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- Use therapeutic drug monitoring with appropriate indications as part of the clinical decision-making process to help optimize the efficacy and safety of antipsychotics

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Blood Levels to Optimize Antipsychotic Treatment in Clinical Practice:

A Joint Consensus Statement of the American Society of Clinical Psychopharmacology and the Therapeutic Drug Monitoring Task Force of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie

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ABSTRACT

Objective: The quantification of antipsychotic levels in blood, also known as therapeutic drug monitoring (TDM), is a potentially useful tool of modern personalized therapy that can be applied to augment antipsychotic use and dosing decisions. The application of TDM for antipsychotics can be helpful in numerous challenging clinical scenarios, such as lack of therapeutic response, relapse, or adverse drug reactions (ADRs) related to antipsychotic treatment. The benefits of TDM may be particularly evident in the treatment of highly vulnerable patient subgroups, such as children, adolescents, pregnant women, and the elderly. The main aim of this article is to aid clinicians who routinely prescribe antipsychotics to successfully apply TDM in routine clinical practice in order to help optimize the efficacy and safety of those antipsychotics.

Participants: Participants were clinicians and researchers, members of the American Society of Clinical Psychopharmacology, and the Therapeutic Drug Monitoring Task Force of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (Association of Neuropsychopharmacology and Pharmacopsychiatry).

Evidence: TDM literature on antipsychotics was critically reviewed to provide a condensed clinical decision-making algorithm with therapeutic reference ranges for blood antipsychotic levels, within which patients are most likely to respond and tolerate treatment, although TDM is not equally recommended/supported for all antipsychotics.

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Consensus Process: A preliminary draft was prepared and circulated to the writing group members. Consensus was achieved in all cases, and resulting recommendations focused on following areas: steady-state and sampling time, levels of recommendations, indications, therapeutic reference ranges and laboratory alert levels, practical issues, and interpretation, as well as limitations.

Conclusions: The utilization of TDM as a tool for problem solving in antipsychotic treatment offers a unique method to improve safety and efficacy. This consensus statement summarizes essential information on the routine use of TDM for antipsychotics and encourages clinicians to perform TDM with the appropriate indications as part of the clinical decision-making process.

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Clinical Points

- There is an urgent need for improvement of treatment response and safety for antipsychotic treatment.
- Measuring blood levels of antipsychotics, also known as therapeutic drug monitoring (TDM), in several patient subgroups and under appropriate indications can efficiently guide clinicians in clinical routine.
- This work provides a framework for the implementation of TDM as part of antipsychotic treatment.

Measurement of drug levels in blood provides valuable insight in several areas of medicine including oncology, immunology, infectious diseases, clinical toxicology, pediatrics, and psychiatry. Specifically, in psychopharmacotherapy there is an established role for therapeutic drug monitoring (TDM) for antidepressants and mood stabilizers, such as lithium, valproate, and carbamazepine.[1,2] Additionally, the quantification of antipsychotic levels in blood allows tailoring the dosage of drugs based on patients' individual pharmacokinetic patterns.[3,4] Implementation of precision medicine tools like TDM in the pharmacologic treatment of patients with severe mental disorders may help overcome suboptimal efficacy and/or tolerability related to antipsychotic treatment.[5] TDM may be particularly valuable in the management of specific subgroups, such as children and adolescents, pregnant women, and the elderly, as well as patients with intellectual disabilities, patients with substance use disorders, and forensic patients.[6] Regardless of patient profiles, specific indications for TDM include poor treatment response within the therapeutic dose ranges,[7] evaluation of drug adherence, tolerability issues, and drug-drug interactions.[5] Evidence in support of the utility of TDM as part of routine pharmacotherapy is increasingly available for the majority of the widely prescribed antipsychotic agents,[8] although few trials have been performed directly comparing outcomes between TDM and treatment as usual. The aim of this consensus statement is to guide clinicians in the application of TDM as part of antipsychotic treatment to improve therapeutic outcomes. Specifically, the use of TDM is particularly meaningful in the context of prevention and treatment of several antipsychotic-related adverse drug reactions (ADRs).[9–11] Clinicians further interested in TDM are encouraged to read previous work of the TDM task force of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP; in English, Association of Neuropsychopharmacology and Pharmacopsychiatry),[6,12,13] which provides details on the theoretical framework for the use of TDM in clinical practice enhancing the efficacy and safety of pharmacotherapy. The latest update of the AGNP consensus is publicly available at https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0043-116492.

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METHODS

2.1. Participants, Evidence, and Consensus Process

Drawing on prior work by the TDM task force of the Association of Neuropsychopharmacology and Pharmacopsychiatry (AGNP),[6,12,13] this group of authors reviewed the relevant literature on TDM, applying basic principles to the prescribing of antipsychotics and focusing on the practical aspects of enhanced antipsychotic prescribing via appropriate use of TDM. A preliminary draft was prepared and circulated to the members of the writing group. Revision suggestions were received, and the manuscript was revised accordingly. Consensus was achieved in all cases. Following a brief review of the theoretical framework of TDM, the resulting recommendations for clinical care are centered around the following areas: steady-state and sampling time, levels of recommendations, indications, therapeutic reference ranges and laboratory alert levels, practical issues, and interpretation, as well as limitations.

2.2. TDM for Antipsychotics: Theoretical Framework

In the past decades, the development of TDM science has been mainly based upon the increasing knowledge of the pharmacokinetic/pharmacodynamic (PK/PD) target attainment. Pharmacokinetic pathways have received attention with the identification of enzymes and efflux transporters mediating the metabolism and distribution of antipsychotics. Particularly, the cytochrome P450 (CYP) isoenzyme system has been embraced as a major source of pharmacokinetic variability of medications, including antipsychotics, with 4 CYP enzymes being involved in the phase 1 metabolism of the majority of antipsychotics (CYP1A2, CYP2C19, CYP2D6, and CYP3A4).[14] As regards the so-called polymorphic isoenzymes (CYP2C19, CYP2D6), their activity is crucially determined by genetic variants,[15] which are increasingly tested in clinical routine with the integration of pharmacogenetic tests in clinical practice.[16] Genetic variants of crucial impact also encompass genes encoding blood-brain barrier (BBB) transporters, such as the ABC transporters, including P-glycoprotein.[10] While TDM can circumvent the effects of variations in metabolism related to transporters in the gut, it does not overcome variability in bioavailability related to transporters that modify passage across the BBB. Other determinants of blood antipsychotic levels include interactions with comedications from similar or different pharmacologic classes.[17] Numerous medications exert inhibiting or inducing effects on drug metabolizing enzymes or transporters and can ultimately alter the metabolism and blood levels of concomitantly administered antipsychotics when affecting overlapping metabolic pathways. Therefore, the interpretation of blood antipsychotic concentrations requires information on the coprescribed medications with inducing or inhibiting properties, also known as "perpetrator" drugs. Table 1 provides a list of metabolic pathway inducers and inhibitors. Interactions at a pharmacodynamic level comprise more complicated challenges for clinicians prescribing antipsychotics and have not yet been sufficiently integrated into TDM.[18]

RESULTS

3.1. TDM for Antipsychotics: Steady-State and Sampling Time

In the area of pharmacokinetics, the term *steady-state* concentration for a drug in blood refers to the time point when the rate of medication input is equal to the rate of medication loss. Practically, the time to reach steady state is approximately 4–5 times the elimination half-life ($t_{1/2}$) of the antipsychotic (see Table 2), and, thus, steady state is reached within 1 week of maintenance dosing for the majority of antipsychotics. Exceptions are compounds with a particularly long half-life, such as aripiprazole, brexpiprazole, cariprazine (and its principal active metabolite, didesmethyl-cariprazine), and sertindole. During stable dosing, the appropriate sampling time is immediately before intake of the morning dose or, in other words, 24 hours after the last dose, if the antipsychotic is prescribed once daily in the morning. For antipsychotics prescribed to be taken in the evening, the blood draw interval is 12 hours.

The pharmacokinetics of long-acting injectable antipsychotics (LAIs) differ from their oral formulations. In LAI-treated patients, the appropriate sampling time is immediately before the next injection. Peak concentrations in blood are reached within 1–14 days after the LAI injection, and the apparent $t_{1/2}$ is about 2–3 weeks for first-generation LAIs, as well as for paliperidone palmitate once-monthly.[19,20] The maximal plasma concentrations for the 3-monthly paliperidone palmitate are reached between days 30 and 33, with median half-lives ranging between 84–95 and 118–139 days for deltoid and gluteal injection, respectively.[6] For risperidone LAI microspheres, peak concentrations are reached after 4 weeks, and its $t_{1/2}$ is 4–6 days.[19] A newly available risperidone subcutaneous monthly injection displays different pharmacokinetic characteristics; single-injection data reported 2 plasma peaks, the first at 4–6 hours and the second at 10 to 14 days, with a half-life of 9–11 days.[21] For aripiprazole monohydrate, LAI peak levels are reached 5–7 days after injection, with the apparent $t_{1/2}$ after 400 or 300 mg aripiprazole monthly being 47 and 30 days, respectively.[22] Aripiprazole lauroxil is another aripiprazole formulation that differs in terms of pharmacokinetics in that it has a substantially longer half-life ranging between 53.9 and 57.2 days, with maximum concentrations reached 20–34 days after last injection.[23]

3.2. TDM for Antipsychotics: Levels of Recommendations

For several antipsychotics, therapeutic reference ranges have been established based on their association with treatment response in clinical trials with sufficient reliability such that TDM can be strongly recommended and supported by data. Specificity and sensitivity vary

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Table 1. Inhibitors and Inducers of Metabolic Enzymes and Transporters[a]

Metabolic Enzymes and Transporters	Inhibitors	Inducers
CYP1A2	cimetidine, **ciprofloxacin**, **enoxacin**, **fluvoxamine**, isoniazid, norfloxacine, **perazine**, **phenylpropanolamine**, propafenone, **zileuton**	carbamazepine, modafinil, phenobarbital, phenytoin, **rifampicin**, **smoking (aromatic hydrocarbons found in cigarette smoke)**
CYP2A6	isoniazid, **tranylcypromine**	
CYP2B6	clopidogrel, ticlopidine, **voriconazole**	**carbamazepine**, **efavirenz**, modafinil, **phenobarbital**, **phenytoin**, **rifampicin**
CYP2C8	fluvoxamine, **gemfibrozil**	
CYP2C9	**amiodarone**, **fluconazole**, fluvoxamine, isoniazid, **miconazole**, valproate, voriconazole	carbamazepine, phenobarbital, phenytoin, primidone, **rifampicin**, **ritonavir**, St John's wort
CYP2C19	**esomeprazole**, felbamate, **fluoxetine (norfluoxetine)**, **fluvoxamine**, isoniazid, **moclobemide**, **omeprazole**, **ticlopidine**, **voriconazole**	phenobarbital, phenytoin, primidone, **rifampicin**
CYP2D6	amiodarone, **bupropion**, cimetidine, **duloxetine, fluoxetine (norfluoxetine)**, **levomepromazine**, **melperone**, metoclopramide, **moclobemide**, **paroxetine**, propafenone, **quinidine**, ritonavir	
CYP2E1	**clomethiazole, disulfiram**	**ethanol**, **isoniazid**
CYP3A4	amiodarone, **amprenavir**, **aprepitant**, **atazanavir**, **boceprevir**, cimetidine, **ciprofloxacin**, **clarithromycin**, **crizotinib**, **diltiazem**, **erythromycin, fluconazole**, fluoxetine (norfluoxetine), fluvoxamine, **fosamprenavir**, **grapefruit juice**, **indinavir**, isoniazid, **itraconazole**, **ketoconazole,** miconazole, **nelfinavir**, **posaconazole**, **ritonavir**, **saquinavir**, **telaprevir**, **telithromycin**, **verapamil**, **voriconazole**	**bosentan**, **carbamazepine**, **efavirenz**, **modafinil**, **oxybutynin**, **phenobarbital**, **phenytoin**, **primidone**, **rifabutin**, **rifampicin**, ritonavir (high dose), **St John's wort**
MAO	**isoniazid**, **tranylcypromine**	
MAO-A	**moclobemide**	
P-glycoprotein		**carbamazepine**, **St John's wort**
UGT		**carbamazepine**, **lamotrigine**, **phenytoin**, ritonavir
UGT1A1		**phenobarbital**

[a]Inhibitors of enzymes indicated in bold markedly increase concentrations of victim drugs, while inducers of enzymes indicated in bold decrease concentrations of victim drugs by more than 50%.
Abbreviations: CYP = cytochrome P450, MAO = monoamine oxidase, UGT = UDP-glucuronosyltransferase.

between drugs and between trials, but the evidence from positron emission tomography has been very helpful when defining thresholds.[6] For example, the reference range for clozapine has been based on 1 landmark prospective trial that randomized patients to 3 different blood level ranges of clozapine and provided rigorous data validating TDM.[24] For clozapine and some other antipsychotics, including fluphenazine, haloperidol, olanzapine, perazine, and perphenazine, TDM is recommended for titration to target dose, as well as for special indications (Table 2). Specifically, blood antipsychotic concentrations within the therapeutic range are linked to favorable clinical outcomes in terms of efficacy, such as response, remission, and relapse prevention, as well as safety and tolerability. For a second group of antipsychotics, including aripiprazole, chlorpromazine, flupenthixol, paliperidone, quetiapine, risperidone, sertindole, and ziprasidone, TDM is recommended with a lower level of clinical confidence (level 2 recommendation), due to fewer data linking therapeutic blood level ranges to either benefit or harm.[8,25] Nevertheless, TDM will increase the probability of response or remission in nonresponders, in that subtherapeutic blood antipsychotic concentrations may be associated with risk of poor response, whereas supratherapeutic concentrations may be related to an increased risk of intolerance or adverse effects.[8,10,26–30] Evidence is less supportive for TDM application for a third group of antipsychotics, such as brexpiprazole, cariprazine, chlorprothixene, iloperidone, loxapine, lurasidone, melperone, and pimozide, where the link between blood antipsychotic concentrations and clinical effects has not been addressed yet or only in a retrospective fashion or in single case reports.[31–36] For this group of antipsychotics, TDM can still potentially be useful, but more data are needed. Lastly, for asenapine, no evidence associating clinical effects and blood concentrations is available, and, thus, TDM is only considered potentially useful. It is important to emphasize that, as discussed below, some very strong indications for TDM do not necessarily depend on the definitive establishment of a therapeutic dose range. For example, in the patient experiencing a relapse of psychotic symptoms, the absence of a detectable blood level is very important information that can have a strong influence on clinical decision-making.

3.3. TDM for Antipsychotics: Indications

Regardless of recommendation levels for any specific antipsychotic, TDM is strongly recommended for a series of specific indications. These indications reflect challenging clinical situations for which the availability of evidence supporting TDM varies from case reports to clinical trials. However, absence of evidence is not evidence of absence. Large-scale evidence from patients with chronic

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Table 2. Therapeutic Reference Ranges and Laboratory Alert Levels (in ng/mL), Elimination Half-Lives ($t_{1/2}$), Major CYP Enzymes Involved, and Metabolite-to-Parent Ratios (When Applicable)[a]

Drug or Active Metabolite	Therapeutic Reference Range in Blood (ng/mL)	Laboratory Alert Level (ng/mL)	$t_{1/2}$[b]	Major CYP Enzymes Involved	MPR
Antipsychotic drugs for which TDM is strongly recommended (level 1)[c]					
Clozapine	350–600	1,000[d]	12–16 h	CYP1A2, CYP2C19	0.5–0.6
Fluphenazine	1–10	15	16 h	CYP2D6	
Haloperidol	1–10	15	12–36 h	CYP2D6	0.14–0.42
Olanzapine	20–80	100	30–60 h	CYP1A2	0.1–0.3
Perazine	100–230	460	8–16 h	CYP2C19	1.1–3.3
Perphenazine	0.6–2.4	5	8–12 h	CYP2D6	0.6–2.8
Antipsychotic drugs for which TDM is recommended (level 2)[c]					
Aripiprazole	100–350[e]	1,000	60–80 h	CYP3A4, CYP2D6	0.3–0.5
Chlorpromazine	30–300	600	15–30 h	CYP1A2, CYP2D6	
Flupenthixol	0.5–5 (cis-isomer)	15	20–40 h	CYP2D6	
Paliperidone	20–60	120	17–23 h		
Quetiapine	100–500[f]	1,000	6–11 h	CYP3A4	0.54–3.1
N-desalkylquetiapine	100–250		10–13h		
Risperidone plus 9-hydroxyrisperidone	20–60	120	2–4 h 17–23 h	CYP2D6, CYP3A4	3.6–22.77
Sertindole	50–100	200	55–90 h	CYP2D6	1.1–2.7
Ziprasidone	50–200	400	4–8 h	CYP3A4	
Antipsychotic drugs for which TDM is useful (level 3)[c]					
Brexpiprazole	40–140	280	91 h	CYP2D6, CYP3A4	
Cariprazine[g]	5–15	40	48–120 h[g]	CYP3A4	3–6[h]
Chlorprothixene	20–300	400	8–12 h		
Iloperidone	5–10	20	18–33 h	CYP3A4, CYP2D6	
Loxapine	5–10	20	6–8 h	CYP1A2, CYP3A4, CYP2D6	
Lurasidone	15–40	120	20–40 h	CYP3A4	
Melperone	30–100	200	4–6 h		
Pimozide	15–20	20	23–43 h	CYP3A4, CYP1A2	
Antipsychotic drug for which TDM is potentially useful (level 4)[c]					
Asenapine	1–5	10	13–39 h	CYP1A2	

[a]Data from Hiemke et al.[6]
[b]Elimination half-lives refer to the oral formulations of antipsychotics. For flupenthixol decanoate $t_{1/2}$ = 17 days, for fluphenazine decanoate $t_{1/2}$ = 14 days, for olanzapine pamoate $t_{1/2}$ = 30 days, for paliperidone palmitate $t_{1/2}$ = 25–49 days, for perphenazine enanthate $t_{1/2}$ = 4–6 days, and for risperidone LAI $t_{1/2}$ = 26 days, and metabolite-to-parent ratio 1.2–4.3.
[c]For the definition of the levels of recommendation, see section 3.2.
[d]Alternatively, a threshold of 1,200 ng/mL for clozapine plus norclozapine can be considered, as norclozapine seems to be implicated in several ADRs such as seizures.
[e]For active moiety (aripiprazole + dehydroaripiprazole) = 150–500 ng/mL.
[f]For intake of the extended release formulation in the evening and blood withdrawal in the morning, expected concentrations are 2-fold higher than trough levels.
[g]Based on AUC data, 73% of the circulating active moieties at steady state are didesmethyl- and desmethyl-cariprazine. The half-lives of desmethyl-cariprazine and didesmethyl-cariprazine are 29.7–37.5 and 314–446 hours, respectively.
[h]Refers to didesmethyl-cariprazine.
Abbreviations: ADR = adverse drug reaction, AUC = area under the curve, CYP = cytochrome P450, h = hours, LAI = long-acting injectable, MPR = metabolite-to-parent ratio, TDM = therapeutic drug monitoring, $t_{1/2}$ = elimination half-life.

schizophrenia has shown that the treatment of almost the half of the patients will dictate additional actions apart from dose titration, such as change of target dose or switching the antipsychotic.[37] Instead of applying a so-called trial-and-error approach, TDM can provide valuable information for the decision-making process (Figure 1).[37]

TDM may be valuable in the following situations:

1. Uncertain adherence to antipsychotics[38]
2. No clinical response within established therapeutic dose ranges[8]
3. Symptom recurrence or relapse during maintenance treatment[39]
4. Adverse drug reactions (ADRs)[9]
5. Combination treatment with medication(s) with inducing or inhibiting properties[40]
6. Genetic peculiarities for the pathways involved in the metabolism of antipsychotics (the prevalence of specific genetic variants affecting drug metabolism may vary highly in different ethnic groups, eg, Caucasian versus Asian, middle Eastern vs the rest of the world)[41]
7. Patients with abnormally high or low body weight or body mass index[42]
8. Pregnant or lactating patients[43]
9. Child or adolescent patients[44]
10. Elderly patients[6]
11. Patients with intellectual disabilities[45]
12. Forensic patients or court mandated individuals,[46] as the treatment of this patient subgroup presents special challenges that underscore the need for tracking and mitigating nonadherence

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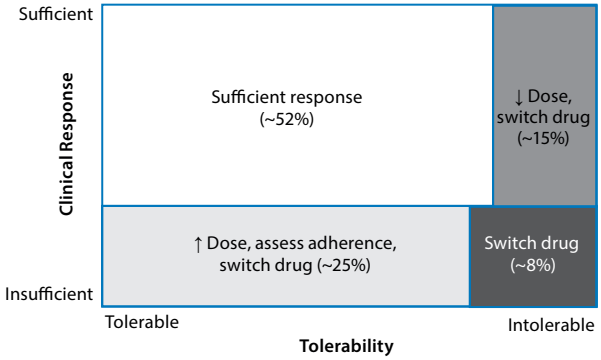
13. Patients with pharmacokinetically relevant comorbidities, such as hepatic or renal dysfunction and severe cardiovascular disease (affecting hepatic and renal blood flow)[47,48]
14. Patients with acute or chronic inflammatory conditions and infections[49]
15. Postoperative care for patients undergoing restrictive gastrointestinal resection or bariatric surgery[50]
16. Switching between the original preparation and generic forms of antipsychotics due to potential therapeutic equivalence differences, as well as related adherence aspects[51,52]
17. Switching between oral antipsychotics and LAIs[53]
18. Pharmacovigilance programs[54]
19. Research[55]

Figure 1. Estimates of Percentages for Patient Categories Based on Response and Tolerability Including Suggestions for Decision-Making[a]



[a]Adapted with permission from Horvitz-Lennon et al.[37]
Symbols: ↑ = increase; ↓ = decrease.

3.4. TDM for Antipsychotics: Therapeutic Reference Ranges and Laboratory Alert Levels

The therapeutic reference range for antipsychotic levels in blood consists of a lower limit, below which therapeutic response is relatively unlikely, and an upper limit, above which ADRs, especially extrapyramidal symptoms or seizures, but also (depending on the nondopaminergic properties of the specific antipsychotic) other dose-dependent ADRs such as sedation, hypersalivation, dizziness/orthostasis, QTc prolongation, are more likely to occur[56,57] or above which it is relatively unlikely that therapeutic response will occur. Reference ranges have been invariably obtained from studies of patients receiving antipsychotic monotherapy at presumed therapeutically effective dosages. However, clinicians need to bear in mind that ranges are an orienting, population-based tool that may not always be applicable to every patient. For example, some patients may respond despite having blood antipsychotic levels below the therapeutic reference range, while others may respond only at levels above the therapeutic reference range and tolerate those blood levels without ADRs. In fact, TDM can assist clinicians in identifying the individual's unique therapeutic concentrations when measured regularly. For example, since only a blood level of zero clearly indicates complete nonadherence, it may indeed be useful within a measurement-based framework to obtain a blood antipsychotic level at an efficacious and well-tolerated ingested target dose in order to have a benchmark of the dose-concentration-efficacy-tolerability relationship for the individual patient. This way, partial nonadherence or variations in blood antipsychotic levels due to, among others, drug-drug interactions, intercurrent illness, or changes in liver or renal functioning can be detected and rationally addressed. Reference ranges for antipsychotics involve in most cases the parent compound, with the exception of risperidone, where active moiety concentrations are also used to determine efficacy/tolerability thresholds. *Active moiety* refers to the sum of parent compound and its active metabolite, as the latter is pharmacologically active (eg, active moiety = risperidone plus 9-OH-risperidone [paliperidone]).[6] The literature regarding blood clozapine level monitoring is based on clozapine levels alone, even though the active metabolite norclozapine is often reported as well. However, norclozapine has only 10% activity of clozapine, and the 2 reported levels should not simply be added, but the target level of clozapine should determine the clinical decision-making for efficacy.

Further, the reference ranges derive mainly from oral antipsychotic studies. Nevertheless, they can be effectively applied for LAIs as well, although there has been some debate as to their precision in the latter context.[58] From a pharmacokinetic point of view, potential deviations of LAIs from the suggested reference ranges may be more likely attributed to variations in the correctly applied, deep intramuscular injection (with lower levels when medication is wrongly placed into fat tissue) and study design issues, such as injection sites (longer $t_{1/2}$ after gluteal than deltoid injections, but higher peak concentration after deltoid than gluteal injections) and sampling times.[6] Lastly, therapeutic ranges apply to the primary/specific indication of the antipsychotic prescription. However, antipsychotics are increasingly prescribed for other indications apart from schizophrenia.[59] Nevertheless, evidence regarding diagnosis-specific TDM is rarely available. Therefore, we are limited to providing diagnosis-specific reference ranges only for patients with schizophrenia.

Along with therapeutic reference ranges, we also provide laboratory alert levels (Table 2). Laboratory alert levels represent threshold levels above which the risk for ADRs is expected to increase. Antipsychotic levels higher than the alert levels need to be immediately reported by the laboratory to the prescribing clinicians, who may consider a dose adjustment when ADRs are present or suspected. If ADRs are not suspected or present, clinicians need to first check if the blood level was indeed obtained at 24 hours (for morning-dosed antipsychotics) or 12 hours (for evening-dosed antipsychotics) after the last dose, assure that the patient is taking the antipsychotic as prescribed,

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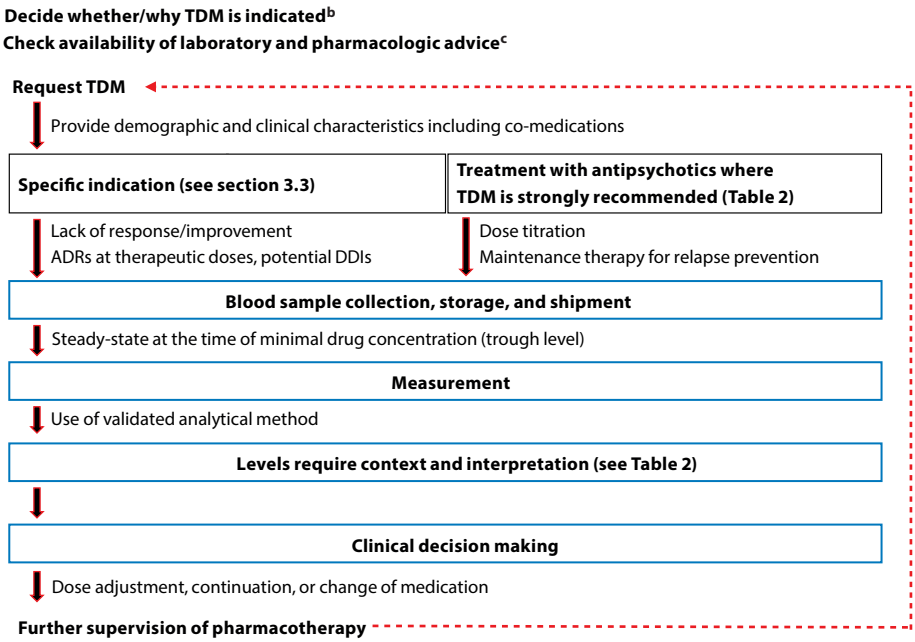
Figure 2. Therapeutic Drug Monitoring Process in Everyday Clinical Practice[a]



[a]Adapted with permission from Hiemke et al.[6]
[b]See section 3.3 for specific indications.
[c]Pharmacologic advice as well as supervision of pharmacotherapy needs to be provided by experts including clinical pharmacists and/or trained experts.
Abbreviations: ADR = adverse drug reaction, DDI = drug-drug interaction, TDM = therapeutic drug monitoring.

rule out accidental or intentional overdose, eliminate the possibility of white coat compliance (ie, medications ingested in anticipation of the blood draw in the context of nonadherence), rule out use of comedications (prescribed by other providers or purchased over the counter) that can alter the metabolism of the antipsychotic, and be vigilant for clinical signs indicative of an overdose/excessive blood antipsychotic levels and act accordingly.

3.5. TDM for Antipsychotics: Practical Issues and Interpretation

Table 2 provides clinically useful information, including the therapeutic reference ranges, laboratory alert levels, and elimination half-life ($t_{1/2}$) of the drugs, as well as major CYP enzymes implicated and the metabolite-to-parent ratios (MPRs). The latter is calculated by dividing the concentrations of the major metabolite by the concentrations of the parent drug. The MPRs reflect the enzymatic activity implicated in the metabolism of the antipsychotics. Hence, they indirectly provide crucial information for poor or ultrarapid metabolizer status, adherence, and drug-drug interactions.[60] Drug-drug interactions affecting antipsychotics (ie, antipsychotics as victim drugs) can be predicted in light of the metabolic pathways of antipsychotics, as reported in Table 2.

In Figure 2, we provide a schematic overview of how to apply TDM in everyday clinical practice. Regarding pharmacologic advice, recent developments in team-based care provide the opportunity to include other professionals, such as psychiatric pharmacy specialists, who can assist the psychiatrist in TDM applications.[61] Electronic databases can provide additional assistance. When interpreting the antipsychotic levels, several pieces of information are required. First, comedications need to be taken into consideration, focusing on medications with antipsychotic metabolic pathways inhibiting or inducing properties. Moreover, contextual information is necessary, such as demographic and clinical characteristics, including age, sex, diagnosis, and smoking habits, as well as the indication for the TDM request. In fact, blood antipsychotic levels always need to be understood/interpreted in relationship to clinical information regarding symptom severity and response or remission, as well as ADRs. Further, the antipsychotic formulation, time since the last dose change and the time point of the blood draw must be considered. As data are more robust for clozapine, we provide a framework as an example for the clinical decision-making process previously reported elsewhere (although with a slightly lower upper clozapine level of the therapeutic range).[62] It is important to note that even if rigorous clinical trial data are not available for each step of this framework, this algorithm proposes a logically structured process as an aid for the clinical practice considering response and tolerability aspects (Table 3). Additionally, patients' case vignettes with examples of TDM that can inform clinicians on how to best utilize TDM have been published previously.[6]

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Table 3. TDM-Based Decision Making Algorithm for Clozapine-Treated Patients[a]

Clozapine Level[b]	Response	Tolerability	Action
Subtherapeutic (< 350 ng/mL)	Insufficient	Intolerable	↑ Clozapine dose slowly to reach reference range
	Insufficient	Tolerable	↑ Clozapine dose to reach reference range
	Sufficient	Intolerable	Consider ↓ clozapine dose
	Sufficient	Tolerable	Continue to monitor
Within the reference range (350–600 ng/mL)	Insufficient	Intolerable	↑ Clozapine dose slowly to remain within the reference range accordingly to tolerability
	Insufficient	Tolerable	↑ Clozapine dose slowly to remain within the reference range if possible
	Sufficient	Intolerable	If tolerability does not improve, ↓ clozapine dose, monitor to remain within the range if possible
	Sufficient	Tolerable	Continue to monitor
Supratherapeutic (> 600 ng/mL)	Insufficient	Intolerable	Consider ↓ clozapine dose, monitor. Consider prophylactic anticonvulsant
	Insufficient	Tolerable	Consider augmentation/ prophylactic anticonvulsant
	Sufficient	Intolerable	↓ Clozapine dose slowly, monitor to be within the range if possible
	Sufficient	Tolerable	Monitor concentrations. Be vigilant for tolerability/ consider prophylactic anticonvulsant

[a]Based on Taylor et al.[62]
[b]Refers to clozapine levels only and not to clozapine plus norclozapine. For patients' levels higher than the laboratory alert levels (> 1,000 ng/mL), clinicians need to be additionally cautious (see section 3.4) while applying the supratherapeutic algorithms.
Abbreviation: TDM = therapeutic drug monitoring.
Symbols: ↓ = decrease, ↑ = increase.

DISCUSSION

4.1. TDM for Antipsychotics: Limitations and Future Directions

Despite the promise of TDM as a measurement-based tool to improve the effectiveness of antipsychotics in clinical care, several limitations must be acknowledged. These limitations may account for potential differences of opinion regarding the utility of TDM in clinical practice. First, as mentioned above, therapeutic blood level ranges are derived from groups of patients who agree to be studied. Their data might not generalize to usual care patients, who are more likely to have psychiatric and physical comorbidities and receive multiple comedications and who may have more severe/chronic psychiatric disorders that may possibly respond to different blood antipsychotic level ranges. In fact, although the pharmaceutical industry has routinely included PK assessments in their antipsychotic registration trials and other studies for at least the last 15 years (including studies conducted in highly controlled inpatient settings), for none of the recently approved antipsychotics have therapeutic blood antipsychotic level ranges been published. Since these data exist, our group strongly urges the pharmaceutical companies either to publish (even negative) correlational data between antipsychotic blood levels and efficacy as well as key safety/tolerability parameters or to make these data available to groups for further analysis. In fact, the scarcity of the data has resulted in pooling data from samples with patients in different treatment phases (eg, acute vs maintenance treatment),[63] which may pose limitations for the precision of the estimated reference ranges. Second, blood antipsychotic level ranges available for clinically applied TDM are almost exclusively derived from patients with schizophrenia. In fact, the percentage of antipsychotic-treated patients with schizophrenia where TDM is applied is unclear; some transdiagnostic data suggest a low, however increasing, prevalence of around 4% for TDM in treatment with antipsychotics.[64] Therefore, it is most likely that TDM is applied in a very small fraction of patients with schizophrenia treated with antipsychotics. Thus, more data should be collected in the many additional approved, and even off-label, indications for which antipsychotics are used. Third, TDM results are only helpful if a true 12-hour trough level is obtained and sufficient contextual data are provided to the laboratory and used for a careful interpretation of the results. Fourth, TDM is of only limited help in cases of partial antipsychotic nonadherence, unless a blood antipsychotic level is obtained at steady state of an efficacious and well-tolerated target dose to provide a dose-concentration-efficacy-tolerability relationship for the given patient that can be used as a benchmark for the interpretation of future variations in the clinical picture and blood antipsychotic levels. Apart from blood levels, the decision-making process will also need to integrate increasingly available technologies for the assessment of adherence.[65,66] Fifth, as mentioned above, data are still quite limited for many, if not most, antipsychotics that could firmly establish a relationship between explicit blood level ranges for specific antipsychotics and clinical efficacy and tolerability. The scarcity of the data linking treatment outcomes and blood antipsychotic levels likely contributes to the limited use of TDM in clinical practice. Thus, clearly, more research is needed. Additionally, available data should be analyzed and published to fill this evidence gap. A typical example of urgent need for more evidence refers to the elderly, as well as children and adolescents. Ethical issues in psychopharmacology of children and adolescents discussed over recent years relate to PK/PD peculiarities and concern the safety, the indication, and the evidence-based prescription of antipsychotics in minors.[67] The complexity of using TDM for antipsychotics in adolescents and children also relates to limited knowledge on therapeutic dose ranges for younger age groups and the amounts of blood volume required to perform TDM.[68] However, age-dependent patterns for blood levels were reported for some antipsychotics used in adolescents, such as olanzapine[69] and quetiapine,[70] but not for others, such as risperidone[69] and aripiprazole.[71] Apart from legislative efforts to improve safety and discourage "off-label"

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use of antipsychotics in youth,[72] additional TDM evidence is expected to guide clinicians to reduce the direct risk of under- or overdosing and the delayed risk of long-term side effects. To this aim, a Competence Network on Therapeutic Drug Monitoring in Child and Adolescent Psychiatry (http://tdm-kjp.de) was established in December 2007, including 12 departments of child and adolescent psychiatry in 3 European countries. The Network uses a multicenter TDM system including both standardized measurements of blood antipsychotic levels and the documentation of efficacy and side effects of these medications. Sixth, use of TDM depends on the availability of laboratories that analyze the blood level of any or specific antipsychotics. Parallel to the access to TDM, the availability of constantly updated reference ranges for antipsychotic levels in electronic databases will further facilitate the TDM integration in clinical practice. Finally, cost may be a considerable barrier to conducting TDM in some clinical care settings, making the collection of cost-effectiveness data mandatory in the area of TDM in general and of TDM of antipsychotics in particular. The cost-effectiveness of TDM is beyond the scope of this review. These limitations justify some skepticism regarding the rigor of the data supporting TDM use. Nevertheless, despite these limitations that are mostly addressable by more research, data indicate that TDM is an important yet underutilized measurement-based care and precision medicine tool that requires more attention and application. It is also likely that greater appreciation of the potential utility of TDM in clinical practice will lead to increased demand for the collection and publication of still needed data.

CONCLUSION

Despite the general call for personalized therapy, available relevant tools in standard psychiatric care are scarce. TDM presents a unique, evidence-based method that considers interindividual pharmacokinetic variability, which can be leveraged to enhance safety and efficacy of antipsychotic treatment. In fact, TDM has a long tradition in psychiatry, with the first attempt to establish guidelines dating back to 1985 from the American Psychiatric Association.[1] Two decades later, the TDM taskforce of the AGNP published a first consensus statement on TDM in neuropsychopharmacology,[13] updated twice in the past years.[6,12] Nevertheless, the implementation of TDM into clinical practice has not progressed sufficiently and there are reports of TDM underutilization.[73] The writing group members of this consensus statement may hold different views regarding the proven benefits of TDM for specific drugs as part of clinical routine. However, the potential of TDM as a tool for problem solving is unanimously embraced. In fact, TDM needs to be part of a clear temporal and contextual framework. Thus, it is no surprise that previous attempts to unravel pharmacokinetic correlates of clinical response several months after dose titration were of limited success.[74] Likewise, blood clozapine levels measured at baseline in patients presenting with clozapine-related myocarditis at various later time points may be less accurate in estimating the risk of a clozapine-related myocarditis.[75] Thus, we hope that the present collaborative work between the American Society of Clinical Psychopharmacology and the TDM Task Force of the AGNP will lead to a wider implementation, as well as stimulate further, much needed research in this area. To this end, TDM needs to receive more attention in educational programs, for example, psychopharmacology curricula for postgraduate training of specialists in psychiatry, including pharmacokinetics, metabolism, and pharmacogenetics of psychotropic drugs, and the use of TDM as a tool for optimizing psychopharmacotherapy. The authors of the Psychopharmacology section of the European Psychiatric Association created a psychopharmacology-pharmacotherapy catalog of learning objectives and a curriculum in Europe for teaching psychopharmacology during postgraduate training.[76] This document contains an extensive section on TDM in psychiatry and should therefore help to encourage and implement appropriate use of this tool.[74] In this consensus statement, we summarize essential information on the routine use of TDM in the antipsychotic treatment of patients with schizophrenia, including implementing and interpreting TDM results. Specifically, this joint consensus aims to encourage clinicians to perform TDM under the appropriate indications in order to inform clinical decision-making algorithms for antipsychotic prescription in patients with schizophrenia. In parallel, increasing the database on the utility of TDM for use of other psychotropic medications should also be pursued. It is hoped that with broader clinical implementation of TDM in the treatment of schizophrenia and other severe psychiatric disorders, reinforced by much needed additional research in this important area, patient outcomes can be further improved.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Psychosis section. Please contact Ann K. Shinn, MD, MPH, at ashinn@psychiatrist.com.

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1. **Clear indications for therapeutic drug monitoring (TDM) with patients taking antipsychotics in routine clinical practice include all of the following scenarios except:**
   a. Assessment of adherence
   b. Discontinuation of antipsychotics
   c. Presence of somatic comorbidities affecting clearance of antipsychotics
   d. Antipsychotic-induced adverse reactions

2. **Mr Jackson, who has been receiving a stable clozapine dose for the past few years, says that he wishes to quit smoking. What action should you take to avoid changes in his currently good treatment outcome?**
   a. Dose adjustment is unlikely to be necessary because Mr Jackson has been stable over a considerable amount of time.
   b. Nicotine patches should not be considered, as they are likely to interact with clozapine.
   c. Clozapine levels should be monitored closely to guide dose adjustment, as smoking cessation may lead to elevated clozapine levels due to the inducing effects of smoking on clozapine.
   d. Cardiovascular monitoring is needed to improve Mr Jackson's somatic health outcomes.

3. **Therapeutic reference range refers to:**
   a. A range of blood antipsychotic concentrations, within which patients are more likely to have adverse reactions
   b. A range of blood antipsychotic concentrations, below which therapeutic response is relatively unlikely and above which adverse reactions are more likely to occur
   c. A range of antipsychotic doses that are most effective
   d. A range of antipsychotic doses that are unlikely to be related with adverse reactions

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