Acta Pharm. **64** (2014) 387–401
DOI: 10.2478/acph-2014-0036

Review

Therapeutic drug monitoring of atypical antipsychotic drugs

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Schizophrenia is a severe psychiatric disorder often associated with cognitive impairment and affective, mainly depressive, symptoms. Antipsychotic medication is the primary intervention for stabilization of acute psychotic episodes and prevention of recurrences and relapses in patients with schizophrenia. Typical antipsychotics, the older class of antipsychotic agents, are currently used much less frequently than newer atypical antipsychotics. Therapeutic drug monitoring (TDM) of antipsychotic drugs is the specific method of clinical pharmacology, which involves measurement of drug serum concentrations followed by interpretation and good cooperation with the clinician. TDM is a powerful tool that allows tailor-made treatment for the specific needs of individual patients. It can help in monitoring adherence, dose adjustment, minimizing the risk of toxicity and in cost-effectiveness in the treatment of psychiatric disorders. The review provides complex knowledge indispensable to clinical pharmacologists, pharmacists and clinicians for interpretation of TDM results.

Keywords: therapeutic drug monitoring, antipsychotic drugs, therapeutic reference ranges

Accepted July 3, 2014

INTRODUCTION

Therapeutic drug monitoring (TDM) of antipsychotic drugs is the specific method of clinical pharmacology for the monitoring of therapy by using measurement of drug serum concentrations followed by interpretation and good cooperation with the clinician (1–3). Phenotyping and genotyping can raise therapeutic drug monitoring to a higher level. Optimal outcomes of TDM require appropriate use of available analytical methods and basic knowledge, which must be amalgamated with the clinical situation of the patient, a complex joint effort of laboratory specialists, pharmacologists, pharmacists, treating physicians and the patient (4). Antipsychotic medication is the primary intervention for stabilization of acute psychotic episodes and prevention of recurrences and relapses in patients with schizophrenia (5). There are two groups of antipsychotic drugs. The older class of antipsychotic agents – typical antipsychotics, includes haloperidol, fluphenazine, and

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perphenazine (6). Currently, these medications are used much less frequently than newer atypical antipsychotics. They have fallen somewhat out of favor because of side effects (extrapyramidal symptoms, tardive dyskinesia, neuroleptic malignant syndrome).

Atypical antipsychotics

Newer or atypical or second generation antipsychotics include clozapine, risperidone, olanzapine, quetiapine, sertindole, ziprasidone, aripiprazole and amisulpride (6). These agents tend to be characterized by a low propensity to produce acute extrapyramidal symptoms and tardive dyskinesia, a weak potential to cause elevation of serum prolactin levels, and a broad spectrum of activity involving not only positive and negative symptoms, but also other symptom dimensions of schizophrenia (*i.e.*, cognitive, aggressive and depressive symptoms). On the other hand, treatment with some of these medications has been associated with a substantial risk of metabolic effects (such as weight gain, hyperglycaemia and lipid dysregulation), cerebrovascular adverse events (stroke, in particular), and cardiovascular adverse events (particularly prolongation of heart-rate corrected QT interval of the electrocardiogram) (7–9). Metabolic side effects seem to be greatest with clozapine and olanazapine, intermediate with resperidon/paliperidon and quetiapine, and relatively minimal with ziprasidone and aripiprazole (10).

This review provides complex knowledge indispensable to clinical pharmacologists, pharmacists and clinicians for interpretation of TDM results.

Therapeutic drug monitoring

Wanted and unwanted drug effects depend on concentrations of the drug at its target site (11). After a given dose, the resulting blood concentrations of antipsychotic drugs are higly variable among individuals. The resulting plasma concentration at a given dose cannot be predicted by the dose. This is certainly a result of interindividual variabilities in drug metabolism by hepatic and extrahepatic enzymes. However, other factors, such as drug transporters involved in absorption, distribution and elimination, are probably also relevant. The patients' adherence to taking the drug at the prescribed dose and at recommended times is another factor that contributes to the highly variable blood concentrations. Antipsychotic drugs exert most therapeutic actions by blocking the dopamine D2-like receptors. It has been shown that plasma concentrations of antipsychotic drugs correlate well with receptor occupancy. In accordance with the high variability of drug concentrations in plasma under the same doses, it was found that receptor occupancy correlates better with plasma concentrations than with daily doses. Optimal response was seen at 70–80 % receptor occupancy, and 80 % receptor occupancy was defined as the threshold for the occurrence of extrapyramidal side effects (12, 13). Therefore, the antipsychotic drug plasma concentration is a valid measure of the drug at its primary target structure in the brain (11). Therapeutic drug monitoring of atypical antipsychotics affords the opportunity to reduce toxicity and increase adherence (14). However, the clinical value of using plasma concentrations of antipsychotics to monitor patients with schizophrenia is a contentious issue. Excessively high concentrations may be associated with clinical deterioration of the patient because of antipsychotic toxicity. The rationale for using therapeutic drug monitoring of atypical antipsychotics is still a matter of debate, but there is growing evidence that it can improve efficacy, especially when patients do not respond to

therapeutic doses or when they develop adverse effects (15). Monitoring of plasma concentrations has contributed to our understanding of cases of non-response to pharmacological therapy by distinguishing ‚pseudo' drug resistance (characterized by low plasma concentrations as a result of greater metabolic activity or poor adherence) and ‚true' drug resistance (characterized by appropriate plasma concentrations for the administered dose but poor receptor sensitivity). The importance of TDM remains when it comes to identifying ‚pseudo-pharmacoresistance' problems such as poor adherence, high individual levels of metabolism, excessive water consumption by patients, excessive smoking, drug abuse, and appearance of unpredictable adverse effects and possible drug interactions.

At usual clinical doses, atypical antipsychotics generally appear not to markedly affect the metabolism of co-administered medications (16, 17). However, 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 major drug-metabolizing enzymes involved in their biotransformation, *i.e.*, the cytochrome P450 (CYP) monooxygenases and/or uridine diphosphate-glucuronosyltransferases (UGT). Most documented metabolic interactions involve antidepressant and antiepileptic drugs (Table I). Tobacco smoking is associated with induction of drug metabolizing enzymes, namely, CYP1A2 and, possibly, UGTs. Smoking may influence elimination of antipsychotics, such as clozapine and olanzapine, whose metabolism is mainly dependent on CYP1A2 and UGTs.

Table I. Effect of various selective serotonin reuptake inhibitors (SSRIs) and antiepileptics on plasma concentrations of antipsychotics[a]

Antipsychotic	SSRI	Effect on plasma level	Antiepileptic	Effect on plasma level
Clozapine	Fluoxetine	Increase (40–70 %)	Carbamazepine	Decrease (50 %)
	Paroxetin	Increase (20–40 %)	Valproic acid	No change/minimal increase
	Fuvoxamine	Increase (up to 5–10 times)	Phenobarbital	Decrease (30–40 %)
Risperidone	Fluoxetine	Increase (75 %)	Carbamazepine	Decrease (50–70 %)
	Paroxetine	Increase (40–50 %)		
	Fluvoxamine	Minimal increase (10–20 %)		
	Sertraline	Minimal increase		
Olanzapine	Fluoxetine	No change/minimal increase	Carbamazepine	Decrease (30–70 %)
	Fluvoxamine	Increase (up to 100%)	Lamotrigine	No change/minimal increase
Quetiapine			Carbamazepine	Decrease (80 %)
			Valproic acid	Increase (70–80 %)
			Phenytoin	Decrease (80 %)
Aripiprazole			Valproic acid	Decrease (20–30 %)
Ziprasidone			Carbamazepine	Decrease (20–40 %)

[a] Only data from controlled studies are used (14).

Determination of psychotropic drugs

Various methods are used for the determination of drugs in biological fluids: imunonochemical, electromigration or electrophoretic and chromatographic methods, which provide high detection sensitivity and determination of drugs and their active and non-active metabolites in one run (18). Immunochemical methods, in comparison with chromatographic methods, do not allow determination of a single drug and its metabolites. Another disadvantage is the cross-reaction in which antibodies react differently with different metabolites, which hinders accurate quantification. The risk of interferences increases with structural similarities (19). In 1979, Brunswick *et al*. (20) described a specific radioimmunoassay for the determination of amitriptyline and nortriptyline. As the immunochemical methods have a relatively high limit of detection, they are preferably used as a screening of overdose rather than for therapeutic drug monitoring. Chromatographic methods, which have been most commonly used in recent years, include high performance liquid chromatography (HPLC) and gas chromatography (GC). Gas chromatography is used for the determination of antidepressant drugs, since many of them are structured amines. GC is a simple, high-resolution, sensitive, reproducible and inexpensive method. Fernandes *et al.* (21) published a method for the determination of fluoxetine in plasma by gas chromatography with mass spectrometric detection (GC-MS). Eap *et al*. (22) published a GC-MS method for the determination of citalopram, paroxetine, sertraline and their metabolites in plasma after derivatization. We have developed an LC-MS method for determination of five antidepressants and four atypical antipsychotics and their main metabolites in human serum (23). The method can be used for phenotyping, since it enables simultaneous measurement of parent drugs and the main metabolites. Kirchherr and Kühn-Velten (24) published a method for determination of forty-eight antidepressants and antipsychotics in human serum by HPLC-tandem mass spectrometry. Among the advantages of HPLC-MS is its wide range of applications, and the possibility to identify different combinations of active ingredients together with their active metabolites.

TDM of particular atypical antipsychotic drugs

Clozapine. – After oral administration, the drug is rapidly absorbed. Only 27–50 % of the dose reaches the systemic circulation unchanged because of extensive first-pass metabolism (25–28). It is 95 % bound to plasma proteins, primarily alpha-1-acid glycoprotein. The maximum plasma concentration (c_{max}) is reached within 1–4 hours after dosing. The mean half-life ranges from 9 to 17 hours. Steady-state plasma concentrations are reached after 7–10 days of dosing. Clozapine is primarily metabolized by CYP1A2, with additional contributions of CYP2C19, CYP2D6 and CYP3A4. Glucuronidation by UGT1A1, 1A3 and 1A4 is an important pathway in clozapine metabolism. The main active metabolites of clozapine are norclozapine (CYP1A2) and clozapine-N-oxide (CYP3A4), which are found in plasma concentrations that are usually 50–90 and 10–35 %, respectively, of clozapine concentrations (15). It has also been reported that clozapine and clozapine-N-oxide can interconvert, and this reversible metabolic pathway could at least partly explain the variability of plasma clozapine concentration among patients. Plasma clozapine concentrations vary widely between individuals, so the oral dose is not a reliable indicator of plasma drug concentrations (29). This wide variability is a result of interindividual differences in bioavailability and the fact that clozapine is metabolized by the highly variable activity of

CYPlA2. However, serum determinations showed an acceptably low mean intrapatient variability of 20 %, which means that serum clozapine determinations can be used to assess patient adherence. The high interindividual and low intraindividual variability of plasma clozapine concentrations confirm the usefulness of TDM. Both the antipsychotic efficacy and the adverse effects of clozapine are positively correlated with the plasma concentration of the drug. Norclozapine is not a useful predictor of therapeutic response (30). Most researchers have found that the threshold plasma clozapine concentration at steady-state of 350–420 ng mL^{-1} is associated with increased probability of a good clinical response to the drug (15). Furthermore, in a follow-up study of a sample, the concentration--response relationship was found to be consistent over a 2.5-year period. In addition, five of seven previous non-responders became responders when plasma clozapine concentrations were increased to above 350 ng mL^{-1}. There is also a relationship between serum clozapine concentrations and CNS adverse effects. For example, Olesen *et al.* (31) found a significant correlation between clozapine concentrations and EEG changes. Concentrations above 1000 ng mL^{-1} significantly increased the risk of confusion, delirium and generalized seizures (31, 32). Clozapine-induced obsessive/compulsive symptoms have been reported by many authors as 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 (33). Inflammatory reactions may suddenly increase clozapine concentrations and lead to toxic delirium (34). Plasma clozapine concentrations (and the probability of reaching a given threshold) may be influenced by some factors, such as age, sex and smoking (15). Because of the degree of interindividual variability of the clozapine concentration-to-dose ratio, dosages of 900 to 1800 mg day^{-1} are necessary in 15 % of patients to obtain clozapine concentrations of ≥ 400 ng mL^{-1}. These patients are most likely to be males who smoke cigarettes. Thus, patients requiring these higher dosages should probably be titrated more cautiously to avoid the adverse effects associated with higher dosages, such as seizures and confusion (14). Changes in the habitual caffeine intake alter the metabolism of clozapine in schizophrenic patients (35). Thus, a patient's intake of caffeine should be medically supervized and the monitoring of clozapine and metabolite levels may be warranted. Interindividual variability in CYP1A2 activity may potentially explain treatment resistance to clozapine in some patients (36). CYP1A2 phenotyping with a simple caffeine test may contribute to individualization of clozapine dosage and differentiation between treatment non-adherence and high CYP1A2 activity. TDM can potentially decrease the lag time to response by administering dosages to patients that produce a therapeutic clozapine concentration in plasma (14). Empirically determined regimens may require months to optimize clozapine treatment in patients with schizophrenia. Logically, however, TDM should shorten the patient response time, since patients with lower plasma clozapine concentrations consistently have significantly lower response rates and will eventually be titrated to higher dosages and plasma drug concentrations. Reduction of relapse rates by TDM is highly cost-effective, as relapses can lead to hospitalization (37). It has been shown that fluctuations of clozapine plasma concentrations in schizophrenic patients are predictive of relapses and rehospitalizations. In these patients, TDM may help reduce the risk of relapse or recurrence by increasing medication adherence. One day in the hospital is 4–16 times more expensive than a single drug concentration measurement in the laboratory. Clozapine still represents the gold standard in the treatment of pharmacoresistant schizophrenia and optimal plasma levels for acute and maintenance clozapine treatment are well known

(38). Literature experiences show that TDM in clinically defined patient subgroups such as pharmacoresistant schizophrenia is clinically advantageous.

Risperidone. – It is rapidly absorbed after oral administration, with the c_{max} reached in approximately 1 hour (15). Its oral bioavailability is 70–85 %. Risperidone is 89 % bound to plasma proteins. It mainly undergoes 9-hydroxylation in the liver, which yields the active 9-hydroxyrisperidone (9-OH-RSP – paliperidone) metabolite, a step that is mainly catalyzed by CYP2D6 and, to a lesser extent, by CYP3A4. Alicyclic dehydroxylation and oxidative N-dealkylation are minor metabolic pathways. Genetic influences, such as the CYP2D6 status, play an important role in determining the variability of its pharmacokinetic parameters. The mean elimination half-life of risperidone is 3 hours in extensive metabolizers and 22 hours in poor metabolizers. Steady-state concentrations are reached within 4–6 days of treatment. The mean elimination half-life of the active moiety (risperidone + its main metabolite) is almost constant at about 22 hours in both groups. There are large intra- and inter-individual variations in plasma concentrations of both risperidone and 9-OH-RSP. As the pharmacological properties of 9-OH-RSP are similar to 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. The overall pharmacological effects of risperidone depend on the sum of plasma concentrations of risperidone and its 9-OH-RSP metabolite (total active moiety), so monitoring plasma concentrations of the parent compound (risperidone) alone can lead to erroneous interpretations. Therapeutic drug monitoring of risperidone may be beneficial in certain circumstances, including assessing potential non-adherence and supporting adherence, ruling out therapeutic failure as a result of low drug concentrations, and identifying and managing drug interactions, adverse effects, and use in special populations (39). Moreover, risperidone TDM should be particularly useful when medication is switched from the oral to injectable depot form or *vice versa* (15). In chronic schizophrenic patients experiencing an acute exacerbation of the disorder, plasma levels of risperidone and its active metabolite correlate with the occurrence of parkinsonian side effects (40). Risperidone plasma concentration/dose ratio (C/D) accumulation peaks of 49 % at 2 months (from baseline concentration) and 9-hydroxy-risperidone and total moiety C/D accumulation peaks of 66 and 55 % above the 2-month level at 6 months were found (41). Risperidone conversion to 9-hydroxy-risperidone by CYP2D6 suggests CYP2D6 inhibition or DNA down-regulation in the first 2 months. The time course of the accumulations identified suggests that both CYP inhibition and DNA regulatory mechanisms may be involved in the metabolism of the drug. Therefore, long-term TDM can optimize treatment with risperidone.

Paliperidone. – The 9-hydroxyrisperidone is now marketed as an antipsychotic in its own right (15, 42, 43). The absolute oral bioavailability of paliperidone is 28 %. It is 74 % protein bound, primarily to albumin and α1-acid glycoprotein. Peak plasma concentrations are reached approximately 24 hours after dosing. Paliperidone undergoes a very limited hepatic metabolism, with approximately 60 % of unchanged drug eliminated renally and 11 % eliminated unchanged in the feces. The terminal half-life of paliperidone is about 23 hours with the steady state concentration attained in 4–5 days.

Olanzapine. – Approximately 85 % of an oral olanzapine dose is absorbed, but as 40 % is inactivated by first-pass hepatic metabolism, its oral bioavailability is 60 % (15). The c_{max}

is reached within 6 hours. The drug is 93 % bound to plasma proteins, mainly albumin (90 %) and alpha1-acid glycoprotein (77 %). It has a mean elimination half-life of 33 hours (range 21–54 hours) and steady-state concentrations are achieved within 5–7 days of administration. Olanzapine is metabolized primarily by direct glucuronidation and CYP1A2 and to a lesser extent by CYP2D6, CYP3A4 and flavin monooxygenase to its 10-N- and 4'-N-glucuronides, 4'-N-desmethylolanzapine, olanzapine-N-oxide, and 2-hydroxymethyl-olanzapine. The 10-N-glucuronide is the most abundant metabolite. Glucuronidation by the UDP-glucuronosyltransferase family of enzymes (1A4 and 2B10) is the major mode of olanzapine metabolism, and polymorphisms in these enzymes could contribute to inter-individual variability in olanzapine metabolism and therapeutic response (44). Studies have shown that mean plasma olanzapine concentrations vary widely, depending on factors such as the prescribed daily dose and the duration of treatment (41). Olanzapine showed a plasma concentration/dose ratio accumulation peak after 4 months of 31 % above baseline, and a slower increase to 47 % above baseline after 18 months with no clear plateau. The time course of the accumulations identified suggests that both CYP inhibition and DNA regulatory mechanisms may be involved in the metabolism of the drug. Therefore, long-term TDM can optimize treatment with both risperidone and olanzapine, and also antipsychotics in general. Smokers and men show greater olanzapine clearance than women and nonsmokers (15). Given their lower olanzapine clearance, women have significantly higher mean plasma olanzapine concentrations, which become evident after the fifth week of treatment. Studies strongly indicate a relationship between clinical outcomes and plasma olanzapine concentrations. A therapeutic range at steady-state between 20 and 80 ng mL^{-1} has been found (37). The positron emission tomography (PET) data available for olanzapine indicate that a threshold level of approximately 15–20 ng mL^{-1} should be targeted in order to get an antipsychotic response in the average patient with schizophrenia (45). Levels above 50 ng mL^{-1} might be associated with a higher risk of extrapyramidal symptoms. Furthermore, given the large interpatient variability in plasma olanzapine concentrations at the same dosages, olanzapine TDM can be considered very useful in assessing therapeutic efficacy and controlling adverse events (15). Stopping smoking may be associated, within a few days, with an increase in side effects, such as extrapyramidal symptoms, unless the dose is adjusted.

Quetiapine. – It is rapidly absorbed following oral administration and 70 % of the administered dose is absorbed (15). Median c_{max} is reached within 1–1.5 hours, 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 2–3 days of administration. The primary route of elimination is hepatic metabolism. Quetiapine is predominantly metabolized by CYP3A4, which is the main iso-enzyme involved in quetiapine sulfoxidation and dealkylation, and by CYP2D6 which is involved in the 7-hydroxylation of quetiapine (along with CYP3A4). Of the 11 metabolites formed as a result of the hepatic metabolism of quetiapine, only two (7-hydroxy-quetiapine and 7-hydroxy-N-desalkyl-quetiapine) are pharmacologically active and they circulate in plasma at rather low concentrations (12 % of those of quetiapine). If this is the case, it is unlikely that they contribute to the pharmacological effects of the drug. Oral clearance of quetiapine seems to be lower (30–50 %) in elderly patients (aged 63–85 years) receiving 300–750 mg per day than in younger patients on similar regimens. It should be noted that the age of > 70 years has been found to be associated with a marked decline in the hepatic content of CYP3A4. Dose titration may therefore

need to be slower in the elderly, and the daily dose lower than in younger patients (15). Although the data from Gefvert *et al*. (46) and Mauri *et al*. (47) argue in favour of the existence of a relationship between plasma quetiapine concentrations and clinical responses, they only provide some preliminary information about the meaning of plasma quetiapine concentrations. Other investigators have failed to identify an optimal therapeutic range for quetiapine (48, 49). Data from the available PET studies provide evidence for a therapeutic reference range at a steady-state of 100–500 ng mL^{-1}. Higher plasma concentrations might be tolerable to many patients, and their tolerability is limited by vegetative side effects and sedation rather than extrapyramidal symptoms (45).

Amisulpride. – It is rapidly absorbed after oral administration, its absolute bioavailability is about 50 % and c_{max} is reached after 1–4 hours (15). Amisulpride has low protein binding (17 %), its elimination half-life is 12–20 hours and the steady state is reached after 2–3 days. It undergoes minimal metabolism in the liver and produces only two main metabolites, both of which are inactive. Excretion occurs mainly *via* kidneys, by glomerular filtration and it is therefore likely that active drug secretion occurs. In patients with renal impairment, its elimination half-life is unchanged, but systemic clearance is reduced by one-third, so dose adjustments are required. Age and sex have a significant effect on dose corrected amisulpride plasma concentrations, which are higher in older patients and in women, possibly because of a sex difference in the drug's renal clearance. Co-medication with lithium and clozapine increases dose-corrected amisulpride plasma concentrations. Like in the case of most antipsychotics, patients commonly show great interindividual variance in plasma amisulpride concentrations. Amisulpride plasma concentration is closely correlated with the dose, dopamine occupancy, response and extra-pyramidal symptoms (EPS). The plasma concentration threshold for response appears to be approximately 200 ng mL^{-1} at steady-state and EPS are more reliably predicted by a plasma level above 320 ng mL^{-1} than by the dose (50). TDM of amisulpride seems to be very useful for clinical decision making (51).

Ziprasidone. – Its oral bioavailability is 60 % but the duration and extent of ziprasidone absorption may be as much as doubled in the presence of food, whereas its elimination half-life is shorter than under fasting conditions (15, 17). Ziprasidone is highly bound to plasma proteins (> 99 %), primarily albumin and alpha-1-acid glycoprotein. Its pharmacokinetics seem to be linear, the elimination half-life has been reported to be 8–10 hours. Steady-state concentrations are achieved within 2–3 days of administration. Ziprasidone is highly metabolized by CYP3A4 and aldehyde oxidase, with < 5 % of the administered dose being excreted in an unchanged form. Clinical improvement or side effects did not correlate significantly with doses or serum levels. However, great interindividual and intraindividual differences in ziprasidone concentrations were observed. TDM of ziprasidone may be used for individual dose adjustments and monitoring of medication adherence (52, 53). The available PET studies with ziprasidone suggest that an antipsychotic effect can be expected above a threshold level at steady-state of approximately 50 ng mL^{-1}. Levels above 200–250 ng mL^{-1} might be associated with a higher incidence of extrapyramidal symptoms (45).

Aripiprazole. – It is well absorbed, its oral bioavailability is 87 % and c_{max} is reached after 3–5 hours of administration (15). It is extensively bound to plasma proteins (> 99 %),

primarily to albumin. The elimination half-life is 47–68 hours, steady-state plasma concentrations being reached by day 14. A linear pharmacokinetic profile has been observed. Aripiprazole is metabolized in the liver *via* CYP3A4 and CYP2D6, primarily as a result of dehydrogenation, hydroxylation and N-dealkylation. At steady state, 40 % of the plasma aripiprazole concentration is represented by the major active metabolite dehydro-aripiprazole.

The dose range for aripiprazole is well defined, and it reliably predicts the plasma level, dopamine receptor occupancy, and clinical response (54). Plasma level variation appears to have a minimal impact on clinical response, but it may predict some adverse effects. Therapeutic drug monitoring has a limited value in the clinical use of aripiprazole, but it may be useful in assuring adherence and optimizing the response in individuals.

Sertindole. – It is well absorbed when administered orally; its bioavailability is 75 %. It is 99.5 % bound to plasma proteins, c_{max} is reached after 8–12 hours (15). The mean elimination half-life is 85–99 hours and steady state is achieved after 15–20 days. The results of *in vivo* experiments suggest that the metabolism of sertindole is principally mediated by CYP3A4 and CYP2D6 and the known variability of these two iso-enzymes probably contributes to the observed variability in the pharmacokinetics of sertindole. It is metabolized to two compounds, dehydro-sertindole (active) and nor-sertindole. Care is needed when calculating effective doses in patients with hepatic insufficiency. It would be useful to follow plasma sertindole concentrations in case of an overdose, because of its long elimination half-life (3–5 days) and capacity to prolong the QT interval. Concentration dependent increase of QT interval by blockade of potassium chanels has been also reported (37). Basic characteristics and enzymes involved in the metabolism of atypical antipsychotic drugs are presented in Tables II and III.

Guidelines for optimal use of TDM in psychiatry

The TDM group of the *Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie* (AGNP) has published literature-based guidelines for optimal use of TDM in psychiatry and defined 4 levels of recommendations, based on empirical evidence: level 1 – strongly recommended, level 2 – recommended, level 3 – useful, and level 4 – potentially useful (Table IV) (37). The so called laboratory alert levels indicate drug concentrations above the recommended reference range that cause the laboratory to feedback immediately to the prescribing physician. The laboratory alert should lead to dose reduction when the patient exhibits signs of intolerance or toxicity. When the high drug concentration is well tolerated by the patient and if dose reduction bears the risk of symptom exacerbation, the dose should remain unchanged. For a number of psychoactive drugs, metabolites actively contribute to the overall clinical effect of the parent compound. For this reason, TDM must include the quantification of active metabolites, *e.g.*, in the case of risperidone. Analysis of pharmacologically inactive metabolites, however, may give useful information on the metabolic state of the patient or on his/her adherence. Table V shows the normal ratios of concentrations of metabolites to parent drugs. Calculated ranges contain 68 % of the ratios expected under standard dosages, *i.e.*, ratios within the range of the mean ± 1 SD assuming normal distribution. A ratio above or below the normal ratio can indicate problems of drug adherence or metabolic abnormalities due to a genetic variation or a drug-drug interaction with co-medications exhibiting enzyme inhibiting or inducing

Table II. Basic characteristics of antipsychotic drugs (12, 14, 38)

Drug	Bioavailability (%)	Protein binding (%)	t_{max} (h)	Half-life (h)	Time to reach steady state (d)
Amisulpride	50	17	1–4	12–20	2–3
Aripiprazole	87	> 99	3–5	47–68	14
Clozapine	27–50	95	1–4	9–17	7–10
Olanzapine	60	93	6	21–54	5–10
Paliperidone	28	74	24	23	4–5
Quetiapine	70	83	1–1,5	5–8	2–3
Risperidone	70–85	89	1	EM: 3, PM: 22	4–6
Sertindole	75	> 99	8–12	85–99	15–20
Ziprasidone	60	> 99	6–8	8–10	2–3

EM – extensive metabolizer, PM – poor metabolizer, t_{max} – time to reach maximum plasma concentration

Table III. Enzymes involved in the metabolism of antipsychotic drugs (12, 14, 38)

Drug	Enzymes responsible for metabolization	Active metabolite
Amisulpride	Excretion *via* the kidney	
Aripiprazole	CYP3A4, CYP2D6	Dehydroaripiprazole
Clozapine	CYP: 1A2, 2C19, 3A4, 2D6 UGT: 1A1, 1A3, 1A4	Norclozapine, Clozapine-N-oxide
Olanzapine	CYP: 1A2, 2D6, 3A4 UGT: 1A4, 2B10 Flavin monooxygenase	
Quetiapine	CYP3A4, CYP2D6	Norquetiapin
Risperidone	CYP2D6, CYP3A4	9-Hydroxyrisperidone
Sertindole	CYP3A4, CYP2D6	Dehydrosertindole
Ziprasidone	CYP3A4, aldehyde oxidase	

CYP – cytochrome P450, UGT – uridine diphosphate-glucuronosyltransferase

properties. In a patient who is genotyped as a poor or ultrarapid metabolizer the medication should not be automatically replaced by another, but the dose can often be adapted, using clinical judgement and TDM. AGNP recommends regular monitoring of plasma

Table IV. Recommended therapeutic reference ranges, laboratory alert levels and levels of recommendation for therapeutic drug monitoring (38)

Drug	Level	Therapeutic reference range (ng mL^{-1})	Laboratory alert level (ng mL^{-1})
Amisulpride	1	100–320	640
Aripiprazole	2	150–500	1000
Clozapine	1	350–600	1000
Olanzapine	1	20–80	150
Paliperidone (9-hydroxyrisperidone)	2	20–60	120
Quetiapine	2	100–500	1000
Risperidone + 9-hydroxyrisperidone	2	20–60	120
Sertindole	2	50–100	200
Ziprasidone	2	50–200	400

1 – strongly recommended, 2 – recommended

Table V. Ranges of metabolite-to-parent drug concentration ratios (38)

Drug	Metabolite	Ratio metabolite concentrations/parent drug [(mean – SD) – (mean + SD)]
Aripiprazole	Dehydroaripiprazole	0.3–0.5; PM of CYP2D6: 0.2
Clozapine	Norclozapine	non smokers: 0.5–0.6; smokers: 0.4–0.7
Olanzapine	*N*-demethylolanzapine	non smokers: 0.1–0.3; smokers: 0.2–0.4
Quetiapine	Norquetiapine	0.1–3.8
Risperidone	9-hydroxy-risperidone	CYP2D6: EM/IM 1.5–10.0; PM ≤ 1
Risperidone depot	9-hydroxy-risperidone	EM: 1.2–4.3
Sertindole	Dehydrosertindole	1.1–2.7; PM of CYP2D6: 1.0

EM – extensive metabolizer, IM – intermediate metabolizer, PM – poor metabolizer, CYP – cytochrome P450

concentrations under maintenance therapy, at least every 3–6 months, to prevent relapses and rehospitalizations. Frequency of TDM requests may be increased if patients are known to be non-adherent to the medication or in case of changes of co-medications or of smoking that affect the pharmacokinetics of the drug. As a rule, trough concentrations are measured, but in some situations peak concentrations would show a better correlation with adverse effects. Blood should be collected after at least four drug elimination half-lives after the start of or a change in dosage. In clinical practice, the appropriate sampling time

for most psychoactive drugs is one week after stable daily dosing and immediately before ingestion of the morning dose. TDM of antipsychotics is also useful when medication is switched from the oral to the depot form, or *vice versa*. There is good evidence for the treatment with antipsychotic drugs that clinical non-improvement at week 2 is highly predictive of later response and remission. Especially, the absence of early improvement appears to be a highly reliable predictor of later non-response. For dose titration with antipsychotic drugs, it is therefore recommended to include symptom rating by the treating physician at baseline and at week 2 in addition to TDM. Plasma concentration determinations for antipsychotic drugs should be carried out regularly even in patients on stable doses over a period of many months (41). Timely plasma concentration determinations of antipsychotics could enhance the physicians' ability to optimize drug dosage and make dosage reductions in a more scientific manner than it is the current standard of practice.

CONCLUSIONS

In conclusion, TDM of antipsychotic drugs is a powerful tool that allows tailoring the treatment to the specific needs of individual patients. It can help in monitoring adherence, in dose adjustment, in minimizing the risk of toxicity and in cost-effectiveness in the treatment of psychiatric disorders.

Acronyms, abbreviations, codes. – 9-OH-RSP – 9-hydroxyrisperidone; AGNP – the TDM group of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie; C/D – concentration/dose ratio; c_{max} – maximum plasma concentration; CYP – cytochrome P450; EM – extensive metabolizer; EPS – extra-pyramidal symptom; IM – intermediate metabolizer; PET – positron emission tomography; PM – poor metabolizer; SSRI – selective serotonin reuptake inhibitor; TDM – therapeutic drug monitoring; t_{max} – time to reach maximum plasma concentration; UGT – uridine diphosphate-glucuronosyltransferase

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