP3A4		
Levomepromazine	CYP2D6		
Melperone	CYP2D6		
Metoclopramide	CYP2D6		
Metoprolol	CYP2D6		
Miconazol	CYP2C9, CYP2C19		
Mifepriston	CYP3A4		
Moclobemide	CYP2C19, CYP2D6		
Nelfinavir	CYP3A4		
Norfloxacine	CYP1A2		
Omeprazole	CYP2C19		
Paroxetine	CYP2D6		
Perazine	CYP1A2		
Pergolide	CYP2D6		
Perphenazin	CYP2D6		
Propafenon	CYP1A2, CYP2D6		
Propranolol	CYP2D6		
Ritonavir	CYP2D6, CYP3A4		
Saquinavir	CYP3A4, CYP2C9		
Troleandomycin	CYP3A4		
Valproate	CYP2C9		
Verapamil	CYP3A4		
Voriconazol	CYP2C9, CYP3A4		

Combination of psychoactive drugs with these inhibitors or inducers can lead to clinically relevant drug-drug interactions (www.mediq.ch or www.psiac.de)
Prepared by CH, reviewed by EJS

Recent investigations indicate that the drug efflux transporter P-glycoprotein (P-gp) in the intestinal mucosa and blood-brain-barrier is also relevant for the pharmacokinetic variability of psychotropic medications [1]. This protein, a member of the ATP-cassette binding (ABC) transporter protein family, is encoded by the multidrug resistance gene (*MDR1*; *ABCB1*). It displays a genetic polymorphism, but as yet, mainly genotyping but not phenotyping (e.g., with digoxin) is more commonly used [129, 183, 210, 389]. Genetic polymorphism of P-gp may be of the same considerable clinical relevance as has been demonstrated for drug-metabolizing enzymes. For antidepressant drugs that are substrates of P-gp, a genotype dependent association of drug response was found [668, 669]. Both plasma concentrations of quetiapine and its clinical effectiveness have been shown to depend on the P-gp genotype of patients suffering from schizophrenia [470]. With regard to the occurrence of wanted or unwanted clinical effects of psychoactive drugs, some first reports suggest the influence of the genetic polymorphism of P-gp [279, 560]. However, further research is needed to evaluate the clinical relevance of the genetic polymorphisms of drug transporters.

Dose and drug concentration in blood

In most situations that use TDM for dose optimization, drugs are administered in a series of repeated doses to attain a steady-state concentration within a given therapeutic reference range. Steady-state is attained when the rate of medication input equals the rate of medication loss, i.e., approximately after 4 times the elimination half life. With multiple dosing, 94% of the steady state are achieved after 4 and 97% after 5 elimination half-lives. For more than 90% of all psychoactive medications, such a steady-state is reached within 1 week of maintenance

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Table 4 Total clearance (Cl_t), bioavailability (F), dosing intervals (τ) and factors (C/D_{low} and C/D_{high}) for calculation of dose-related plasma concentrations (C/D) for psychotropic drugs.

Drug	n	$Cl_t - SD - Cl_t + SD$ [mL/min]	F	τ [h]	C/D_{low} [ng/mL/mg]	C/D_{high} [ng/mL/mg]	Reference
Antidepressant drugs							
Amitriptyline	8	198–373	0.5	24	1.03	1.68	[165]
Amitriptyline oxide	12	331–539	0.8	24	0.93	1.75	[384]
Bupropion	17	2500–11300	1.0	24	0.06	0.28	[665]
Citalopram	8	367–545	0.8	24	1.02	1.51	[616]
Clomipramine	9	583–933	0.5	24	0.37	0.60	[198]
Desipramine	12	1633–2333	0.5	24	0.15	0.21	[2]
Desvenlafaxine	7	233–396	1.0	24	1.75	2.98	[520]
Dothiepin = Dosulepin	22	674–3960	0.3	24	0.05	0.31	[740]
Doxepin	85	769–2644	1.0	24	0.18	0.27	[100]
Duloxetine	12	610–1733	0.5	24	0.20	0.57	[600]
Escitalopram	24	360–960	0.8	24	0.58	1.54	[607]
Fluoxetine	n.r.	600–833	0.7	24	0.60	0.83	[18]
Fluvoxamine	6	807–1960	1.0	24	0.35	0.86	[163]
Imipramine	n.r.	791–1029	0.4	24	0.28	0.37	[100]
Maprotiline	6	503–1747	0.8	24	0.32	1.10	[415]
Mianserin	n.r.	843–1948	0.3	24	0.11	0.25	[137]
Mirtazapine	10	455–945	0.5	24	0.37	0.85	[651]
Nordoxepin	85	504–2738	1.0	24	0.25	1.38	[445]
Nortriptyline	n.r.	300–1117	0.5	24	0.31	1.16	[664]
Paroxetine	30	1561–10856	1.0	24	0.06	0.44	[213]
Reboxetine	n.r.	22–51	1.0	24	12.55	31.10	[141]
Sertraline	11 (m) 11 (f)	1313–2213 (m) 793–2357 (f)	1.0 1.0	24 24	0.31 0.29	0.53 0.88	[565]
Trazodone	8	73–103	1.0	24	6.72	9.47	[473]
Trimipramine	12	898–1215	0.40	24	0.23	0.31	[165, 364]
Venlafaxine	18	747–1540	1.0	24	0.45	0.93	[372]
O-Desmethylvenlafaxine		315–618	1.0	24	1.12	2.2	
Antipsychotic drugs							
Amisulpride	78	520–693	0.5	24	0.50	0.67	[566]
Asenapine	n.r.	867	0.35	24	0.28		[707]
Aripiprazole	6	47–70	0.9	24	8.63	12.85	[417]
Benperidol	14	1073–2240	0.5	24	0.15	0.31	[589]
Bromperidol	14	3570–7938	1.0	24	0.09	0.19	[390]
Chlorpromazine	11	1043–1510	0.1	24	0.05	0.07	[738]
Chlorprothixene	3	918–1448	0.2	24	0.10	0.15	[534]
Clozapine	16	258–728	0.5	24	0.40	0.80	[128, 176, 332]
Flupentixol	3	440–490	0.6	24	0.78	0.87	[348]
Fluphenazine decanoate	12	2380–3940	1.0	24	0.18	0.29	[197]
Haloperidol	6	420–680	0.6	24	0.61	0.99	[123]
Haloperidol decanoate		420–680	1.0	336 672	0.073 0.036	0.118 0.059	[123]
Melperone	6	1484–2898	0.6	24	0.14	0.28	[83]
Levomepromazine	8	913–4737	0.5	24	0.07	0.38	[149]
Olanzapine	491	233–637	0.8	24	0.87	2.38	[67]
Paliperidone	n.r.	31–98	0.3	24	1.99	6.31	[161]
Perphenazine	8	1009–2566	0.4	24	0.11	0.28	[195]
Pimozide	7	21–553	0.5	24	0.64	16.53	[581]
Quetiapine	10	1146–2421	1.0	24	0.13	0.21	[7, 435]
Risperidone, oral	8	91–171	0.7	24	3.50 active moiety	14.00 active moiety	[159]
Risperidone, depot	n.r.	91–171	1.0	336	0.29 active moiety	0.55 active moiety	[606]
Sertindole	6	133–600	1.0	24	1.16	5.22	[728]
Supiride	6	331–499	0.25	24	0.35	0.52	[717]
Thiordazine	11	404–982	0.60	24	0.42	1.03	[117]
Zotepine	14	467–10267	1.0	24	0.07	1.49	[642]
Ziprasidone	12	303–397	0.6	24	1.05	1.36	SPC
Zuclopenthixol	8	867–2300	0.4	24	0.13	0.35	[337]

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Table 4 Continued.

Drug	n	Cl_t – SD – Cl_t + SD [mL/min]	F	τ [h]	C/D_{low} [ng/mL/mg]	C/D_{high} [ng/mL/mg]	Reference
Anticonvulsant drugs Mood stabilizers							
Carbamazepine	n. r.	58–74	1.0	24	9.40	11.93	SPC
Felbamate	10	29.1–33.3	1.0	24	20.85	23.86	[556]
Lamotrigine	129	22–49	1.0	24	14.09	31.28	[118]
Levetiracetam	216	52–72	1.0	24	9.65	13.35	[535]
Lithium	n. r.	10–40	1.0	24	17.36	69.44	[706]
Oxcarbazepine	7	1703–5063	1.0	24	0.14	0.41	[319, 694]
Primidone	8	30–47	1.0	24	14.78	23.15	[423]
Topiramate	6	21–31	1.0	24	22.47	33.55	[179]
Valproic acid	9	4.5–9.8	1.0	24	71.23	154.32	[682]
Anxiolytic and hypnotic drugs							
Alprazolam	6	34–83	0.8	24	6.73	16.53	[496, 604]
Bromazepam	10	50–91	1.0	24	7.67	13.95	[352]
Brotizolam	8	85–141	0.7	24	4.93	8.17	[341]
Buspirone	41	1260–2702	0.04	24	0.01	0.02	[41]
Clonazepam	9	63–90	0.8	24	5.43	7.69	[259]
Diazepam	48	10–43	0.9	24	13.01	52.91	[264]
Lorazepam	15	36–109	0.8	24	5.98	17.93	[266]
Oxazepam	18 (m)	36–167	0.8	24	3.33	15.22	[260]
	20 (w)	29–109	0.8	24	5.12	18.90	
Triazolam	13	326–584	0.9	24	1.01	1.81	[263]
Zaleplon	10	868–1330	0.3	24	0.16	0.25	[265]
Zolpidem	10	266–364	0.67	24	1.02	2.14	[265]
Zopiclone	10	250–883	1	24	0.79	2.78	[411]
Antidementia drugs							
Donepezil	14	112–217	1.0	24	3.20	6.20	[463]
Galantamine	8	268–400	1.0	24	1.74	2.59	[744]
Rivastigmine	20	29–64 (patch)	0.5	24	0.18	0.74	[391]
Drugs for treatment of substance related disorders							
Acamprosate	24	1741–4221	1.0	24	0.16	0.40	[287]
Buprenorphin							no data available
Bupropion	17	2500–11300	1.0	24	0.06	0.28	[665]
Methadone	12	75–148	0.95	24	4.46	8.80	[474,727]
Naltrexone	453	2077–2590	1.0	24	0.27	0.33	[182]
6β-naltrexol		928–1242			0.56	0.75	
Varenicline	1878	170–176	1.0	24	3.95	4.08	[540]

SPC: Summary of product characteristics; n.r.: not reported; active moiety: risperidone plus 9-hydroxyrisperidone; n: number of individuals; SD: standard deviation

Dose related ranges are obtained by multiplying C/D_{low} and C/D_{high} by the dose. Drugs listed in **Table 5** were not included in this table, when clearance data were not available from the literature.

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dosing. The dose required to attain a steady-state concentration of a drug in plasma can be calculated if the dosing interval (τ), the clearance (Cl) and the bioavailability (F) for the drug in a particular patient are known. The calculation is based on the direct correlation of the drug dose D_e (constant dose per day at steady-state) to its blood concentration c, with the total clearance of the drug (Cl_t) being the correlation coefficient:

$$D_e = DxF/\tau = c \times Cl_t$$

Based on this information it is possible to calculate the dose-related plasma concentration of a drug that may be expected in blood specimens of patients under medication with a given dose [285]:

$$c = D_e/Cl_t$$

For psychoactive medications, such data are available from studies in which drug concentrations were measured in plasma of healthy volunteers or patients treated with fixed doses. When the clearance is taken as arithmetic mean ± standard deviation from clinical trials of the drug, a dose related reference range can be calculated [285].

Definition

The **"dose-related reference range"** reported in the present guidelines is calculated as a concentration range within that a drug concentration is expected according to pharmacokinetic studies in human blood specimens from subjects under medication with a given dose of the drug. It contains 68 % of all the drug concentrations determined under normal conditions in the blood of a "normal" patient or subject, "normal" being defined by the population in the respective clinical trial. It usually consists of individuals 18-65 years of age without relevant comorbidity, comedication, and genetic abnormalities in drug metabolism.

Table 4 lists factors for calculation of dose-related reference ranges for the most relevant psychoactive drugs. Dose-related reference ranges are calculated by multiplying C/D_{low} and C/D_{high}

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by the daily dose. One must be aware, however, that many patients encountered in the clinical context do not fulfil all the abovementioned conditions.

Drug concentration in blood and brain

The pharmacological activity of a psychotropic drug depends on its availability in the target organ, the brain. However, the latter is separated from the blood by 2 barriers, which have to be crossed by the drug, the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier [154]. Most psychoactive drugs enter the brain due to their high lipid solubility by passive diffusion and thereby cross the barriers. The BBB is a physical barrier that separates circulating blood and the central nervous system, and it consists of endothelial cells around the capillaries joined together by tight junctions [154]. It efficiently restricts the exchange of solutes between the blood and the brain extracellular fluid. Functionally, it protects the brain against potentially harmful chemicals. As mentioned above, a number of psychoactive drugs, such as risperidone, aripiprazole or venlafaxine are substrates of P-gp [180,370,668]. As a consequence, brain to plasma concentration ratios vary widely for psychotropic drugs with similar physicochemical properties. Animal studies found ratios from 0.22 for risperidone [29] to 34 for fluphenazine [27]. In spite of highly variable ratios of brain to plasma concentrations of the different psychotropic drugs, animal studies have shown that steady-state plasma concentrations of psychoactive drugs correlate well with concentrations in brain, much better than doses. This has been shown for tricyclic antidepressants [249], trazodone [173], or olanzapine [28]. Drug concentrations in plasma can therefore be considered as a valid surrogate marker of concentrations in brain.

Drug concentration in blood and target structure occupancy in brain

Positron emission tomography (PET) enables analysis of central nervous receptor occupancy in vivo [207,274,275]. Antipsychotic drugs exert most of their therapeutic actions by blockade of dopamine D2-like receptors. Blockade of D2 receptors by antipsychotic drugs reduces the binding of radioactive PET ligands [207,272,275]. Using this approach and quantification of the displacement of dopamine receptor radioligands, it has been shown that plasma concentrations of antipsychotic drugs correlate well with receptor occupancy. In accordance with the high variability of drug concentrations in plasma under same doses it was found that receptor occupancy correlates better with plasma concentrations than with daily doses [313]. Optimal response was seen at 70–80 % receptor occupancy, and 80 % receptor occupancy was defined as the threshold for the occurrence of extrapyramidal side effects [207,480]. PET was also used to characterize in vivo serotonin transporter occupancy by SSRIs [442,443]. Using a serotonin transporter radioligand, plasma concentrations of citalopram, paroxetine, fluoxetine and sertraline were shown to correlate well with serotonin transporter occupancy. It was found that at least 80 % occupancy should be attained for optimal clinical outcome [442,443]. PET studies have thus brought about highly relevant information for the determination of optimal plasma concentrations of a considerable number of psychotropic drugs which is reviewed in this special issue by Gründer and co-workers [274].

"Therapeutic window" – therapeutic reference range

TDM is based on the assumption that there is a relationship between plasma concentrations and clinical effects (therapeutic improvement, side effects and adverse effects). It also assumes that there is a plasma concentration range of the drug which is characterized by maximal effectiveness and maximal safety, the so-called "therapeutic window". Studies on relations between plasma concentration and clinical improvement have supported this concept since the sixties for lithium, tricyclic antidepressants and classical antipsychotic drugs. Systematic reviews and meta-analyses that were based on adequately designed studies led to convincing evidence of a significant relationship between clinical outcomes and plasma concentrations for nortriptyline, imipramine and desipramine which are associated with a high probability of response [51]. For amitriptyline as a model compound, a meta-analysis of 45 studies has shown that various statistical approaches provided almost identical results [672,674]. For new antipsychotic drugs like aripiprazole [612], olanzapine [509] or risperidone [737] relationships between plasma concentration and clinical effectiveness have been reported.

For the "therapeutic window" there are many synonymous terms like "therapeutic reference range", "therapeutic range", "optimal plasma concentration", "effective plasma concentration", "target range", "target concentration", or "orienting therapeutic range", the term used in the first consensus [51]. The present consensus uses the term "therapeutic reference range" in accordance with the guidelines on TDM for antiepileptic drugs [499]. The "therapeutic reference range" was defined in this consensus guideline for neuropsychiatric drugs as follows:

Definition

The "**therapeutic reference ranges**" reported in this guideline (▶ **Table 5**) define ranges of medication concentrations which 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, psychopharmacotherapy 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 5**. They were evidence-based and derived from the literature by the structured review process described above. For only 15 neuropsychiatric drugs therapeutic reference ranges based on randomized clinical trials were found in the literature. For most drugs, reference ranges were obtained from studies with therapeutically effective doses. Therefore, there is a need for further studies to define therapeutic ranges.

The reference ranges listed in ▶ **Table 5** are generally those for the primary indication. A number of drugs, however, are recommended for several indications. For example, antidepressant drugs are also used for the treatment of anxiety states, and antipsychotic drugs are increasingly used to treat mania. Little information is available on optimum plasma concentrations in these situations. Exceptions are carbamazepine, lamotrigine and

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Table 5 Recommended reference ranges, laboratory alert levels and levels of recommendation for TDM.

Drugs and active metabolites	Therapeutic reference range/recommended drug concentration	t1/2	Laboratory alert level	Level of recommendation to use TDM (consensus)	Conversion factor (CF, see below)	Reference	Comments
Antidepressant drugs							
Agomelatine	7–300 ng/mL 1–2 h after 50 mg	1–2 h	600 ng/mL	4	4.11	[78]	Because of rapid elimination, trough drug concentrations are not measurable under chronic treatment. Determinations, preferentially of Cmax, should be restricted to specific indications.
Amitriptyline plus nortriptyline	80–200 ng/mL	10–28 h 30 h	300 ng/mL	1	3.41 3.61	[282, 502, 672]	
Bupropion plus hydroxybupropion	225–1500 ng/mL	8–26 h 17–47 h	2000 ng/mL	3	4.17 3.91	[151, 152, 336, 529, 636]	Bupropion, and to a lesser degree its metabolite, are unstable, plasma or serum must be stored frozen (−20°C)
Citalopram	50–110 ng/mL	33 h	220 ng/mL	2	3.08	[42, 73, 111, 339, 388, 442, 471, 491, 549, 598]	N-Demethylated metabolites do not contribute to pharmacological actions
Clomipramine plus norclomipramine	230–450 ng/mL	16–60 h 36 h	450 ng/mL	1	3.18 3.32	[239]	
Desipramine	100–300 ng/mL	15–18 h	300 ng/mL	2	3.75	[502]	Delayed elimination in PM of CYP2D6
Desvenlafaxine	100–400 ng/mL	11 h	600 ng/mL	2	3.80	[520]	
Dosulepin = Dothiepin	45–100 ng/mL	18–21 h	200 ng/mL	2	3.39	[102, 325, 414, 541]	
Doxepin plus nordoxepin	50–150 ng/mL	15–20 h	300 ng/mL	2	3.58 3.77	[172, 321, 393, 445]	
Duloxetine	30–120 ng/mL	9–19 h	240 ng/mL	2	3.36	[21, 640, 703]	No active metabolites
Escitalopram	15–80 ng/mL	30 h	160 ng/mL	2	3.08	[409, 679]	N-Demethylated metabolites do not contribute to pharmacological actions lower level of the reference range was calculated from a PET study (80% 5HTT occupancy) [409], upper level from the SPC
Fluoxetine plus norfluoxetine	120–500 ng/mL	4–6 days 4–16 days	1000 ng/mL	2	3.23 3.39	[84, 187, 410, 442, 545]	Long elimination half life of norfluoxetine (mean 14 days) and long-lasting potent inhibition of CYP2D6
Fluvoxamine	60–230 ng/mL	20 h	500 ng/mL	2	3.14	[353, 587, 631, 634, 639]	Inhibtion of CYP1A2, CYP2C19
Imipramine plus desipramine	175–300 ng/mL	11–25 h 15–18 h	300 ng/mL	1	3.57 3.75	[72, 229, 245, 510, 538]	Hydroxylated metabolites
Maprotiline	75–130 ng/mL	20–58 h	220 ng/mL	2	3.60	[231, 321, 384]	Active metabolite N-desmethylmaprotiline
Mianserine	15–70 ng/mL	14–33 h	140 ng/mL	3	3.78	[191, 192, 453]	
Milnacipran	50–110 ng/mL	5–8 h	220 ng/mL	2	2.24	[206, 315]	
Mirtazapine	30–80 ng/mL	20–40 h	160 ng/mL	2	3.77	[257, 367, 397, 440, 552, 591]	N-Demethylated metabolite does not contribute to pharmacological actions
Moclobemide	300–1000 ng/mL	2–7 h	2000 ng/mL	3	3.72	[225, 291, 327]	Metabolites are pharmacologically inactive
Nortriptyline	70–170 ng/mL	30 h	300 ng/mL	1	3.80	[30, 31, 504, 506, 510]	Hydroxylated metabolites
Paroxetine	30–120 ng/mL	12–44 h	240 ng/mL	3	3.04	[242, 243, 410, 443]	
Reboxetine	60–350 ng/mL	13–30 h	700 ng/mL	3	3.19	[483, 484]	
Sertraline	10–150 ng/mL	26 h	300 ng/mL	2	3.27	[15, 49, 258, 281, 410, 443, 545, 696]	N-Demethylated metabolite has a 2-fold longer elimination half life than sertraline, but only 1/20 of the activity of sertraline
Tranylcypromin	≤ 50 ng/mL	1–3 h	100 ng/mL	4	7.51	[103, 329]	Due to irreversible inhibition of monoamine oxidase, plasma concentrations do not correlate with drug actions
Trazodone	700–1000 ng/mL	4–11 h	1200 ng/mL	2	2.69	[250, 262, 268, 447, 590]	
Trimipramine	150–300 ng/mL	23 h	600 ng/mL	2	3.40	[142, 187, 223, 326]	Active metabolite N-desmethyltrimipramine
Venlafaxine plus O-desmethylvenlafaxine	100–400 ng/mL	5 h 11 h	800 ng/mL	2	3.61 3.80	[85, 241, 316, 443, 545, 550, 592, 684, 696]	In most patients O-desmethylvenlafaxine is the active principle in vivo, N-demethylated venlafaxine does not contribute to pharmacological actions. At low concentrations, the drug acts predominanty as an SSRI

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Table 5 Continued.

Drugs and active metabolites	Therapeutic reference range/recommended drug concentration	t1/2	Laboratory alert level	Level of recommendation to use TDM (consensus)	Conversion factor (CF, see below)	Reference	Comments
Antipsychotic drugs							
Amisulpride	100–320 ng/mL	12–20 h	640 ng/mL	1	2.71	[64, 89, 441, 461, 531, 613, 690]	No metabolites
Aripiprazole	150–500 ng/mL	60–80 h	1 000 ng/mL	2	2.23	[33, 273, 306, 368, 452, 612]	The metabolite dehydroaripiprazole is active in vitro, it remains unclear to which extend it contributes to clinical effects
Asenapine	2–5 ng/mL	24 h	10 ng/mL	4	3.50	[707]	
Benperidol	1–10 ng/mL	5 h	20 ng/mL	3	2.62	[472, 589]	Higher levels may be tolerated in patients under long-term high-dose therapy due to adaptive changes.
Bromperidol	12–15 ng/mL	20–36 h	30 ng/mL	2	4.38	[609, 656, 735]	
Chlorpromazine	30–300 ng/mL	15–30 h	600 ng/mL	2	3.14	[127, 559]	
Chlorprothixene	20–300 ng/mL	8–12 h	400 ng/mL	3	3.17	[542]	
Clozapine	350–600 ng/mL	12–16 h	1 000 ng/mL	1	3.06	[175, 507, 493, 507, 678]	Major metabolite N-desmethylclozapine with unclear antipsychotic activity
Flupenthixol	1–10 ng/mL	20–40 h	15 ng/mL	2	2.30	[40, 543, 564]	
Fluphenazine	1–10 ng/mL	16 h	15 ng/mL	1	2.29	[564, 680]	
Fluspirilen	0.1–2.2 ng/mL	7–14 days	4.4 ng/mL	2	2.10	[611]	
Haloperidol	1–10 ng/mL	12–36 h	15 ng/mL	1	2.66	[74, 214, 480, 494, 508, 674, 680]	Higher levels can be tolerated in patients under long-term high-dose therapy due to adaptive changes.
Iloperidone	5–10 ng/ml	18–33 h	20 ng/ml	3	2.34	[476, 576]	
Levomepromazine	30–160 ng/mL	16–78 h	320 ng/mL	3	3.04	[656]	
Melperone	30–100 ng/mL	4–6 h	200 ng/mL	3	3.80	[83, 324]	Inhibitor of CYP2D6
Olanzapine	20–80 ng/mL	30–60 h	150 ng/mL	1	3.20	[32, 56, 63, 132, 208, 240, 418, 478, 509, 602, 711]	Under olanzapine pamoate, patients exhibited a post injection syndrome when drug concentrations exceeded 150 ng/mL
Paliperidone	20–60 ng/mL	23 h	120 ng/mL	2	2.35	[26, 70, 131, 466]	Paliperidone = 9-hydroxyrisperidone
Perazine	100–230 ng/mL	8–16 h	460 ng/mL	1	2.95	[91]	
Perphenazine	0.6–2.4 ng/mL	8–12 h	5 ng/mL	1	2.48	[564, 637, 680]	
Pimozide	15–20 ng/mL	23–43 h	20 ng/mL	3	2.17	[649]	
Pipamperone	100–400 ng/mL	17–22 h	500 ng/mL	3	2.66	[82, 517]	
Prothipendyl	5–10 ng/mL	2–3 h	20 ng/mL	4	3.35	[436] SPC	
Quetiapine	100–500 ng/mL	7 h	1 000 ng/mL	2	2.61	[112, 212, 236, 299, 498, 603, 627, 689, 723]	When the patient has taken the extended release (XR) formulation in the evening and blood was withdrawn in the morning, expected plasma concentrations are 2-fold higher than trough levels
Risperidone plus 9-hydroxyrisperidone	20–60 ng/mL	3 h 24 h	120 ng/mL	2	2.44 2.35	[150, 406, 426, 437, 469, 475, 553, 557, 617, 729, 737]	
Sertindole	50–100 ng/mL	55–90 h	200 ng/mL	2	2.27	[71, 109, 110, 653, 728, 729]	Active metabolite dehydrosertindole (concentration at therapeutic doses 40–60 ng/mL), concentration dependent increase of QT interval by blockade of potassium chanels
Sulpiride	200–1 000 ng/mL	8–14 h	1 000 ng/mL	2	2.93	[460, 656]	No metabolites, renal eliminiation
Thioridazine	100–200 ng/mL	30 h	400 ng/mL	1	2.70	[190, 656]	Contraindicated in poor metabolizers of CYP2D6
Ziprasidone	50–200 ng/mL	6 h	400 ng/mL	2	2.55	[126, 419, 427, 688, 695]	The drug should be taken with a meal, otherwise absorption is reduced and plasma concentrations will be lower than expected
Zotepine	10–150 ng/mL	13–16 h	300 ng/mL	3	3.01	[376, 642]	
Zuclopentixol	4–50 ng/mL	15–25 h	100 ng/mL	3	2.49	[330, 371, 692]	

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Table 5 Continued.

Drugs and active metabolites	Therapeutic reference range/recommended drug concentration	t1/2	Laboratory alert level	Level of recommendation to use TDM (consensus)	Conversion factor (CF, see below)	Reference	Comments
Mood stabilizing drugs							
Carbamazepine	4–10 µg/mL	10–20 h	20 µg/mL	2	4.23	[512]	Active 10,11-epoxide metabolite contributes to clinical effects
Lamotrigine	3–14 µg/mL	7–23 h	30 µg/mL	2	3.90	[455, 558]	So far no specific reference rang for mood stabilizing effect, valproate increases elimination half life to 48–70 h
Lithium	0.5–1.2 mmol/l (4–8 µg/mL)	24 h	1.2 mmol/l (8 µg/mL)	1	125.8	[593, 721]	Age dependent increase of elimination half life
Valproic acid	50–100 µg/mL	18 h	120 µg/mL	2	6.93	[16, 216, 301, 683]	In individual cases 120µg/mL are also tolerated in acute mania.
Anticonvulsant drugs							
Carbamazepine	4–12 µg/mL	10–20 h	20 µg/mL	2	4.25	[87, 338, 499]	Active 10,11-epoxide metabolite contributes to clinical effects
Clobazam and N-desmethylclobazam	30–300 ng/mL 300–3 000 ng/mL	18–42 h	500 ng/mL 5 000 ng/mL	2	3.33 3.49	[278, 499]	Active N-demethylated metabolite contributes to clinical effects
Clonazepam	20–70 ng/mL	40 h	80 ng/mL	2	3.17	[44, 464, 499]	7-Amino metabolite retains some activity
Ethosuximide	40–100 µg/mL	33–55 h	120 µg/mL	2	7.08	[88, 499]	
Felbamate	30–60 µg/mL	15–23 h	100 µg/mL	2	4.20	[290, 343, 499]	
Gabapentin	2–20 µg/mL	6 h	25 µg/mL	3	5.84	[75–77, 343, 398, 499]	
Lacosamide	1–10 µg/mL	13 h	20 µg/mL		2.66	[47]	
Lamotrigine	3–14 µg/mL	7–23 h	20 µg/mL	2	3.90	[88, 343, 455, 456, 499, 610]	Valproate increases elimination half life to 48–70 h
Levetiracetam	10–40 µg/mL	6–8 h	100 µg/mL (morning levels)	2	3.87	[88, 343, 430, 499]	
Methsuximide plus methsuximide	10–40 µg/mL	1–3 h 36–45 h	45 µg/mL	2	4.92 and 5.29	[88]	The metabolite is the active principle in vivo
Oxcarbazepine plus 10-hydroxycarbazepine	10–35 µg/mL	5 h 10–20 h	40 µg/mL	2	3.96 and 3.73	[88, 343, 428, 499]	
Phenobarbital	10–40 µg/mL	80–120 h	50 µg/mL	1	4.31	[88, 499]	
Phenytoin	10–20 µg/mL	20–60 h	25 µg/mL	1	3.96	[88, 380, 499]	
Pregabalin	2–5 µg/mL	6 h	10 µg/mL	3	6.28	[68, 77, 88, 343, 432, 499]	
Primidone (active metabolite phenobarbital)	5–10 µg/mL	14–15 h	25 µg/mL	2	4.58	[88, 499]	Data given are restricted to primidone, for the active metabolite phenobarbital recommended plasma concentrations are 10–40 µg/mL
Rufinamid	5–30 µg/mL	7 h	40 µg/mL	2	4.20	[511]	
Stiripentol	1–10 µg/mL	4–13 h	15 µg/mL	2	4.27	[503]	
Sulthiame	2–8 µg/mL	3–30 h	12 µg/mL	2	3.46	[88, 375, 429]	
Tiagabine	20–200 ng/mL	7–9 h	300 ng/mL	2	2.66	[88, 235, 343, 499]	
Topiramate	2–8 µg/mL (morning levels)	21 h	16 µg/mL	3	2.95	[88, 226, 343, 431, 499]	
Valproic acid	50–100 µg/mL	18 h	120 µg/mL	2	6.93	[16, 88, 216, 301, 499, 682, 683]	
Vigabatrin	2–10 µg/mL	5–8 h	20 µg/mL	4	7.74	[88, 342, 398, 499, 719]	
Zonisamide	10–40 µg/mL	60 h	40 µg/mL	2	4.71	[247, 448, 449]	
Anxiolytic/hypnotic drugs							
Alprazolam	5–50 ng/mL	12–15 h	100 ng/mL§	4	3.22	[586, 686]	In chronic users of benzodiazepines, effective plasma concentrations can be markedly higher than in non users.
Bromazepam	50–200 ng/mL	15–35 h	300 ng/mL§	4	3.16	[218, 286, 586]	
Brotizolam	4–10 ng/mL (Cmax)	3–6 h	20 ng/mL	4	2.53	[341, 669]	
Buspirone (active metabolite 6-hydroxybuspirone)	1–4 ng/mL	2–3 h	8 ng/mL&	3	2.59 2.49	[178, 580, 586]	

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Table 5 Continued.

Drugs and active metabolites	Therapeutic reference range/recommended drug concentration	t1/2	Laboratory alert level	Level of recommendation to use TDM (consensus)	Conversion factor (CF, see below)	Reference	Comments
Chlordiazepoxide	400–3 000 ng/mL	5–30 h	3 500 ng/mL	4	3.48	[408, 586]	
Clonazepam	4–80 ng/mL	19–30 h	100 ng/mL	4	3.17	[181, 467, 586]	
Diazepam and metabolites	200–2 500 ng/mL	24–48 h	3 000 ng/mL	4	3.51	[224, 261, 264, 586]	Active metabolites are nordazepam, oxazepam and temazepam
Flunitrazepam	5–15 ng/mL	10–30 h	50 ng/mL	4	3.20	[80, 425]	
Lorazepam	10–15 ng/mL	12–16 h	30 ng/mL	4	3.20	[164, 196, 218, 267]	
Lormetazepam	2–10 ng/mL	8–14 h	100 ng/mL	4	2.98	[3, 515]	
Midazolam	6–15 ng/mL Cmax: 60–80 ng/mL	1–3 h	1 000 ng/mL	4	3.06	[35, 261, 323]	
Nitrazepam	30–100 ng/mL	18–30 h	200 ng/mL	4	3.56	[467, 586]	
Nordazepam	20–800 ng/mL	50–90 h	1 500 ng/mL	4	3.69	[586]	
Opipramol	50–500 ng/mL	11 h	1 000 ng/mL	3	2.87	[386]	
Oxazepam	200–1 500 ng/mL	4–15 h	2 000 ng/mL	4	3.49	[586]	
Pregabalin	2–5 µg/mL	6 h	10 µg/mL	3	6.28	[76, 77]	
Temazepam	20–900 ng/mL	5–13 h	1 000 ng/mL	4	3.51	[586]	
Triazolam	2–20 ng/mL	1–5 h	40 ng/mL§	4	4.12	[586]	
Zolpidem	80–150 ng/mL	1–4 h	300 ng/mL	4	3.23	[586]	
Zopiclone	10–50 ng/mL	5 h	150 ng/mL	4	3.48	[586]	Unstable at room temperature
Antidementia Drugs							
Donepezil	30–75 ng/mL	70–80 h	75 ng/mL	2	2.64	[492, 563, 652]	
Galantamine	30–60 ng/mL	8 h	90 ng/mL	3	3.48	[322, 333, 734]	
Memantine	90–150 ng/mL	60–100 h	300 ng/mL	3	5.58	[251, 378]	
Rivastigmine	oral 8–20 ng/mL (1–2 h after dose) Patch 5–13 ng/mL (1 h before application of a new patch)	1–2 h	40 ng/mL	3	4.00	[597] 147, 391]	
Drugs for treatment of substance related disorders							
Acamprosate	250–700 ng/mL	13 h	1 000 ng/mL	3	8.68	[287, 288, 424]	
Buprenorphine	0.7–1.6 ng/mL Cmax: < 9 ng/mL after 24 mg	2–5 h	10 ng/mL (Cmax)	2	2.38	[120, 130, 383]	
Bupropion plus Hydroxybupropion	550–1 500 ng/mL	20 h 20 h	2 000 ng/mL	2	4.17 3.91	[345]	Bupropion is unstable, plasma or serum must be stored frozen (−20°C) after blood withdrawal In a clinical trial 300 mg was the most effective dose with resulting plasma concentrations as indicated
Clomethiazol	100–5 000 ng/mL	2–5 h		4	6.19	[672]	In alcohol dependent patients much higher plasma concentrations may be tolerated than in healthy subjects
Disulfiram	50–400 ng/mL	7 h	500 ng/mL	3	3.37	[203, 344, 586]	Disulfiram (DSF) is a prodrug, its active metabolite diethylthiomethylcarbamate (DDTC-Me) has been suggested as a possible marker for proper dose titration of disulfiram [344]. In a pharmacokinetic study under 300 DSF mean ± SD steady state concentrations of DSF amounted to 170 ± 10 ng/mL those of DDTC-Me to 290 ± 20 ng/mL.
Levomethadone	250–400 ng/mL	14–55 h	400 ng/mL 100 ng/mL§	2	3.23	[146]	§In non users of opiates, effective or toxic plasma concentrations are markedly lower than in users. Chronic users may even need "toxic" concentrations in blood to avoid the occurrence of withdrawal symptoms.
Methadone	400–600 ng/mL	24–48 h	600 ng/mL 300 ng/mL§	2	3.23	[146, 188, 595]	

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Table 5 Continued.

Drugs and active metabolites	Therapeutic reference range/recommended drug concentration	t1/2	Laboratory alert level	Level of recommendation to use TDM (consensus)	Conversion factor (CF, see below)	Reference	Comments
Naltrexone plus 6β-naltrexol	25–100 ng/mL	4 h 13 h	200 ng/mL	2	3.06 3.04	[99, 211, 252, 424]	
Varenicline	4–5 ng/mL	24 h	10 ng/mL	3	4.73	[202, 532]	
Antiparkinson drugs							
Amantadine	0.3–0.6 µg/mL	10–14 h	1.2 µg/mL	3	5.98	[320]	
Biperiden	Cmax. 1–6.5 ng/mL 0.5–2 h after 4 mg	18–24 h	13 ng/mL	3	3.21	[270]	
Bornaprine	Cmax. 0.7–7.2 ng/mL 1–2 h after 4 mg	30 h	14 ng/mL	3	3.04	[433]	
Bromocriptine	Low dose (2.5mg): 0.1–0.3 ng/mL Max. dose (25 mg): 1.0–4.0 ng/mL	38 h	8 ng/mL	3	1.53	[168]	
Cabergoline	Cmax. 58–144 pg/mL at 0.5–4 h after drug intake for 4 weeks	63–68 h	390 pg/mL	3	2.21	[168]	Unstable at room temperature, plasma or serum should be stored frozen (< − 20 °C)
Carbidopa	Cmax. 20–200 ng/mL after 2 h	2 h	400 ng/mL	3	4.42	[574]	Unstable at room temperature, plasma or serum should be stored frozen (< − 20 °C)
Levodopa O-Methyldopa	Cmax.0.9–2.0 µg/mL 0.6–0.9 h after 250 mg combined with 25 mg carbidopa 0.7–10.9 µg/mL	1–3 h	5 µg/mL	3	5.07	[4, 135, 394, 479, 574]	Unstable at room temperature, plasma or serum should be stored frozen (< − 20 °C) Elimination half-life and plasma concentrations increases under comedication with carbidopa or benserazide
Entacapone	Cmax. 0.4–1.0 µg/mL	0.5 h	2 µg/mL	3	3.28	[304, 570]	Unstable at room temperature, plasma or serum should be stored frozen (< − 20 °C)
Pramipexole	0.39–7.17 ng/mL	8–12 h	15 ng/mL	3	4.73	[730]	
Ropinirole	0.4–6.0 ng/mL	3–10 h	12 ng/mL	3	3.84	[657]	
Tiapride	Cmax. 1–2 µg/mL	3–4 h	4 µg/mL	3	3.05	[108]	
Tolcapone	Cmax. 3–6 µg/mL	2 h	12 µg/mL	3	3.66	[177, 346]	
Other Drugs							
Atomoxetine	200–1 000 ng/mL 60–90 min after intake of 1.2 mg/kg/day	4 h	2 000 ng/mL	3	3.91	[233, 302, 446, 583]	Recommended reference ranges indicate Cmax measured in remitters. Elimination half-life is 21 h in PM of CYP2D6
Dexmethylphenidate	13–23 ng/mL 4 h after 20 mg	2	44	2	4.29	[663]	5.2–5.5 ng/mL are associated with 50 % dopamine transporter blockade [614]
Methylphenidate	13–22 ng/mL d-methyl-phenidate 2 h after 20 mg immediate release or 6–8 h after 40 mg extended release	2 h	44 ng/mL	2	4.29	[331, 422, 614, 615]	Methylphenidate is unstable at room temperature, recommended reference range indicates Cmax
Modafinil	1 000–1700 ng/mL after 200 mg/day	10–12 h	3 400 ng/mL	3	4.21	[733]	

Plasma concentrations given in mass units can be converted to molar units by multiplication with the conversion factor (CF) nmol/L = ng/mL x CF

[&]Active metabolite contributes to wanted and unwanted effects. Indicated reference ranges and laboratory alert levels refer to the mother compound only.

For bupropion, carbamazepine, lamotrigine and valproic acid recommended reference ranges were listed twice in accordance with the 2 different indications.

Prepared by CH, PB, SU, BR and HK, reviewed by AC, OD, KE, MF, MG, CG, GG, EH, UH-R, CH, EJS, HK, GL, UL, TM, BP, BS, MU, SU, GZ

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valproic acid, which are therefore listed twice in **Table 5**. Moreover, it should be mentioned that studies are on the way to evaluate therapeutic reference ranges for children or adolescent patients and for elderly patients.

Estimation of the lower limit of the therapeutic reference range

Estimation of a therapeutic reference range (TRR) requires estimation of a lower and an upper limit of drug concentration in plasma. A generally accepted method for calculation of these limits does not exist. Whenever possible the lower limit of a drug's therapeutic range should be based on studies on the relationship between a drug's plasma concentration and clinical effectiveness. Below this limit, therapeutic effects are not significantly different from placebo. The optimum study design for evaluation of the lower limit of the therapeutic range is a prospective double-blind study where patients are treated with drug doses which lead to a defined plasma concentration range of the drug. Such a design was applied by Van der Zwaag and coworkers for patients treated with clozapine [678]. Patients were titrated to 3 different plasma concentrations of the antipsychotic drug. Significant superiority was found in patients with middle and high plasma concentration compared with low concentrations of clozapine. A similar design was applied for a blood-level study comparing imipramine and mirtazapine [98]. To conduct such studies, however, is a considerable logistic challenge. Fixed dose studies are therefore preferred for evaluation of the lower limit of the therapeutic reference range [672, 674].

For the estimation of threshold values of the therapeutic reference range, receiver operating characteristic (ROC) analysis has proven helpful [289]. 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 "medication plasma concentration". The usefulness of the ROC analysis has been demonstrated for a number antipsychotic and antidepressant drugs [461, 505, 510, 703].

Estimation of the upper limit of the therapeutic reference range

In the first study on TDM in psychiatry [31] an U-shaped relationship between plasma concentration and clinical effect was reported for nortriptyline. The lack of effect at high concentrations was attributed to the mechanism of action of the tricyclic antidepressant drug on monoaminergic neurons. According to actual knowledge, however, it seems more likely that reduced amelioration at high concentrations is due to side effects. The upper limit of the therapeutic range is therefore defined by the occurrence of side effects, also in this guideline. For most side effects (type A adverse reactions), it is also assumed that they are a function of dose and drug concentration in the body [335]. This assumption has been confirmed for motor side effects of antipsychotic drugs [536] and for unwanted side effects of tricyclic antidepressant drugs [153, 282]. For paroxetine, a positive correlation was found between drug concentration in plasma and serotonin syndrome symptoms [303]. When such data are available, it is possible to apply ROC analysis for the calculation of the upper limit of the therapeutic range [461]. For many psychotropic drugs listed in **Table 5**, however, valid data on both plasma concentration and the incidence of side effects are lacking. Case reports on tolerability problems or intoxications do often not include drug concentration measurements in plasma. Sporadic reports on fatal cases and intoxications are of limited value. Most blood concentrations reported to have caused death are far above drug concentrations that are associated with maximum therapeutic effects [544, 622]. Post mortem redistribution of medications from or into the blood can lead to dramatic changes in blood levels [382, 518], and the direction of the change does not follow a general rule [359]. Estimation of an upper threshold level above which tolerability decreases or the risk of intoxication increases is therefore more difficult than estimation of the lower threshold level, especially for drugs with a broad therapeutic index like SSRIs.

Estimation and definition of a laboratory alert level

As explained above, plasma concentrations with an increased risk of toxicity are normally much higher than the upper threshold levels of the therapeutic reference ranges for most psychotropic drugs shown in **Table 5**. For the present guidelines, we therefore defined an upper plasma concentration limit above which it seems unlikely that therapeutic effects may be enhanced and added a "laboratory alert level" which was defined as follows:

Definition

The **"laboratory alert levels"** reported in this guideline (**Table 5**) indicate drug concentrations above the recommended reference range that causes the laboratory to feedback immediately to the prescribing physician. The alert levels are based on reports on intolerance or intoxications and plasma concentration measurements. In most cases, however, it was arbitrarily defined as a plasma concentration 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 intolerance or toxicity. When the high drug concentration is well tolerated by the patient and if dose reduction bears the risk of symptom exacerbation, the dose should remain unchanged. The clinical decision, especially in case of unchanged dose needs to be documented in the medical file.

From population-based to subject-based reference values

All therapeutic reference ranges listed in **Table 5** are orienting, population-based ranges. The population-derived ranges constitute descriptive statistical values which may not necessarily be applicable to all patients. Individual patients may show the optimum therapeutic response under a drug concentration that differs from the therapeutic reference range. Psychopharmacotherapy should therefore try to identify a patient's "individual therapeutic concentration" to guide the treatment [61, 523]. For lithium it has been shown that the recommended plasma concentration range depends on whether the patient is in an acute manic episode or needs maintenance therapy [593]. For clozapine, Gaertner and colleagues [232] determined optimal plasma concentrations required for stable remission of individual patients under maintenance therapy in a relapse prevention study.

Recommendations for measuring plasma concentrations of psychoactive drugs

The usefulness of TDM varies with the clinical situation and the particular drug involved. In case of suspected non-adherence to medication or intoxications, quantifying plasma concentrations is a generally accepted tool for all drugs and groups of patients. However, it is still a matter of debate if TDM should be imple-

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mented in clinical routine. Based on empirical evidence, 5 levels of recommendation to use TDM were defined in the guidelines 2004 for 65 psychotropic drugs. These definitions were revised and grading reduced to 4 levels of recommendation, now ranging from "strongly recommended" to "potentially useful" as follows:

Definitions

Level 1: Strongly recommended

Evidence: Reported drug concentrations are established and evaluated therapeutic reference ranges. Controlled clinical trials have shown beneficial effects of TDM, reports on decreased tolerability or intoxications.

Recommendation: TDM is strongly recommended for dose titration and for special indications. For lithium, TDM is a standard of care.

Clinical consequences: At therapeutic plasma concentrations highest probability of response or remission; at "subtherapeutic" plasma concentrations: response rate similar to placebo under acute treatment and risk of relapse under chronic treatment; at "supratherapeutic" plasma concentrations: risk of intolerance or intoxication.

Level 2: Recommended

Evidence: Reported drug concentrations were obtained from plasma concentrations at therapeutically effective doses and related to clinical effects; reports on decreased tolerability or intoxications at "supratherapeutic" plasma concentrations.

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" plasma concentrations: risk of poor response; at "supratherapeutic" plasma concentrations: risk of intolerance or intoxication.

Level 3: Useful

Evidence: Reported drug concentrations were calculated from plasma concentrations at effective doses obtained from pharmacokinetic studies. Plasma concentrations related to pharmacodynamic effects are either not yet available or based on retrospective analysis 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 plasma concentrations are plausible for a given dose, or clinical improvement may be attained by dose increase in non-responders who display too low plasma concentrations.

Level 4: Potentially useful

Evidence: Plasma concentrations 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 literature-based evaluations, TDM was graded as "strongly recommended" for 15 of the 128 surveyed neuropsychiatric compounds, "recommended" for 52 medications, "useful" for 44 drugs and "potentially useful" for 19 drugs (**Table 5**).

TDM is highly recommended for most tricyclic **antidepressants**. It reduces the risk of intoxications [103, 381, 459, 510, 525, 527, 528, 530, 718], and for many tricyclic antidepressants, a plasma concentration – clinical effectiveness relationship has been shown. For SSRIs, TDM is of little clinical importance in clinical practice [6, 537, 644]. Toxicity of this type of antidepressants is low in comparison to most of the pre-SSRI antidepressants [48, 166, 314, 646, 715]. Data from Sweden revealed that TDM of SSRIs is cost-effective in elderly patients where it helped to use minimum effective doses [410]. For citalopram a recent observational study revealed that plasma concentrations on day 7 of treatment are predictive for later non-response [491]. Patients exhibiting citalopram plasma concentrations below 50 ng/mL had a significantly reduced improvement on the Hamilton rating scale for depression. 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, the monoamine oxidase inhibitors moclobemide and tranylcypromine.

TDM is strongly recommended for the **typical antipsychotic drugs** haloperidol, perphenazine and fluphenazine, and for the atypical antipsychotics amisulpride, clozapine, olanzapine, and risperidone (**Table 5**). Overdosing may lead to extrapyramidal side effects. In the case of clozapine, there is a strong correlation between clozapine plasma levels and incidence of seizures. Avoiding overdosing of typical antipsychotic drugs by TDM is for the majority of patients a matter of quality of life rather than safety [136]. TDM of antipsychotics is also useful when medication is switched from the oral to the depot form, or vice versa.

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 5**). For lithium TDM is even the standard of care [133, 170, 185, 280, 395, 593, 706, 721]. For its long-term use, plasma concentrations of 0.5–0.8 nmol/L are advised. 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, though there is evidence that it can be useful. For donepezil, it has been shown that the patients' improvement was significantly better if their plasma concentrations were above 50 ng/mL as compared to patients that showed lower drug concentrations [563].

Most **anxiolytic** and **hypnotic drugs** belong to the class of benzodiazepines. Anxiolytic and hypnotic effects are rapid. Treatment can therefore be guided by immediate clinical impression rather than by TDM. In case of lack of therapeutic effects under usual doses, however, TDM may clarify if non-response was due to drug abuse that has led to tolerance or due to pharmacokinetic abnormalities. For alprazolam, TDM may be useful to suppress panic attacks [722].

The **opiate agonists** methadone, R-methadone (levomethadone), buprenorphine, l-α-acetylmethadol (LAAM) and slow-release formulations of morphine are used for the treatment of opioid addiction. TDM is indicated for patients treated with methadone or R-methadone. The usefulness of TDM for monitoring treatment with "anti-craving" medications such as acamprosate or naltrexone, employed for the treatment of alcohol use disorders, has recently been reviewed elsewhere [99]. TDM was recommended to enhance the moderate efficacy of these drugs.

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For **anticonvulsant drugs**, TDM is well established, especially for old drugs which are more toxic than the new ones [499].

For **antiparkinson drugs**, TDM has not been established so far. For the dopamine agonists, data on reference ranges are scarce. For L-dopa, there is an imperfect correlation between plasma concentrations and short-term clinical response [479]. Nevertheless, we considered the pharmacologic properties of these neurological drugs (**Table 1, 5**), since psychiatric patients may receive antiparkinson drugs that possibly interfere with the action of psychotropic medication. For most of these drugs Cmax values are given.

Indications for measuring plasma concentrations of psychoactive drugs

Table 6 presents a list of indications for TDM in psychiatry. The validity of these indications has to be examined on an individual basis 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 well defined therapeutic reference ranges or with a narrow therapeutic index it makes sense to measure plasma levels 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 these drugs. This holds true for lithium, tricyclic antidepressants, several antipsychotics or anticonvulsants (**Table 5**). For lithium, TDM is even mandatory for safety reasons.

In case of **suspected non-adherence** or lack of clinical improvement under recommended doses: TDM is a valid tool for treatment with all drugs considered in these guidelines. Loss of adherence is a major problem of long-term medication [10,55,401]. In patients with schizophrenia [55,351] and in patients with unipolar or bipolar disorders non-adherence ranges from 10 to 69% [401,439]. Methods used to measure adherence include pill counting, examining case-note recordings, interviewing patients or noting the attending physicians' clinical judgement about adherence [11,355,685,708]. Studies have shown that clinicians cannot reliably predict their patients' adherence [104,579]. TDM is advantageous, since it is an objective method and tells the prescribing physician if the drug is in the body at a concentration that is potentially sufficient for the expected clinical response. Deviations from the expected dose-related reference range (**Table 4**) indicate if the patient has taken his/her medication, and concomitant determination of metabolites is another approach to clarify if the drug was taken continuously as recommended. For interpretation, however, possible interactions with co-medications exhibiting enzyme inhibiting or inducing properties must be considered (**Table 3**). Reis and coworkers [546,547] analysed the compliance 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 ratios of concentrations of norsertraline to sertraline were highly indicative for hidden and partial non-adherence. To be able to use this approach, these guidelines were supplemented with data on ratios of concentrations for 32 psychoactive drugs (**Table 2**). By taking several blood samples per day and by calculation the observed and expected time dependent plasma concentrations it can be differentiated if a low plasma concentration is due to reduced bioavailability, enhanced degradation or poor adherence. Pharmacokinetic modelling of the expected time dependent plasma concentration thereby considers a drug's basic pharmacokinetic properties [4,78,340,626,654].

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

When **adverse effects** are associated with clinical improvement under recommended doses, measurement of the plasma concentration may clarify if side effects are related to excessively high drug levels in the blood and if the dose should be decreased.

When **combining medications** that are inhibitors or inducers of drug metabolizing enzymes (**Table 1**), pharmacokinetic drug interactions will occur if the comedication is a substrate of the inhibited or induced enzyme (**Table 3**). Dose adaptation should be guided by TDM in combination with an inducer or inhibitor and avoid loss of action, poor tolerability or intoxication due to a pharmacokinetic drug-drug interaction [215,244,594]. With regard to environmental factors smoking is of high clinical relevance for drugs that are substrates of CYP1A2 (**Table 1**). The isoenzyme is dose dependently induced by constituents of cigarette smoke (polycyclic aromatic hydrocarbons, not nicotine). Its activity increases by 1.2-fold, 1.5-fold for 1.7-fold for 1–5, 6–10 and >10 cigarettes smoked per day [201]. On the other hand, CYP1A2 activity decreases until the fourth day immediately on cessation of heavy smoking [200]. Smoking effects should therfore be considered when patients are under therapy with a CYP1A2 substrate (**Table 1**) such as clozapine [81,676], duloxetine [222] or olanzapine [749]. It should also be mentioned that many pharmacokinetic drug-drug interactions have been found by TDM either by chance or by retrospective analysis of TDM data bases [112,537].

In **pharmacovigilance programs**, the safety of drug use is supervised under naturalistic conditions [271,285]. In case of observed adverse events, measurement of plasma concentrations is most helpful for clarification [335].

Relapse prevention is a major goal of maintenance treatment. Reduction of relapse rates by TDM is highly cost-effective, as relapses can lead to hospitalization [377]. In schizophrenic patients, it has been shown that fluctuations of clozapine plasma concentrations are predictive for relapses [232,670] and rehospitalizations [627]. In these patients, TDM may help reduce the risk of relapse or recurrence by increasing adherence to the medication. One day in the hospital is 4–16 times more expensive than a single drug concentration measurement in the laboratory.

Recommendation

Though clinical evidence is still scarce, we recommend regular monitoring of plasma concentrations under maintenance therapy, at least every 3–6 months, to prevent relapses and rehospitalizations. The frequency of TDM requests may be increased if patients are known to be non-adherent to the medication or in case of changes of co-medications or of smoking that affect the pharmacokinetics of the drug.

In patients exhibiting **genetic peculiarities** of drug metabolizing enzymes, doses must be adapted. Kirchheiner and coworkers [362,365] calculated doses for PM or UM of CYP2D6 based on pharmacokinetic and pharmacodynamic findings. However, even in the case of a confirmed abnormal CYP genotype, TDM is recommended, because genotyping can only roughly predict to

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which extent the plasma concentration may be changed in the individual patient [496,497,625].

For **special groups of patients**, such as pregnant or breastfeeding patients, children or adolescent patients [22,373,194], individuals with intellectual disabilities [158,300], or elderly patients, especially patients aged above 75 years [374], TDM is highly recommended.

Any psychopharmacologic therapy of pregnant or breastfeeding women should assure that the plasma concentration of the drug is in the therapeutic reference range to minimize the risk of relapse on the mother's side and, at the same time, to minimize risks associated with drug exposure of the fetus or the child [169,174]. Renal clearance and the activity of the CYP isoenzymes 3A4, 2D6 and 2C9, and uridine 5′-diphosphate glucuronosyltransferase are increased during pregnancy, whereas activities of CYP1A2 and 2C19 decrease [21]. TDM in pregnant women and/or mothers should be carried out at least once per trimester and within 24 h after delivery [65].

Many psychoactive drugs are not approved for use in children or adolescents [248]. Pharmacokinetics and pharmacodynamics change during development [194,438,514,516]. In adolescents suffering from psychotic disorders, comorbid drug abuse is very common, and compliance with an antipsychotic treatment is generally marginal [318]. Therefore, TDM is recommended in these patients. To raise data on the effectiveness and tolerability of psychoactive drugs under every day conditions, a TDM network was established for child and adolescent patients [see http://www.tdm-kjp.de/eng/contact.html].

In **elderly patients**, who frequently are hypersensitive to medication, TDM is helpful to distinguish between pharmacokinetic and pharmacodynamic factors when adverse effects occur [666]. Ageing involves progressive impairments of the functional reserve of multiple organs [407], especially renal excretion, and body composition changes significantly [361,374]. Hepatic clearance can be reduced by up to 30%. Phase I reactions are more likely to be impaired than phase II reactions. On the other hand, there are no age-dependent changes in CYP isoenzyme activity [374]. Age-related changes in physiologic and pharmacokinetic functions as well as the comorbidity and polypharmacy complicate pharmacotherapy in the elderly [125]. Therefore, TDM should be used for these patients to improve safety and tolerability of psychopharmacotherapy.

In **individuals with intellectual disabilities**, new generation antipsychotic drugs are frequently used. Recently published guidelines recommend TDM for these patients, at least when treated with risperidone or olanzapine [158]. For ethical and legal reasons, patients with intellectual disabilities are excluded from clinical trials. On the other hand, many of these patients need medication. In these individuals, it may be difficult to differentiate between morbogenic and pharmacogenic reasons for symptom aggravation. Though evidence is poor, TDM is recommended to guide the pharmacotherapy of these patients [158].

In **forensic psychiatry** the primary aim of pharmacotherapy, consisting mostly antipsychotic drugs, is reduction of dangerous behaviour [458,462]. To consistently reduce the risk of violence and aggression, adherence to the prescribed medication is essential [658]. Therefore, TDM is recommended for this group of psychiatric patients. It is, however, not clear if effective plasma concentrations are identical in forensic and general psychiatry patients. Castberg and Spigset [113] analyzed data obtained by survey in a high security forensic unit and found higher doses in forensic patients than in a control group. The dose related plasma concentrations were significantly lower for olanzapine but higher for quetiapine in the forensic patients than in the control group.

Table 6 Typical indications for measuring plasma concentrations of medications in psychiatry.

– Dose optimization after initial prescription or after dose change
– Drugs, for which TDM is mandatory for safety reasons (e. g., lithium)
– Suspected complete or partial non-adherence (non-compliance) to medication
– Lack of clinical improvement under recommended doses
– Adverse effects and clinical improvement under recommended doses
– Combination treatment with a drug known for its interaction potential or suspected drug interaction
– TDM in pharmacovigilance programs
– Relapse prevention under maintenance treatment
– Recurrence under adequate doses
– Presence of a genetic particularity concerning drug metabolism (genetic deficiency, gene multiplication)
– Pregnant or breast feeding patient
– Children and adolescent patient
– Elderly patient (>65 y)
– Individuals with intellectual disabilities
– Patients with pharmacokinetically relevant comorbidities (hepatic or renal insufficiency, cardiovascular disease)
– Forensic patient
– Problems occurring after switching from an original preparation to a generic form (and vice versa)

The indication "**problem occurring after switching from an original preparation to a generic form (and vice versa)**" is still under-investigated and data are scarce [124,139].

Another potential indication for TDM not listed in ◉ **Table 6** is the increasing availability of counterfeit drugs on the internet [599]. WHO launched a program in 2006 to combat this illegal industry. There are no data published on this type of market concerning psychotropic drugs, but patients may be co-medicated (mostly auto-medication) with other drugs obtained from this source. The counterfeit medications may not comply with purity and dosage standards and therefore increase the risk for interactions.

Practical Aspects for TDM in Psychiatry

Essential for an effective TDM service is the availability of appropriate analytical methods that produce results within a reasonable time, i. e., 48 h, and advice from someone who understands pharmacokinetics and therapeutics [184]. As shown in ◉ **Fig. 1**, the TDM process starts with the request and ends with the final decision about how to adjust a given patient's therapeutic regimen by the health care professional.

Request for plasma concentration quantification

As mentioned above, TDM should only be requested when there is evidence that the result will provide an answer to a specific question. If it is not clear what the question is, the answer is of little value. Typical indications are listed in ◉ **Table 6**. 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 plasma concentration is either due to poor compliance, reduced bioavailability or abnormally rapid elimination.

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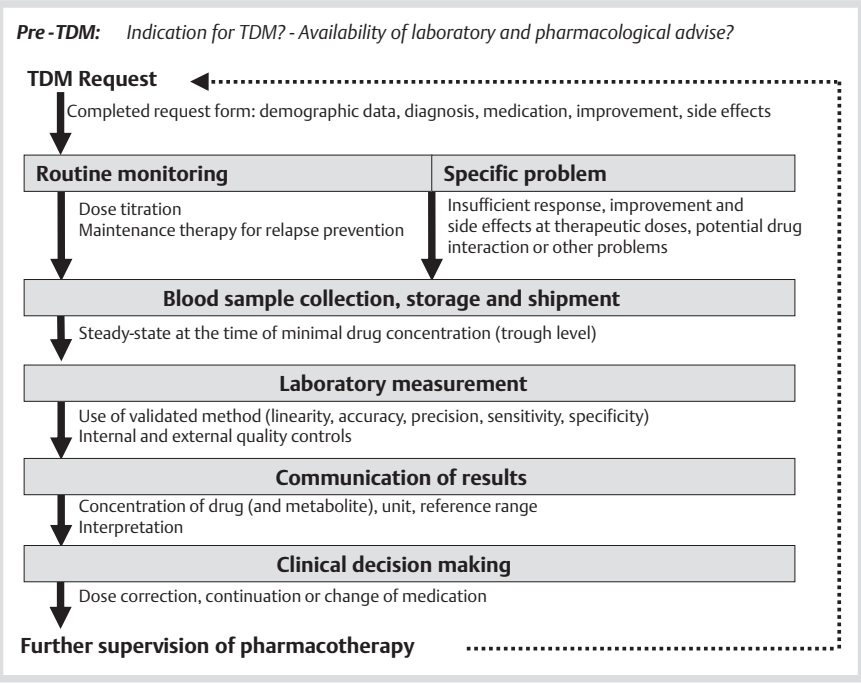

Fig. 1 Schematic overview of the TDM process as a guide for psychopharmacotherapy. Routine TDM is primarily applied to drugs with a narrow therapeutic index and a well-defined therapeutic reference range. However, TDM is useful for any psychotropic drug when addressing special therapeutic problems such as "therapy refractoriness" or side effects under recommended dosage.

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 (>10cig/day) Genotype to be considered (e.g. CYP2D6, CYP2C9, CYP2C19): _____	

REASON FOR REQUEST
(tick more than one if applicable)
☐ Control of adherence
☐ Dose adaptation
☐ Insufficient improvement
☐ Adverse effects (specify below)
☐ 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)

SIDE EFFECTS *(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 ☐ Hypokinesia/Akinesia ☐ Hyperkinesia ☐ Tremor
☐ Akathisia ☐ Epilepticseizures ☐ 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**	**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 2 ml serum or plasma.*

Date of sample receipt: _____

Signature: _____

Fig. 2 Request form for therapeutic drug monitoring in psychiatry.

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TDM requests must include a completed request form (**Fig. 2**) which is essential for effective drug concentration measurements and an adequate interpretation of the results [501,635]. The form should contain the patient 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 blood withdrawal. A brief comment on the clinical situation should be given for interpretation of the results. We recommend to use objective symptom rating, e.g., application of the clinical global impression (CGI) scale [283], to measure severity of illness and therapeutic improvement. The summary form of the UKU scale is useful to evaluate the occurrence and severity of side effects [402]. However, documented feedback to questionnaires indicates that clinicians often do NOT want to put that much information on the form. Moreover, the filled-in information is often not accurate. As an alternative, feedback by phone may be offered for interested physicians.

When interpretation of the results is requested from the laboratory, it is absolutely necessary to fill out the request forms adequately and completely. Thereby 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. Computerized ordering, however, is still not widely used. But effective packages are on the way to become available (e.g., www.konbest.de).

Blood sample collection

Generally, TDM is carried out in plasma or serum samples. The analysis of whole blood, which is long established for immunosuppressant drugs by using immunoassays [693], has been abandoned for TDM in psychiatry. There is no consensus whether plasma or serum should be preferred. Definite experimental data are still lacking which clearly demonstrate differences in the drug concentrations using either plasma or serum. The few available comparisons indicate that values obtained from serum or plasma can be used interchangeably [308]. Most psychoactive drugs are intensively bound to blood cells of plasma proteins. Concentrations of neuropsychiatric drugs reported in this guideline refer to the total drug fraction in accordance with the literature. 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 [555]. 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 [506]. Therefore it seems likely that the clinical response depends on the total drug fraction. Analysis of psychotropic medications 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. Saliva offers the advantage of non-invasive collection [20,25,356]. However, the drug concentration in saliva corresponds to the free (i.e., non-protein-bound) fraction of the drug in blood – which is for most psychopharmacologic medications only 10% or less of the total concentration. Thus detection problems may occur when using saliva instead of blood plasma or serum. In any case, more data will have to be obtained for saliva as a matrix for measurement of drug concentrations.

With few exceptions, TDM relies on trough steady-state plasma concentrations. Blood should therefore be collected after at least 4 drug elimination half-lives after the start of or a change in dosage and during the terminal ß-elimination phase. For most psychotropic drugs, elimination half-lives vary between 12 and 36 h (**Table 5**). Notable exceptions are quetiapine, trazodone, or venlafaxine, which display elimination half-lives around 6 h. Fluoxetine and aripiprazole have longer elimination half-lives. In clinical practice, the appropriate sampling time for most psychoactive 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 if the drug is given once daily in the morning) after the last medication. If, for logistics 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 for interpretation. Trough levels can then be extrapolated by pharmacokinetic modelling.

In patients treated with a depot preparation of an antipsychotic drug, blood should be sampled immediately before the next injection. Formulations of antipsychotic drugs such as haloperidol decanoate or risperidone microspheres are characterised by a slow absorption after intramuscular administration. Maximum plasma concentration of first generation depot antipsychotics are reached after 1–14 days after injection, and the apparent elimination half-life is 2–3 weeks [647]. Similar properties exhibits the newly introduced paliperidone palmitate [131]. For risperidone microspheres the mean time to peak concentrations is 4 weeks and its plasma half life 4–6 days [647]. For other drugs delivered in extended or retarded release formulations like paliperidone [70] or quetiapine [212], special attention has to be given to the time of drug intake for correct interpretation (see **Table 5**). In these formulations, the time of maximum plasma concentration is delayed but the elimination half-life remains essentially unchanged. The long acting olanzapine pamoate is a new depot formulation [399]. The salt 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 plasma concentrations and may lead to marked sedation and delirium, the so called post-injection syndrome [399,647]. Considering this special problem it could be useful to control plasma concentrations of olanzapine shortly (i.e., about 2 h) after the i.m. injection to monitor if plasma concentrations increase. This approach, however, relies on the rapid quantification of olanzapine.

TDM may of course be carried at any time after drug ingestion if unexpected side effects are observed. It is not necessary to measure trough levels, but the dosing schedule should be reported for interpretation.

Storage and shipment of blood samples

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. 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 [305]. Exceptions are light and/or oxygen sensitive substances. For the determination of bupriopion or methylphenidate, however, serum samples must be frozen or extracted and stabilized immediately after blood withdrawal and centrifugation (see **Table 5**). Olanzapine must be stored frozen (–20 °C) if not analysed within 72 h [305]. The laboratory should give instructions on its web site or the request form how

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to collect (plasma volume, labelling of the samples), store and mail the sample.

Laboratory measurements

Selective and sensitive analytical methods for the quantitative evaluation of drugs and their metabolites (analytes) are essential for the successful conduct of TDM. Methods must be validated which includes all of the procedures that demonstrate that a particular method used for quantitative measurement of analytes in a given biological matrix is reliable and reproducible for the intended use. The fundamental parameters for this validation include (1) accuracy, (2) precision, (3) selectivity, (4) sensitivity, (5) reproducibility and (6) stability. Validation involves documenting, through the use of specific laboratory investigations, that the performance characteristics of the method are suitable and reliable for the intended analytical applications. The acceptability of analytical data corresponds directly to the criteria used to validate the method [114,219].

For psychoactive drugs, chromatographic techniques (gas chromatography (GC), and high-performance liquid chromatography (HPLC), in combination with suitable detection methods, are preferred [186]. They are sufficiently precise, accurate and robust and can be adapted to the analysis of a huge number of drugs. 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 GC or 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 [269,292–294,297, 298,702,710] and antipsychotic drugs [368,369,571–573,709–712]. Another high-throughput chromatographic method is liquid chromatography coupled with mass spectroscopy (LC-MS) especially tandem MS (LC-MS/MS). LC/MSMS methods can be applied to almost any psychotropic drug including metabolites [577]. They are most sensitive and selective and can be used without time-consuming sample preparation. Many compounds can be analysed simultaneously. An excellent example is the LC-MS/MS method described by Kirchherr and Kühn-Felten [366]. This method was validated for over 50 psychoactive drugs. Disadvantageous for LC-MS/MS methods are high costs. Moreover, quantification can be problematic due to ion suppression and the availability of suitable calibration standards, preferentially deuterated analogues [584].

In case of suspected intoxications, TDM methods should enable drug analysis within 1–2 h [215]. For this purpose automated methods are advantageous.

The laboratory should not only analyse the drug but also its active metabolites, e.g., bupropion plus hydroxybupropion, clomipramine plus desmethylclomipramine, fluoxetine plus norfluoxetine, naltrexone plus naltrexol, risperidone plus 9-hydroxyrisperidone or venlafaxine plus O-desmethylvenlafaxine (**Table 5**). For some drugs, the determination of metabolites that do not contribute to the overall clinical effect (e.g., norsertraline, normirtazapine, norcitalopram) is also useful to monitor drug adherence of the patient [546], to get information on his/her capacity to metabolise drugs, or to interprete drug-drug interactions when drugs are involved exhibiting enzyme inhibiting or inducing properties (**Table 2**). "Normal" ratios of concentrations of metabolites to parent drugs that are expected in 68.3 % of the patients are listed in **Table 3**. Any ratio outside the reported "normal" range should be considered as a signal pointing to individual abnormalities due to a drug-drug-interaction, gene polymorphism, altered liver function, non-adherence or drug intake few hours before blood withdrawal.

The assay of enantiomers of chiral compounds requires either stereoselective derivatisation of the drugs prior to their quantification, or their separation by chiral chromatographic GC or HPLC columns. LC-MS/MS may be 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 comedication or by coconsumption 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 [114,219].

To ensure quality and reliability of plasma concentrations 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 those performing the assays and by separate weighing of reference material. Reporting of results requires that the results of the quality controls are within the expected range. 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 was introduced by Cardiff Bioanalytical Services Ltd in 1972 [720]. It has currently 450 participants from 36 countries (www.heathcontrol.com). Instand e.V. (www.instanddev.de/ringversuche/) is another recommended provider of external control, the external quality control scheme was recently expanded to multiple psychoactive drugs samples. Moreover, reference materials are also available from forensic chemistry (http://www.pts-gtfch.de/).

Communication of results

The concentration of the psychoactive drug as well as that of active metabolites contributing to the therapeutic action should be reported with reference ranges (**Table 5**) either in mass or molar units. We recommend the use of mass 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 TDM 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 5**.

When drug concentrations are below the limit of quantification (LOQ), which refers to the lowest concentration of the standard curve that can be measured with at least 20 % accuracy and precision, this limit should be indicated.

The results should be available for decision making within a clinically meaningful time. Although 24 h TDM service would be desirable, 48 h turnaround time is sufficient in most cases. In case of suspected intoxications, a few hours service is necessary [215]. To assist rapid intervention in patients at risk for toxicity or loss of tolerability, prompt information (phone call) of the

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treating physician is required when the laboratory measures drug concentrations above the "laboratory alert level" which was newly defined (see above) in the present consensus guidelines (**Table 5**).

Interpretation of results

We recommend that interpretation and pharmacologic advice are provided with every report. Expert interpretation of a drug concentration measurement and the adequate use of the information are essential to ensure the full clinical benefit of TDM. 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 therefore 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 [335].

Diagnosis and drug dose are important information for interpretation, since they permit a judgement on whether a result is plausible or not. Moreover, it must be controlled if blood samples were collected under recommended conditions, especially when the plasma concentration is unexpectedly high in an outpatient. When the drug was taken a few hours before blood sampling the drug concentration can be several-fold higher than the trough level.

For the interpretation of the results, it should not only be considered whether the plasma concentration of the drug is within the "therapeutic reference range" (**Table 5**). It must also be considered if the drug plasma concentration is consistent with the dose (**Table 4**). A plasma concentration may be outside the therapeutic reference range, just because a low or high dose was taken. In addition, it is wise to take into account the level of evidence underlying the "therapeutic reference range" of the particular drug (**Table 5**). It should also be considered if the daily drug dose was given as a single or a multiple dose.

Often it is necessary to deal with pharmacokinetic properties such as 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 (**Table 3**) to deal with possible drug-drug interactions.

Any drug concentration outside its dose-related reference range (**Table 5**) should alert the TDM laboratory to actively look for non-average pharmacokinetic drug disposition of the patient, drug-drug-interactions, gene polymorphisms that give rise to poor or ultra rapid metabolism, altered function of the excretion organs liver and kidneys, age and/or disease-related changes in the patient's pharmacokinetics, compliance (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) in the laboratory analysis. It may also be informative to calculate the dose related reference range (**Table 4**) if the drug concentration lies outside the recommended therapeutic reference range (**Table 5**) [285].

Plasma concentrations must be interpreted with the clinical presentation in mind. Recommendations on dosage changes constitute the most frequent advice. Other information which could be of help for the physician are those related to genetic polymorphisms, risks of pharmacokinetic interactions in the case of polypragmasy, pharmacokinetic properties of the drug in patients belonging to a "special population", e.g., elderly patients, or patients with hepatic or renal insufficiency. For the treatment of pain, relatively low plasma concentrations of tricyclic antidepressants may be sufficient. They may be within the "dose related reference range" (**Table 4**) but outside the "therapeutic reference range" of **Table 5** 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 plasma 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 abnormal metabolizer.

Since the interpretation of TDM results relies on complex quantitative relationships, training in clinical psychopharmacology and pharmacokinetics and the application of TDM 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.

Clinical decision making

A TDM result is a guide to proper dosing of the individual patient. 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 guided by the best available evidence [310]. The laboratory, however, has only a restricted knowledge of the clinical situation. On the other hand, most treating physicians have limited pharmacokinetic knowledge. Therefore it is essential to be aware that optimal TDM is an interdisciplinary task that requires close communication between laboratory and clinical experts.

If the plasma concentration of the drug is within the therapeutic reference range, an adaptation of the dose is, of course only recommended when clinical reasons, such as adverse effects or non-response clearly justify such a decision. Evidently, 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 for this course of action 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 recently published by the TDM-AGNP group [741].

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

When **adverse effects** are associated with clinical improvement under recommended doses, measurement of the plasma concentration may clarify if side effects 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 or antipsychotic drugs, there is good evidence that clinical non-improvement at week 2 is highly predictive for later response and remission [119, 138, 392, 620, 621, 638]. Especially the absence of early improvement

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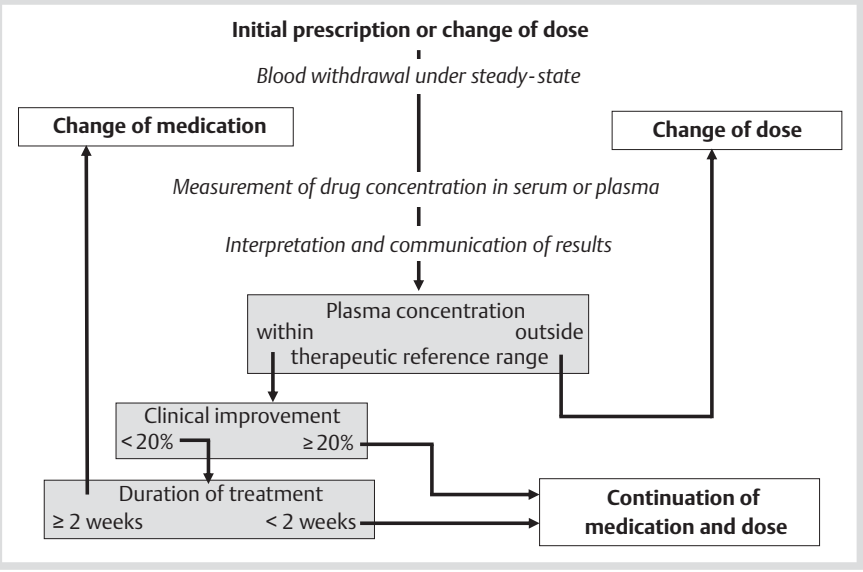

Fig. 3 TDM-guided dose titration of antidepressant or antipsychotic drug treatment (adapted from [311]). Clinical decision making has to consider the clinical improvement, the duration of treatment, and steady-state concentration of the drug in plasma or serum. The steady-state is reached by 94 % after 4 elimination half-lives of the drug or active metabolites (see **Table 5**).

appears to be a highly reliable predictor of later non-response [358]. For dose titration with antidepressant and antipsychotic drugs we therefore recommend to include symptom rating by the treating physician [138] at baseline and at week 2 in addition to drug concentration measurements. **Fig. 3** summarizes the above recommendations in a flow chart.

When further plasma concentration measurements 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 of the drug has to be considered (**Table 5**).

Pharmacogenetic tests in addition to TDM

Concentrations outside the reference range may be due to gene polymorphisms that give rise to slow/rapid metabolizers. As a consequence, the laboratory may also suggest that a pharmacogenetic test should be carried out [14, 144, 158, 193, 335, 362, 365, 377, 623, 624, 675]. Genotyping, however, is not available in all TDM laboratories, and we recommend consultation of specialized laboratories for interpretation of the results.

Situations and cases where pharmacogenetic tests could advantageously be combined with TDM are explained in more detail by Jaquenoud Sirot and coworkers [335]. Some of the most important indications for the combination of genotyping with TDM are the following:

- the patient is treated with a substrate the metabolism of which shows a wide interindividual variability;
- a drug is characterized by a small therapeutic index: risk of toxicity in the case of a genetically impaired metabolism, or on the other hand, risk of non-response due to an ultrarapid metabolism and the inability to reach therapeutic drug levels;
- the patient presents unusual plasma concentrations of the drug or its metabolite(s) and genetic factors are suspected to be responsible;
- the patient suffers from a chronic illness, which requires lifelong treatment.

In a patient who is genotyped as a PM or UM, the medication should not automatically be replaced by another as suggested by some authors, but the dose can often be adapted, using clinical judgement and TDM.

Conclusions and Perspectives

The choice of pharmacologic treatment should always take into account the clinical presentation of the patient and consider psychopathology and drug history. TDM is, if used appropriately, a valid tool for optimising pharmacotherapy. During the past decades, knowledge on the metabolic fate and actions of psychotropic drugs in the human body has markedly advanced. Pharmacogenetic and environmental factors have been identified and summarized in the first part of this review. The present updated AGNP guidelines describe the best practice of TDM in psychiatry in order to promote the appropriate use of TDM.

Although a considerable body of data for plasma concentrations of psychotropic drugs has been accumulated and although our knowledge about the quantitative relationship between plasma concentration and therapeutic response has improved, there is still a need to conduct further controlled and randomised concentration-response studies to improve the quality of data on therapeutic reference ranges. We also recommend inclusion of pharmacokinetic measurements during phase III and IV studies. Product information should be supplemented with TDM related data to enhance the therapeutic effectiveness of psychoactive drugs. Analyses of German [671] and French [568] summaries of product characteristics (SPC) revealed that many SPC do not contain TDM related information in spite of available valid clinical-scientific evidence. Another need for research is to study cost-effectiveness of TDM when the method is used in an appropriate way. Polypharmacy is very common in psychiatry while essentially all TDM recommendations are based on single-medication trials. Thus, the efficacy of drug combinations constitutes a severely under-investigated area of TDM. Finally, one should never forget that TDM is an interdisciplinary task that sometimes requires the respectful discussion of apparently discrepant data so that, ultimately, the patient can profit from such a joint effort.

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Conflicts of Interest

Christoph Hiemke has received speaker's or consultancy fees from the following pharmaceutical companies: Bristol-Meyers Squibb, Pfizer, Lilly and Servier. He is managing director of the psiac GmbH which provides an internet based drug-drug interaction program for psychopharmacotherapy. He reports no conflict of interest with this publication. Pierre Baumann has received speaker's or consultancy fees from almost all pharmaceutical companies selling psychotropic drug in Switzerland. He reports no conflict of interest with this publication. Niels Bergemann, Mirjam Fric, Christine Greiner, Hartmut Kirchherr, Ulrich C Lutz, Bernhard Rambeck, Bernd Schoppek, Julia C Stingl, Manfred Uhr and Roland Waschgler have no conflict of interest to declare. Andreas Conca has served as a consultant for Lilly, BMS, Pfizer. He has served on the speakers' bureau of Lilly, BMS, Astra Zeneca, Lundbeck, Italfarma, Janssen. He reports no conflict of interest with this publication. Otto Dietmaier has received speaker's or consultancy fees from Bristol-Myers Squibb, Janssen, Eli Lilly and Lundbeck. He reports no conflict of interest with this publication. Ursula Havemann-Reinecke has received speaker's or consultancy fees or unrestricted educational grants from AstraZeneca, Bristol-Myers Squibb, Cephalon, Essex, Janssen Cilag, Lundbeck, Pfizer, Schering-Plough, Wyeth. She reports no conflict of interest with this publication. Ekkehard Haen has served as a consultant and received speaker's fees from Janssen-Cilag, Lilly, Pfizer, GlaxoSmithKline, AstraZeneca, Bristol-Myers Squibb, Otsuka, Bayer Vital, Servier and Südmedica GmbH. He reports no conflict of interest with this publication. Karin Egberts has received speaker's fees or travel grants from Wyeth and Medice. She participated in performing clinical trials for AstraZeneca, Janssen-Cilag, Lilly and Shire. She reports no conflict of interest with this publication. Gerhard Gründer has served as a consultant for Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, and Otsuka. He has served on the speakers' bureau of Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, Janssen Cilag, Otsuka, Pfizer, Servier, and Wyeth. He has received grant support from Alkermes, Bristol-Myers Squibb, Eli Lilly, and Johnson & Johnson. He is co-founder of Pharma-Image – Molecular Imaging Technologies GmbH. He reports no conflict of interest with this publication. Eveline Jaquenoud Sirot is managing director of mediQ which sells an internet based drug-drug interaction program for psychiatry. She reports no conflict of interest with this publication. Gerd Laux has received speaker's or consultancy fees or unrestricted educational grants from AstraZeneca, Bayer, Eli Lilly, Lundbeck, Merz, Pfizer, Servier and Wyeth. He reports no conflict of interest. Bruno Pfuhlmann has received speaker's or consultancy fees from AstraZeneca, Janssen and Pfizer. He reports no conflict of interest with this publication. Manfred Gerlach has received speaker's or consultancy honoraria or restricted research grants from Boehringer Ingelheim Pharma GmbH & Co. KG, Desitin Arzneimittel GmbH, Janssen Cilag GmbH, Lundbeck GmbH and Merz Pharmaceuticals GmbH. He reports no conflict of interest with this paper. Thomas Messer has received speaker's or consultancy fees or unrestricted educational grants from Eli Lilly, Bristol-Myers Squibb, Janssen, Servier, Pfizer, Lundbeck and Bayer Vital Health Care. He reports no conflict of interest with this publication. Matthias J. Müller has received speaker's or consultancy fees from Janssen, Servier, Pfizer, and Astra-Zeneca. He reports no conflict of interest with this publication. Sven Ulrich is an employe of Ariston Pharma GmbH, Berlin, Germany. He reports no conflict of interest with this publication. Gerald Zernig has received speaker's or consultancy fees or unrestricted educational grants from AlcaSynn, AstraZeneca, Bio-Rad, Bristol-Myers Squibb, Eli Lilly, Lundbeck, Mundipharma, Novartis, Pfizer, and Wyeth. He reports no conflict of interest with this publication.

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