Evidence for Therapeutic Drug Monitoring of Atypical Antipsychotics

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Abstract: Second-generation antipsychotics (SGAs), also known as atypical antipsychotics, are a newer class of antipsychotic drugs used to treat schizophrenia, bipolar disorder, and related psychiatric conditions. The plasma concentration of antipsychotic drugs is a valid measure of the drug at its primary target structure in the brain, and therefore determines the efficacy and safety of these drugs. However, despite the well-known high variability in pharmacokinetics of these substances, psychiatric medication is usually administered in uniform dosage schedules. Therapeutic drug monitoring (TDM), as the specific method that can help personalised medicine in dose adjustment according to the characteristics of the individual patient, minimizing the risk of toxicity, monitoring adherence, and increasing cost-effectiveness in the treatment, thus seems to be an elegant tool to solve this problem. Non-response to therapeutic doses, uncertain adherence to medication, suboptimal tolerability, or pharmacokinetic drug-drug interactions are typical indications for TDM of SGAs. This review aims to summarize an overview of the current knowledge and evidence of the possibilities to tailor the dosage of selected SGAs using TDM, including the necessary pharmacokinetic parameters for personalised pharmacotherapy.

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Introduction

Schizophrenia is a neurodevelopmental disorder associated with deficits in cognition, affect, and social functioning, with estimated prevalence in the general population of 0.5–1% (McGrath et al., 2008). The course of schizophrenia is chronic, with relapses in psychotic episodes, disturbed cognitive functioning, poor quality of life, and social decline. Antipsychotic medications have unique efficacy in the treatment of acute psychosis from any cause and in the management of chronic psychotic disorders such as schizophrenia. As a class, antipsychotics are also effective in the treatment of acute agitation, the manic phase of bipolar disorder, and other psychiatric conditions (Taylor et al., 2021). Psychotropic drugs have been used in practice since around 1950s, and today a wide range of effective molecules is available, with recommendations for optimal dosing from the results of randomised controlled trials.

Second-generation antipsychotics (SGAs), also known as atypical antipsychotics, are a group of medications that include among others clozapine, olanzapine, quetiapine, risperidone, paliperidone, lurasidone, aripiprazole, brexpiprazole, cariprazine. The basic pharmacodynamic characteristics of SGAs is summarised in Table 1.

SGAs have a lower risk of extrapyramidal symptoms and tardive dyskinesia compared with first-generation antipsychotics (FGAs). First- and second-generation antipsychotic drugs are more comparable in their clinical efficacy. Factors that influence the selection of an antipsychotic for individual patients include dosing, administration route, pharmacokinetics, side effect profile, and cost (Taylor et al., 2021). Antipsychotic pharmacokinetics and pharmacodynamics exhibit high interindividual variability due to genetic differences – polymorphism (Zhang et al.,

Table 1 – Basic pharmacodynamic characteristics of SGAs

Pharmacodynamic effect	Drug	Blockade of receptors				
		D_2	5-HT_2	α_1	H_1	M
Serotonin-dopamine antagonists (SDAs)	Lurasidone	+	+			
	Paliperidone	+	+	+	±	
	Risperidone	+	+	+	±	
Multi-acting receptor targeted antipsychotics (MARTA)	Clozapine	+	+	+	+	+
	Olanzapine	+	+	+	+	+
	Quetiapine	+	+	+	+	
Serotonin-dopamine activity modulators (SDAMs)	Aripiprazole	+	±			
	Brexpiprazole	+	+	+		
	Cariprazine	+	+			

Source: SmPCs – www.ema.europa.eu
SGAs – second-generation antipsychotics; D_2 – dopamine D_2 receptors; 5-HT_2 – serotonin receptors; α_1 – alpha-1 receptors; H_1 – histamine receptors; M – muscarinic receptors

2018), but also intraindividual variability can arise due to various factors such as comorbidities, lifestyle, and drug interactions. Genetic polymorphism determines a different phenotypic manifestation during drug metabolism and affects its bioavailability, elimination and subsequently dynamics both in terms of the expected effect and in terms of toxicity (Nofziger et al., 2020). Comorbidities have a significant impact on various pharmacokinetic and pharmacodynamic processes. Therefore, population parameters are often inadequate for setting the optimal pharmacotherapy for each patient (Mauri et al., 2017; Hiemke et al., 2018; Baldelli et al., 2021).

The concentration of a drug at its target site determines its efficacy and toxicity. For antipsychotic drugs, the brain, as the target organ, is not directly accessible to drug monitoring. As a result of interindividual variabilities in drug metabolism by hepatic and extrahepatic enzymes or drug transporters involved in absorption, distribution, and elimination, blood concentrations following administration of uniform dose of antipsychotics are highly variable among individuals. Thus, the dose cannot accurately predict the resulting plasma concentration (Mauri et al., 2017). Antipsychotic drugs demonstrated most therapeutic actions by blockade of dopamine D_2-like receptors, with plasma drug concentrations correlating with receptor occupancy (Yokoi et al., 2002). By the high variability of drug concentrations in plasma under the same doses it was found that receptor occupancy correlates better with steady-state plasma concentrations than with daily doses (Agid et al., 2007). The optimal response was observed when the receptors were occupied by 70–80%, and a receptor occupancy of 80% was considered the limit for extrapyramidal side effects (Grundmann et al., 2014; Urban and Cubała, 2017).

It is common for SGAs to use a fixed dose. Due to the above mentioned significant variability in drug pharmacokinetics, therapeutic drug monitoring (TDM) appears to be a useful tool to improve the dosage regimen of psychotropic drugs for the patient by identifying the most appropriate dose (Horvitz-Lennon et al., 2017). Optimised therapy also minimizes the occurrence of adverse effects, which in turn reduces mortality and morbidity rates, resulting in overall cost savings for the treatment. After excluding cases of noncompliance, the most likely causes of pharmacological resistance are genetic and exogenous factors affecting plasma drug concentrations, which are known as “pseudo-pharmacoresistance” (Mauri et al., 2017; Hiemke et al., 2018).

Therefore, the aim of this review was to summarize available up to date evidence about TDM of SGAs.

Literature search

The PubMed database was searched for articles using the paradigm “second-generation antipsychotics” OR “atypical antipsychotics” OR individual international

non-proprietary names (INNs) of these agents AND "pharmacokinetics" OR "pharmacodynamic" OR "TDM" OR "therapeutic drug monitoring".

Results were limited to studies in adult humans and English full-text articles published from January 2000 to January 2024. A total of 834 reports were identified from the initial literature search, out of which 111 relevant publications were found. The list of references for each reviewed paper was analysed and supplementary searches were performed, if they were found within the aim of this paper.

Also, all summaries of product characteristics (SmPCs) for the agents of interest were reviewed (European Medicines Agency, EMA-authorized) to find information about the pharmacologic variables, and one TDM guideline (Hiemke et al., 2018) was also included in the analysis. Sources not containing clear reference to one of the SGAs were excluded, as were the papers without data regarding the pharmacokinetic and pharmacodynamic properties of the previously mentioned antipsychotics.

Pharmacokinetics of SGAs

Since knowledge of pharmacokinetics is essential for the right implementation of TDM, a brief pharmacokinetic characteristics of the individual selected SGAs was also reviewed. The basic pharmacokinetic parameters are summarised in Table 2.

As the basic, lipophilic molecules, most psychoactive drugs have similar chemical properties. A consequence of this similarity is also mirrored in pharmacokinetics. SGAs are well absorbed from the gastrointestinal tract (i.e. with good bioavailability), with easy passage through the blood-brain barrier, with a large volume of distribution (V_d), with linear pharmacokinetics, and a large part of them is metabolised by hepatic enzymes, which results in their susceptibility to drug interactions and relatively slow elimination. However, there are also exceptions (e.g. longer/shorter biological half-life, the existence of an active metabolite, significant renal elimination, etc.) that need to be known to correctly interpret TDM results (Stahl, 2014; Mauri et al., 2018; Taylor et al., 2021).

These agents are subject to drug-drug interactions with other psychotropic agents or with medications used in the treatment of concomitant physical illnesses. Most pharmacokinetic interactions with newer antipsychotics occur at the metabolic level and usually involve changes in the activity of the major drug-metabolising enzymes involved in their biotransformation, i.e. the cytochrome P450 (CYP) monooxygenases and/or uridine diphosphate-glucuronosyltransferases (UGT) (Urichuk et al., 2008). Cytochrome P450 forms involved in the metabolism of SGAs are presented in Table 3.

Tobacco smoking is associated with the induction of drug-metabolizing enzymes, namely CYP1A2 and probably also UGTs (Kroon, 2007; Moschny et al., 2021). Therefore, smoking may influence the elimination of clozapine and olanzapine,

Table 2 – Basic pharmacokinetics parameters of SGAs

Drug	F (%)	Protein binding (%)	T_{max} (hours)	Half-life (hours)	Time to reach steady-state (days)	Usual oral dose range (mg/day)	Usual maximum oral dose (mg/day)
Aripiprazole	87	>99	3–5	75	14	10–30	30
Brexpiprazole	95	>99	4	91	10–12	2–4	4
Cariprazine	100	91–97	3–4	48–96	10–20	1.5–6	6
Clozapine	27–50	97	1–4	9–17	5–7	150–600	900
Lurasidone	9–19	>99	1–3	18–37	7	40–160	160
Olanzapine	60	93	5–8	21–54	5–10	10–20	30
Paliperidone	28	74	24	23	4–5	6–12	12
Quetiapine IR Quetiapine ER	70	83	1–1.5 6	5 8	1–2 2–3	150–750 400–800	800 800
Risperidone	70–85	90	1	EM: 3 PM: 20	4–6	2–6	8

SGAs are listed alphabetically; source: Hiemke et al. (2018); SmPCs – www.ema.europa.eu

SGAs – second-generation antipsychotics; F – bioavailability; T_{max} – time to reach maximum plasma concentrations; IR – immediate release; ER – extended release; EM – extensive metaboliser; PM – poor metaboliser

Table 3 – Forms of cytochrome P450 involved in the metabolism of SGAs and their active metabolites (major metabolic routes are in bold)

Drug	Enzymes responsible for metabolisation	Active metabolite
Aripiprazole	**CYP3A4, CYP2D6**	dehydroaripiprazole
Brexpiprazole	**CYP3A4, CYP2D6**	–
Cariprazine	**CYP3A4**, CYP2D6	desmethyl cariprazine and didesmethyl cariprazine
Clozapine	**CYP1A2, CYP3A4**, CYP2C19, CYP2C9, CYP2D6	norclozapine
Lurasidone	**CYP3A4**, BCRP	two active metabolites (ID-14283 and ID-14326)
Olanzapine	**CYP1A2**, CYP2D6, UGT1A4	N-desmethylolanzapin
Paliperidone	CYP3A4, P-glycoprotein	–
Quetiapine	**CYP3A4**, CYP2D6	norquetiapine
Risperidone	**CYP2D6, CYP3A4, P-glycoprotein**	9-hydroxyrisperidone (= paliperidone)

SGAs are listed alphabetically; source: Hiemke et al. (2018); Carrascal-Laso et al. (2021)
SGAs – second-generation antipsychotics; CYP – cytochrome P450; UGT – uridine diphosphate-glucuronosyltransferase; BCRP – breast cancer resistance protein

whose metabolism is mainly dependent on CYP1A2 and UGTs. Different studies have shown that plasma concentrations of clozapine (and its metabolite norclozapine) and olanzapine are lower, at the same dose, in smokers as compared to non-smokers (Tsuda et al., 2014; Moschny et al., 2021). Smoking cessation, if not accompanied by a dosage decrease, may be associated with increased plasma concentrations of these antipsychotics, possibly resulting in dose-related toxic effects (Gee et al., 2017).

Aripiprazole

Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3 to 5 hours after dosing. Aripiprazole undergoes minimal pre-systemic metabolism. The absolute oral bioavailability of the tablet formulation is 87% (Harrison and Perry, 2004; Mauri et al., 2017). At therapeutic concentrations, aripiprazole and dehydro-aripiprazole are more than 99% bound to serum proteins, primarily to albumin (Aripiprazole, 2009; Gettu and Saadabadi, 2023). Aripiprazole is extensively metabolised by the liver by three major biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for the dehydrogenation and hydroxylation of aripiprazole, while N-dealkylation is catalysed by CYP3A4

(Mauri et al., 2017; Gettu and Saadabadi, 2023). Aripiprazole is the predominant medicinal product moiety in systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole area under the concentration-time curve (AUC) in plasma (Aripiprazole, 2009). The mean elimination half-lives for aripiprazole are 75 and 146 hours in extensive and poor metabolisers of CYP2D6, respectively (Aripiprazole, 2009; Hart et al., 2022).

Brexpiprazole

Following its oral administration, brexpiprazole is extensively absorbed, with peak plasma concentrations occurring within 4 hours and the absolute oral bioavailability of the tablet formulation of 95% (Ishigooka et al., 2018). Brexpiprazole steady-state concentrations are attained within 10 to 12 days of dosing (Markovic et al., 2017; Mauri et al., 2017; Brexpiprazole, 2018). Brexpiprazole is highly protein-bound in plasma (more than 99%) (Brexpiprazole, 2018). The metabolism of brexpiprazole was shown to be mainly mediated by CYP3A4 and CYP2D6 leading to the formation of oxidative metabolites, with only one metabolite, DM-3411, present in plasma with more than 10% of plasma exposure. At steady-state, DM-3411 represents 23.1 to 47.7% of brexpiprazole exposure (AUC) in plasma (Brexpiprazole, 2018; Ishigooka et al., 2018). It should be noted that *in vivo* preclinical studies have shown that at clinically relevant plasma exposures of brexpiprazole, DM-3411 brain exposures were below the detection limit. Thus, DM-3411 is considered not to contribute to the therapeutic effects of brexpiprazole (Markovic et al., 2017; Brexpiprazole, 2018). After multiple once-daily administration of brexpiprazole, the terminal elimination half-life of brexpiprazole and DM-3411 is 91 and 85 hours, respectively (Markovic et al., 2017; Brexpiprazole, 2018). Population pharmacokinetic evaluation shows that CYP2D6 poor metabolisers have 47% higher exposure to brexpiprazole compared to extensive metabolisers (Ishigooka et al., 2018).

Cariprazine

The pharmacokinetics of cariprazine was tested in small short-term studies in both healthy volunteers and subjects with schizophrenia, with similar results (Nakamura et al., 2016; Cariprazine, 2017). Cariprazine is rapidly absorbed, reaching peak concentrations between 3 and 4 hours after oral dosing in healthy subjects. Its pharmacokinetics was linear in terms of AUC, but maximum concentration was more than proportional within the dose range from 3 to 5 mg in healthy subjects. Mean half-life was 2–5 days (1.5–12.5 mg/day) in the subjects with schizophrenia (Nakamura et al., 2016). Cariprazine is then primarily cleared by hepatic metabolism, mostly by CYP3A4 and, to a lesser extent, by CYP2D6. There are two active metabolites of note: desmethyl-cariprazine (DCAR) and didesmethyl-cariprazine (DDCAR): cariprazine activity is thought to be mediated by cariprazine itself and its two major active metabolites, which are pharmacologically equipotent to the maternal drug (Nakamura et al., 2016; Mauri et al., 2017). Cariprazine and its major

active metabolites are highly bound to plasma proteins (Cariprazine, 2017). Total cariprazine (sum of cariprazine + DCAR and DDCAR) exposure approaches 50% of steady state exposure in ~1 week of daily dosing while 90% of steady state is achieved in 3 weeks. At a steady state, exposure to DDCAR is approximately two to three-fold higher than to cariprazine, and exposure to DCAR is approximately 30% of cariprazine exposure (Nakamura et al., 2016; Cariprazine, 2017).

Clozapine

After oral administration, the drug is rapidly absorbed. The bound fraction is 97%. In steady-state conditions, peak blood levels occur 2.1 hours after administration (range 0.4 to 4.2 hours), and the Vd is 1.6 l/kg. Its elimination is biphasic, with a mean terminal half-life of 9–17 hours (Clozapine, 2002), resulting in achieving of steady-state plasma concentrations after 5–7 days of dosing. Clozapine is metabolized primarily by CYP1A2, with additional contributions by CYP2C19, CYP2C9, CYP2D6 and CYP3A4. Glucuronidation by UGT1A1, 1A3 and 1A4 is an important pathway in its metabolism (Erickson-Ridout et al., 2012). The main active metabolites are norclozapine (CYP1A2) and clozapine-N-oxide (CYP3A4), that are found in plasma at concentrations that are usually 50–90% and 10–35% of the concentrations of clozapine, respectively (Clozapine, 2002; Mauri et al., 2017; Correll et al., 2022).

Lurasidone

Lurasidone is rapidly absorbed and reaches peak serum concentration in approximately 1–3 hours after oral administration (Mauri et al., 2014). In a food effect study, lurasidone mean C_{max} and AUC were increased approximately by 2–3-times and 1.5–2-times, respectively, when administered with food compared to the levels observed under fasting conditions (Citrome, 2012a; Lurasidone, 2018). Its pharmacokinetics was linear in the range of 20–60 mg in healthy subjects and subjects with schizophrenia, but inter-individual variability was high (30–60%) in terms of C_{max} and AUC. Lurasidone shows a high rate of binding to human plasma albumin and α-1-glycoprotein (99%) (Citrome, 2013). The mean terminal half-life at steady state ranges from 18 to 37 hours in patients with schizophrenia (Lurasidone, 2018). Thus, after repeated oral doses in patients with schizophrenia, steady-state concentrations of lurasidone are reached within 7 days of starting lurasidone (Caccia et al., 2012; Citrome, 2013). Elimination is essentially by metabolism, primarily involving CYP3A4. The two main metabolites, the acidic derivative ID-20219 and its hydroxylated derivative ID-20220, have negligible affinities for D2 receptors and 5-HT1A, 5-HT2A and 5-HT7 receptors (Caccia et al., 2012; Citrome, 2013; Lurasidone, 2018).

Olanzapine

Approximately 85% of an oral olanzapine dose is absorbed, but due to inactivation by first-pass hepatic metabolism, overall oral bioavailability is around 60%. The peak

plasma concentration is reached within 5 to 8 hours (Olanzapine, 2006). The drug is 93% bound to plasma proteins. A mean elimination half-life of 33 hours (range 21–54 hours) leads to achieving the steady-state concentrations within 5–10 days of usage (Darby et al., 2008; Thomas and Saadabadi, 2023). Olanzapine is metabolized primarily by CYP1A2 and UGTs and with lesser extent by CYP2D6, CYP3A4 and flavin monooxygenase. The predominant pharmacologic activity comes from the parent olanzapine (Erickson-Ridout et al., 2011).

Paliperidone

Paliperidone is commercialised as an extended-release (XR) formulation. Following a single dose, paliperidone exhibits a gradual ascending release rate, allowing the plasma concentrations of paliperidone to steadily rise to reach C_{max} approximately 24 hours after dosing (Citrome, 2012b). With once-daily dosing of paliperidone XR, the terminal half-life is about 23 hours with a steady-state concentration attained in 4–5 days of dosing in most subjects (Paliperidone, 2021). The absolute oral bioavailability of paliperidone following paliperidone XR administration is 28% (Paliperidone, 2021). The plasma protein binding of paliperidone is 74% (Citrome, 2012b). Paliperidone XR undergoes very limited hepatic metabolism, with approximately 60% of the unchanged drug excreted via the kidneys and 11% eliminated unchanged in the faeces. Paliperidone XR does not appear to possess enzyme-inducing or enzyme-inhibiting properties as shown by the lack of CYP inhibition in *in vitro* studies with human liver microsomes (Citrome, 2012b; Mauri et al., 2017).

Quetiapine

After oral administration, quetiapine is well absorbed and extensively metabolized. The volume of distribution is 10 ± 4 l/kg. The pharmacokinetics of quetiapine and norquetiapine remains linear across approved dosing ranges (Mauri et al., 2017). Median C_{max} is reached within 1–1.5 hours for immediate-release (IR) formulation, and in 6 hours for extended-release (ER) formulation, respectively (Quetiapine, 2014). The drug is 83% bound to plasma proteins and is eliminated with an elimination half-life of 5–8 hours. Steady-state concentrations are achieved within 1–3 days of administration (Quetiapine, 2014; Maan et al., 2023). Quetiapine is extensively metabolised by the liver (Quetiapine, 2014), predominantly by CYP3A4-mediated sulfoxidation and dealkylation, and by CYP2D6 which is involved in the 7-hydroxylation of quetiapine (together with CYP3A4) (Mauri et al., 2017; Maan et al., 2023).

Risperidone

Risperidone is well and rapidly absorbed after oral administration with peak plasma concentration being reached in about 1 hour and oral bioavailability of about 70–85%. It mainly undergoes 9-hydroxylation in the liver that yields the active

metabolite 9-OH-risperidone, a step that is mainly catalysed by CYP2D6 and, to a lesser extent, by CYP3A4 (Zhou et al., 2006). As the pharmacological properties of 9-OH-risperidone are like those of risperidone, both are regarded as being able to contribute to the drug's overall antipsychotic effects in the treatment of schizophrenia, and thus represent the active moiety (Risperidone, 2008). For this reason, the ratio between risperidone and 9-OH-risperidone may play a crucial role in mediating the clinical effect (Paulzen et al., 2016; Schoretsanitis et al., 2016). Genetic influences, such as CYP2D6 genotype, play an important role in determining the variability of the pharmacokinetic parameters of risperidone (Vandenberghe et al., 2015). The mean half-life of risperidone is 3 hours in extensive metabolisers (most of the population), and 20 hours in poor metabolisers; the mean half-life of the active moiety (risperidone and its main metabolite) is almost constant at about 22 hours in both groups (Risperidone, 2008). Steady-state concentrations are reached within 5 days of treatment. Risperidone and its main metabolite are 89 and 77% bound to plasma proteins, respectively (Risperidone, 2008). Most of the 9-OH-risperidone is removed through renal excretion (Risperidone, 2008).

Therapeutic drug monitoring of SGAs

TDM allows responding to individual differences revealed during treatment by correct interpretation of clinical and laboratory findings. It gives the opportunity to avoid side effects, toxicity or lack of efficacy. Such optimization is intended to reduce the cost of treatment while increasing the patient safety.

In 2018, the TDM group of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) has published literature-based guidelines for the optimal use of TDM in psychiatry, and defined 4 levels of recommendation, based on empirical evidence (Table 4) (Hiemke et al., 2018).

Routine TDM is recommended especially for substances with a well-defined therapeutic reference range and a narrow therapeutic index (e.g. clozapine, olanzapine etc.). For other antipsychotics, TDM is recommended in specific situations. Table 5 presents a list of indications for TDM in psychiatry. The validity of these indications has to be examined and evaluated for each case individually (Bhavsar et al., 2024). Like any diagnostic test, TDM should only be requested when there is evidence that the result will provide an answer to a well-defined question (Steen et al., 2016; McCutcheon et al., 2018; Baldelli et al., 2021).

As for the timing of blood collection, it must be considered that TDM-guided psychopharmacotherapy mostly relies on trough drug concentrations (C_{trough}) at steady-state. A steady-state is reached under constant doses after at least 4 to 6 elimination half-lives and C_{trough} at the end of the longest dosing interval. For practicability, most blood samples taken for determination of C_{trough} are withdrawn in the morning before the first dose of the day, which is mostly the time of minimal

Table 4 – Levels of recommendation for TDM in psychiatry

Level	Evidence	Recommendation	Clinical consequences
1 = strongly recommended	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.	TDM is strongly recommended for dose titration and for special indications.	At therapeutic PC highest probability of response or remission; at "subtherapeutic" PC: response rate like placebo under acute treatment and risk of relapse under chronic treatment; at "supratherapeutic" PC: risk of intolerance or intoxication.
2 = recommended	Reported drug concentrations were obtained from PC at therapeutically effective doses and related to clinical effects; reports on decreased tolerability or intoxications at "supratherapeutic" PC.	TDM is recommended for dose titration and for special indications or problem solving.	TDM will increase the probability of response in non-responders. At "subtherapeutic" PC: risk of poor response; at "supratherapeutic" PC: risk of intolerance or intoxication.
3 = useful	Reported drug concentrations were calculated from PC at effective doses obtained from pharmacokinetic studies. PC 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.	TDM is useful for special indications or problem solving.	TDM can be used to control whether PC are plausible for a given dose, or clinical improvement may be attained by dose increase in nonresponders who display too low PC.
4 = potentially useful	PC 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.	TDM is not recommended for dose titration but may be potentially useful for special indications or problem solving.	TDM should be restricted to special indications.

Source: modifying according to Hiemke et al. (2018)
TDM – therapeutic drug monitoring; PC – plasma concentration

Table 5 – Typical indications for measuring drug concentrations in the blood of psychiatric patients

Uncertain adherence to medication
Narrow therapeutic range
Patients with abnormally high or low body weight
Clinical improvement and adverse effects under recommended doses
Combination treatment with a drug known for its interaction potential or suspected drug interaction
Lack of clinical improvement under recommended doses
Patients with pharmacokinetically relevant comorbidity (hepatic or renal insufficiency, cardiovascular disease)
Specific patient groups (pregnant or breastfeeding, children or adolescents, elderly patients > 65 years)
Patients with intellectual disability
Forensic psychiatric patients
Patients with restrictive gastrointestinal resection or bariatric surgery
Problem occurring after switching from an original preparation to a generic form
Presence of a genetic peculiarity concerning drug metabolism (genetic deficiency, gene multiplication)

Source: modifying according to Hiemke et al. (2018)

Table 6 – Recommended therapeutic reference ranges, laboratory alert levels and levels of recommendation for TDM

Drug	Level	Therapeutic reference range (ng/ml)	Laboratory alert level (ng/ml)
Aripiprazole	2	100–350	1000
Brexpiprazole	3	40–140	280
Cariprazine	3	10–20	40
Clozapine	1	100–350	1000
Lurasidone	3	15–40	120
Olanzapine	1	20–80	100
Paliperidone	2	20–60	120
Quetiapine	2	100–500	1000
Risperidone	2	20–60	120

SGAs are listed alphabetically; source: Hiemke et al. (2018); Schoretsanitis et al. (2020)
SGAs – second-generation antipsychotics; TDM – therapeutic drug monitoring

drug concentrations (Urban and Cubała, 2017; Baldelli et al., 2021). A frequent problem, however, is blood sampling at different time points throughout the dosing interval. This leads to concentrations that may be misinterpreted when true trough levels are lower or higher. It is also necessary to consider the pharmaceutical form, which can change the pharmacokinetics of the drug itself (e.g. long-acting injectable antipsychotics or extended-release tablets).

For most used psychotropic drugs, a reference therapeutic range is established, usually given in ng/ml (Table 6) (Hiemke et al., 2018; Schoretsanitis et al., 2020). It is defined by a minimum therapeutic concentration below which there is a risk of ineffectiveness of the drug, and a maximum therapeutic concentration, after exceeding which there is a significantly higher risk of adverse effects and toxicity. Blood concentrations with an increased risk of toxicity are normally much higher than the upper thresholds of therapeutic reference ranges and are defined as "laboratory alert level" (Table 6) (Hiemke et al., 2018). The laboratory alert should lead to a 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 (Schoretsanitis et al., 2020; Baldelli et al., 2021).

Reference therapeutic ranges of antipsychotics are established for patients aged 18–65 years. These limits are not set for children and seniors. In the case of antipsychotics, they are intended only for patients with psychotic disorders. It is not clear whether they can be applied, for example, to patients with affective disorders,

Table 7 – Ranges of metabolite-to-parent drug concentration ratios

Drug	Active metabolite	Metabolite to compound ratios
Aripiprazole	dehydroaripiprazole	0.3–0.5
Brexpiprazole	–	–
Cariprazine	N, N-didesmethyl-cariprazine	3–6
Clozapine	norclozapine	non-smokers: 0.5–0.6 smokers: 0.4–0.7
Lurasidone	two active metabolites (ID-14283 and ID-14326)	–
Olanzapine	N-desmethyl-olanzapine	non-smokers: 0.1–0.3 smokers: 0.2–0.4
Paliperidone	–	–
Quetiapine	N-desalkyl-quetiapine	0.54–3.10
Risperidone	9-hydroxy-risperidone (= paliperidone)	3.6–22.7

SGAs are listed alphabetically; source: Hiemke et al. (2018); Schoretsanitis et al. (2020)
SGAs – second-generation antipsychotics

which is a group of patients that are relatively often treated with antipsychotics (Hiemke et al., 2018; McCutcheon et al., 2018; Baldelli et al., 2021).

For several SGAs, metabolites actively contribute to the overall clinical effect of the parent compound. For this reason, TDM should contain the quantification of active metabolites. Table 7 shows the ratios of concentrations of metabolites to parent drugs. The calculated ranges contain 68% of the ratios expected at standard doses, i.e. ratios within the range of mean ± 1 SD (standard deviation) assuming a normal distribution (Hiemke et al., 2018; Schoretsanitis et al., 2020). A ratio above or below the "normal ratio" may indicate drug adherence problems or metabolic abnormalities due to genetic variation or drug-drug interactions with comedications exhibiting enzyme-inhibiting or inducing properties.

Aripiprazole

The dose range for aripiprazole is well-defined, and it reliably predicts the plasma level, dopamine receptor occupancy, and clinical response (Sparshatt et al., 2010). Plasma level variation appears to have a minimal impact on clinical response, but it may predict some adverse effects. TDM has a limited value in the clinical use of aripiprazole, but it may be useful in assuring adherence and optimizing the response in individuals.

Kirschbaum et al. (2005, 2008) measured and related to dose, co-medication, and clinical effects of aripiprazole and dehydroaripiprazole serum concentrations in patients with psychiatric disorders, including therapeutic effects and side effects. In several studies, patients were treated with mean doses of 20 mg/day (± 8 SD); range 7.5–60 mg/day of aripiprazole (Kirschbaum et al., 2005, 2008). Serum concentrations correlated significantly with the dose. Mean concentrations of the active metabolite dehydroaripiprazole amounted to 40% of the parent compound. Co-medication with CYP3A4 and CYP2D6 inducers or inhibitors changed serum concentrations up to 51% (Kirschbaum et al., 2008). The authors reported the best improvement with serum concentrations between 150 and 300 ng/ml. None, or only mild side effects were detected in patients, with aripiprazole plasma concentrations between 110 and 249 ng/ml (Kirschbaum et al., 2008). In literature analysing the studies, the safe and effective plasma concentration of aripiprazole is suggested to be in the range of 150–210 ng/ml (Sparshatt et al., 2010; Hart et al., 2022).

In most patients, the relationship between the dose and the achieved concentration is proportional. It should be noted that at a concentration above 100–150 ng/ml, the occupancy of D2 and D3 receptors reaches maximum saturation (Gründer et al., 2008). In other studies, the concentrations achieved by patients of different age, sex, BMI (body mass index), having different smoking habits, and taking other medicines (such as fluoxetine, and paroxetine) were compared. There were no significant effects of these factors on the plasma concentrations of aripiprazole (Molden et al., 2006; Bachmann et al., 2008; Kim et al., 2008). Significant differences

were expressed in patients with different CYP2D6 genotypes who metabolize the drug to a variable extent and reach similar concentrations at doses that differ by up to 40% (Hendset et al., 2007; Zhang et al., 2018).

The EMA recommends (Aripiprazole, 2009) dose adjustment for aripiprazole in patients who are known CYP2D6 poor metabolizers (PMs). Concentration/dose (C/D) ratios recorded in 62 patients treated with oral aripiprazole indicated that PMs typically need 30–40% lower doses to achieve similar serum concentrations as normal metabolizers (NMs) (Hendset et al., 2007). Suzuki et al. (2014b) demonstrated that subjects with any or reduced functional alleles (×5 and ×10) for CYP2D6 had higher C/D ratios of the active moiety of the two compounds than those without the alleles. In a retrospective cohort study including pharmacokinetic data from 890 patients, it was found that aripiprazole active moiety exposure increased 1.6 times and 1.4 times for PMs and intermediate metabolizers (IMs), respectively (Jukic et al., 2019).

Because serum concentrations of aripiprazole and dehydroaripiprazole were highly variable between individuals and distinct ranges were associated with good therapeutic response and minimal side effects (Lopez and Kane, 2013; Bustillo et al., 2018; Jovanović et al., 2020), the authors suggested that TDM could help improve the antipsychotic therapy. According to the AGNP consensus guidelines (Hiemke et al., 2018), aripiprazole TDM is recommended (recommendation level 2) indicating a therapeutic range between 150 and 350 ng/ml (Table 6).

Brexpiprazole

There are limited data available. In any case, following a multiple oral administration, the C_{max} and AUC_{24h} of brexpiprazole and its metabolite DM-3411 increased in a dose-dependent manner (Ishigooka et al., 2018). These results showed dose proportionality for C_{max} and AUC_{24h} of brexpiprazole. Moreover, the C_{max} and AUC_{24h} of brexpiprazole showed an accumulation of about 2.5- to 5.5-fold on day 14, compared with those on day 1 (Ishigooka et al., 2018). Brexpiprazole C_{max} values following multiple once-daily administrations of 1 mg, on days 1 and 14 were 10.2 ± 5.0 ng/ml and 29.3 ± 15.1 ng/ml; of 4 mg, 37.0 ± 13.5 ng/ml and 165 ± 102 ng/ml; of 6 mg, 69.9 ± 29.1 ng/ml and 206 ± 123 ng/ml, respectively. For its metabolite DM-3411, C_{max} values were for the brexpiprazole dosage of 1 mg, 3.04 ± 1.30 ng/ml and 15.3 ± 9.3; for the drug dosage of 4 mg, 11.7 ± 6.7 and 66.9 ± 29.2; for the drug dosage of 6 mg, 25.8 ± 8.4 and 128 ± 52 ng/ml, respectively (Ishigooka et al., 2018). According to the AGNP consensus guidelines (Hiemke et al., 2018), cariprazine TDM is potentially useful (recommendation level 3), indicating a therapeutic range of 40–140 ng/ml (Table 6).

Cariprazine

At present, no data regarding cariprazine TDM is available. Prescribing information of the pharmaceutical company demonstrated that after 12 weeks of treatment

with 6 mg/day of cariprazine, steady-state plasma concentrations range from 32 to 49 ng/ml (Frankel and Schwartz, 2017). However, a therapeutic range of cariprazine has not been established (Cariprazine, 2017). According to the AGNP consensus guidelines (Hiemke et al., 2018), cariprazine TDM is potentially useful (recommendation level 3), indicating a therapeutic range of 10–20 ng/ml (Table 6).

Clozapine

Plasma concentrations of clozapine vary widely among individuals, so oral dose is not a reliable indicator of plasma drug concentrations (Dettling et al., 2000; Spina et al., 2000; Samanaite et al., 2018). This wide variability results from interindividual differences in bioavailability and the fact that clozapine is metabolized by highly variable CYP1A2 activity (Spina et al., 2000; Khan and Preskorn, 2005). However, serum determinations showed an acceptably low mean inter-patient variability of 20%, which means that serum clozapine determinations can be used to assess patient compliance. The high inter-individual and low intra-individual variability of clozapine plasma concentrations confirms the utility of TDM. Both the antipsychotic efficacy and adverse effects of clozapine are positively correlated with plasma drug concentration (Spina et al., 2000; Khan and Preskorn, 2005; Tralongo et al., 2023).

Most investigators have found that a threshold plasma concentration of 350–420 ng/ml is associated with an increased likelihood of a good clinical response to the drug. In addition, most of the data reviewed suggest that increasing the oral dose of clozapine in non-responders to achieve a plasma concentration of at least 350–420 ng/ml may improve response rates to treatment (Fabrazzo et al., 2002; Wong et al., 2006; Kitchen et al., 2021).

Concentrations above 1,000 ng/ml significantly increase the risk of confusion, delirium and generalized seizures (Khan and Preskorn, 2005; Kitchen et al., 2021; Skokou et al., 2022; Tralongo et al., 2023). Clozapine-induced obsessive/compulsive symptoms have been reported by many authors and they were not uncommon side effects. The authors suggest that the emergence of these side effects may be related to higher plasma concentration of clozapine and clinicians should routinely check for and manage these side effects (Lin et al., 2006; Kim et al., 2019).

Plasma concentrations of clozapine (and the probability of reaching a given threshold value) can be influenced by many factors, such as age, sex, and smoking (Krivoy et al., 2021). TDM is useful especially when poor compliance is suspected, in patients with altered pharmacokinetics (e.g. ultrarapid CYP1A2 metabolizers, concomitant treatment with strong CYP1A2 inhibitor), and in non-responders who require the use of very high doses (Eap et al., 2004; Schoretsanitis et al., 2023). Inflammatory reactions may suddenly increase clozapine concentrations and lead to toxic delirium (Clark et al., 2018; Moschny et al., 2021).

Clozapine still represents the gold standard in the treatment of drug-resistant schizophrenia, and the optimal plasma levels for acute and maintenance clozapine

treatment are well known. Experience from the literature shows that TMD in clinically defined subgroups of patients, such as pharmacoresistant schizophrenia, is clinically beneficial.

Lurasidone

At present, no evidence about lurasidone TDM is available. It is reported that following single-dose administration of 40 and 80 mg lurasidone-hydrochloride (corresponds to 37 and 74 mg of the free base), the mean C_{max} values in serum were approximately 54 and 64 ng/ml, respectively. Following steady-state administration of 40 mg and 80 mg, the mean C_{max} values in serum were approximately 48 and 79 ng/ml, respectively (Caccia et al., 2012; Greenberg and Citrome, 2016). According to the AGNP consensus guidelines (Hiemke et al., 2018), lurasidone TDM is potentially useful (recommendation level 3), indicating a therapeutic range of 15–40 ng/ml (Table 6).

Olanzapine

The studies showed that mean plasma olanzapine concentrations vary widely, depending on factors such as the prescribed daily dose and the duration of treatment (Darby et al., 2008). The reviewed studies strongly indicate a relationship between clinical outcomes and plasma olanzapine concentrations (Lane et al., 2002; Bergemann et al., 2004; Mauri et al., 2005). However, a large inter-patient variability in plasma olanzapine concentrations after administration of the same dose is described (Mauri et al., 2007; Citrome et al., 2009). Smokers and men show greater olanzapine clearance than women and non-smokers, which is mirrored in significantly lower mean plasma concentrations that become evident after the fifth week of treatment (Moschny et al., 2021). Stopping smoking may be associated with an increase in side effects, such as extrapyramidal symptoms, within a few days, unless the dose is adjusted (Spina and de Leon, 2007; Urichuk et al., 2008).

The monitoring of blood olanzapine concentrations can be considered very useful in assessing therapeutic efficacy and controlling adverse events. A therapeutic range has been established between 20 and 50 ng/ml. Levels above 50 ng/ml might be associated with a higher risk of extrapyramidal symptoms (Perry et al., 2001; Lane et al., 2002; Fellows et al., 2003; Mauri et al., 2005). A positron emission tomography study analysed the differences in D2 receptor occupancy based on olanzapine dose/plasma olanzapine concentrations. It found a relationship between plasma olanzapine concentrations and D2 occupancy (Gründer et al., 2011). Olanzapine is a potent 5-HT2 blocker and shows greater 5-HT2 than D2 occupancy at all doses. At a plasma concentration of 10.3 ng/ml, olanzapine occupied 50% of the available D2 receptors. Within the usual clinical range of 10–20 mg/day, D2 occupancy varies from 71 to 80% (Moresco et al., 2004; Gründer et al., 2011). Attarbaschi et al. (2007) have explored the relationship between striatal D2 receptor occupancy and extra-pyramidal symptom (EPS) in 17 patients with bipolar disorder receiving

olanzapine 5–45 mg/day for at least 14 days, and found a significant correlation between plasma concentrations and occupancy. The bipolar patients did not show any EPS at D2 occupancy levels of 28–80 ng/ml (Attarbaschi et al., 2007).

Further investigations, including long-term studies, may provide more specific indications and possibly indicate a narrower therapeutic range. According to the AGNP TDM consensus group, olanzapine TDM is strongly recommended (recommendation level 1), as an established therapeutic range (20–80 ng/ml) is proposed to yield an optimal response and minimise side effects (Hiemke et al., 2018) (Table 6).

Paliperidone

In a 6-week study of patients with schizophrenia receiving paliperidone daily doses of 3, 9 and 15 mg, the optimal range of doses was calculated based on position emission tomography measures (receptor occupancy in the striatum and the temporal cortex) and the plasma concentrations of the drug (Arakawa et al., 2008). An optimal D2 receptor occupancy was found at the level of 70–80% at doses of 6–9 mg/day (Arakawa et al., 2008). In the study by Muly et al. (2012), D2 receptor occupancy was evaluated in different areas of the brain in macaques receiving risperidone and paliperidone, and compared with plasma and cerebrospinal fluid concentrations. The optimum plasma concentration range of 40–80 ng/ml for both substances was confirmed (Muly et al., 2012).

The retrospective analysis of data obtained from 217 patients from four medical centres investigated the relationship between serum paliperidone concentrations and clinical outcomes (Nazirizadeh et al., 2010). Intra-individual variability of trough serum concentrations was also analysed in patients treated with either paliperidone XR or risperidone IR (Nazirizadeh et al., 2010). The mean paliperidone concentration was 36 ± 25 ng/ml, and the mean dose-corrected concentration was 4.7 ± 2.9 ng/ml/mg. Among patients receiving paliperidone as antipsychotic monotherapy, who showed at least a much-improved level according to the Clinical Global Impressions Scale (CGI Score), the 25^{th}–75^{th} percentiles of paliperidone concentrations were 20–52 ng/ml; these were very similar to the recommended therapeutic range of 20–60 ng/ml for risperidone plus 9-hydroxy-risperidone (Nazirizadeh et al., 2010).

In other reports, the same therapeutic range of 20–60 ng/ml is proposed, as for risperidone (Liu et al., 2015). In paliperidone therapy, the relation between clinical improvement, risk of extrapyramidal symptoms, increased prolactin levels and plasma concentrations, is not linear (Suzuki et al., 2014a). It has also been noticed that CYP2D6 polymorphism does not significantly affect the plasma concentrations of the drug (Patteet et al., 2015).

The authors concluded that risperidone and paliperidone have a similar therapeutic range and similar intra-individual variability in terms of trough serum concentrations. For treatment optimisation, monitoring of plasma concentrations may be as

useful for paliperidone as for risperidone (Nazirizadeh et al., 2010). According to the AGNP consensus guidelines (Hiemke et al., 2018) paliperidone TDM is recommended (recommendation level 2) (Table 6).

Quetiapine

Only a few short-term studies have investigated the relationship between quetiapine plasma concentrations and clinical responses (DeVane and Nemeroff, 2001; Sparshatt et al., 2008; Handley et al., 2013). Although the data from Takano et al. (2004) argue in favour of the existence of a relationship between plasma quetiapine concentrations and clinical responses, they provide only some preliminary information about the significance of plasma quetiapine concentrations. Other authors have failed to identify an optimal therapeutic range for quetiapine (Melnik et al., 2010; Sparshatt et al., 2011). Only a relationship between the dose and D2 receptor occupancy and preferential D2 receptor binding in the extrastriatal areas was observed (Vernaleken et al., 2010; Gründer et al., 2011; Sparshatt et al., 2011). Similar results were obtained in 80% of patients in mono and polytherapy, significantly lower concentrations were obtained only in patients co-administered with carbamazepine (Hasselstrøm and Linnet, 2004; Castberg et al., 2007).

The influence of age and sex on the increase of quetiapine concentrations was confirmed, with higher concentrations in women having no clinical significance (Aichhorn et al., 2006). An exceptional increase in the concentration of quetiapine has been noticed with valproate co-administration. An additional factor is the polymorphism of CYP3A4 among patients. CYP3A4*22 allele is responsible for an increase in quetiapine concentration (van der Weide and van der Weide, 2015).

The therapeutic range of 100–500 ng/ml was proposed in the AGNP guidelines (Hiemke et al., 2018). TDM is therefore recommended to check that plasma concentrations are acceptable for administered doses and to optimize clinical response in non-responders with low concentrations (Hiemke et al., 2018). However, only a few results are currently available and they do not entirely support the value of plasma concentration for adjusting quetiapine doses in clinical practice; further investigations are therefore necessary.

Risperidone

The overall pharmacological effects of risperidone depend on the sum of the plasma concentrations of risperidone and its metabolite 9-OH-risperidone, and thus monitoring plasma concentrations of the parent compound alone may lead to erroneous interpretations (Yoshimura et al., 2001; Aravagiri et al., 2003). It appears that monitoring plasma concentrations of the active moiety may be useful, but further investigations are needed to clarify the discrepancies in the results obtained so far (Paulzen et al., 2016; Korell et al., 2017). This discrepancy may be due to large variability in plasma drug concentrations and a lack of studies using fixed doses. An important indicator of the efficacy of treatment is the D2 receptor occupancy, which

should reach 65% for a minimal therapeutic effect (Remington et al., 2006; Muly et al., 2012).

Both risperidone and 9-OH-risperidone have large intra- and inter-individual differences in plasma concentrations. Since the pharmacological properties of 9-OH-risperidone are like those of risperidone, both can contribute to the overall antipsychotic effects of the drug in the treatment of schizophrenia and thus constitute the active ingredient (Seto et al., 2011).

In chronic schizophrenic patients with an acute exacerbation of the disorder, plasma levels of risperidone and its active metabolite are correlated with the occurrence of Parkinsonian side effects (Spina et al., 2001; Riedel et al., 2004; Darby et al., 2008). The range of therapeutic plasma concentrations of risperidone has not been established yet: the plasma threshold for Parkinsonian side effects is 74 ng/ml, but the minimum effective plasma concentration of the active ingredient is unclear. Some data suggests that the normal range is between 15 and 60 ng/ml, but this needs to be confirmed (Mauri et al., 2001; Puangpetch et al., 2016; Lu et al., 2021).

The effect of the CYP2D6 genotype on risperidone metabolites clearance, with comparable efficiency of treatment, was proven. Poor metabolizers achieved concentrations of active moiety up to 3.3-fold higher at the same doses (Riedel et al., 2004; Locatelli et al., 2010). Similarly, patients with parkinsonism or dystonia as well as chronic patients, achieved higher concentrations (Spina et al., 2001; Yasui-Furukori et al., 2009). Monitoring levels of prolactin could be an effective indicator of the patient's cooperation. Regarding the unequivocally determined relationship between doses, receptor occupancy levels and therapeutic plasma concentrations, monitoring of the latter would seem appropriate only in individual situations, for example, lack of therapeutic response, unexplained adverse effects, or co-medication.

Studies on the pharmacokinetics of risperidone and its metabolites depending on age, gender, body weight, smoking habits, co-administered drugs, and CYP2D6 genotype have been conducted (Feng et al., 2008; Zhang and Malhotra, 2018; Nofziger et al., 2020). It was shown that there is a linear relationship between age and 9-OH-risperidone clearance (Feng et al., 2008).

The conversion of risperidone to 9-hydroxy-risperidone by CYP2D6 suggests inhibition of CYP2D6 or down-regulation of DNA in the first 2 months. The time course of identified accumulations suggests that both CYP inhibition and DNA regulatory mechanisms may participate in drug metabolism. Therefore, long-term TDM may optimize risperidone therapy (Zhang and Malhotra, 2018; Nofziger et al., 2020).

According to the AGNP consensus guidelines (Hiemke et al., 2018), risperidone TDM is recommended (recommendation level 2) as there are suggested therapeutic ranges obtained from plasma concentrations at therapeutically effective doses: the proposed plasma risperidone concentration range is 20–60 ng/ml (Table 6).

Discussion and Conclusion

TDM of antipsychotics is a specific clinical pharmacology method for monitoring therapy by measuring serum drug concentrations, with subsequent interpretation and good collaboration with the clinician. In personalised medicine, it can help individualise dosing for rational therapy, minimize side effects, reduce mortality and morbidity, and reduce healthcare costs. Studies suggest that the pharmacokinetics of certain drugs is characterized by large inter- and intra-individual differences (age, gender, lifestyle, genetic and metabolic characteristics, drug interactions), a narrow therapeutic range or non-linear dose-concentration ratio. All these features provide the need and desirability for TDM for dose optimization or flexible dosing according to clinical symptoms. Phenotyping and genotyping can enhance TDM at a higher level. Antipsychotic plasma concentrations are a valuable but underutilized tool in several clinical conditions. Improving decision-making through better access to information on the plasma concentration of antipsychotics can have a significant impact on the quality of care and outcomes of patients with schizophrenia. However, it is important to emphasize that TDM is not necessarily required for all new antipsychotics, as there is no clear data supporting a relationship between plasma drug concentrations and clinical outcomes or side effects.

A proven exception is the concentration-dependent proconvulsant effects of clozapine, which make TDM highly recommended for overdose prevention (Dettling et al., 2000; Spina et al., 2000; Samanaite et al., 2018), as outlined in the AGNP-TDM general guidelines (Hiemke et al., 2018). Likewise, TDM is recommended to determine the optimal tolerability of olanzapine and risperidone (Yoshimura et al., 2001). Furthermore, there are no clinical pharmacokinetic data, particularly long-term data, for some other atypical antipsychotics, which will require future research. It should be kept in mind that optimal plasma concentration ranges for clozapine, risperidone and olanzapine are suggested by some authors, but not all. Studies of quetiapine provide limited information, and there is no direct data for aripiprazole; however, there are a few reported investigations that need to be confirmed and expanded.

In addition, TDM is a powerful tool that enables treatment tailored to the specific needs of individual patients, identifying “pseudo-pharmacoresistance” issues such as poor compliance, high individual metabolic levels, excessive patient water consumption, excessive smoking, drug abuse, as well as the occurrence of unpredictable side effects and possible drug interactions. The implementation of TDM is based on several disciplines, following pharmacokinetic, pharmacodynamic, analytical and pharmacoeconomic aspects. Determining the serum concentration of the drug alone cannot be considered sufficient. It is necessary to interpret the result in context of the clinical condition of the patient and other available data, considering the basic diagnosis and the pharmacokinetics of the administered drug.

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