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REVIEW

Assessing drug-drug interactions through therapeutic drug monitoring when administering oral second-generation antipsychotics

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ABSTRACT

Introduction: Second-generation antipsychotics (SGAs) are frequently co-prescribed with drug metabolic inducers and inhibitors. SGA pharmacokinetic drug-drug interactions (DDIs) with inducers and inhibitors have not received enough attention in the literature but can be studied in by using therapeutic drug monitoring (TDM).

Areas covered: The limited information available on oral SGA pharmacokinetic DDIs is reviewed. A systematic literature search on the available oral SGA TDM studies is completed. By integrating TDM studies with the information on in vitro metabolism studies, case report/series and prospective studies, a table is provided to manage average SGA patients taking inducers or inhibitors by using TDM and/or dose SGA changes. Adding an inhibitor or discontinuing an inducer may increase plasma concentrations and cause adverse drug reactions (ADRs) on clozapine or risperidone. Quetiapine and lurasidone, which are very sensitive to decreases of plasma concentrations by induction, should not be administered with potent inducers. Prescribing sertindole with TDM may make its use safer.

Expert opinion: Reading our article may encourage: 1) clinicians using these combinations to publish TDM case reports/series to demonstrate whether our dose indications are correct or not, in their patients with DDIs; and 2) pharmacokinetic researchers to study these DDIs in prospective and retrospective ways using large TDM databases.

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1. Introduction

Multiple drug therapy is common in current medical practice and carries the risk of drug-drug interactions (DDIs).[1] A clinically relevant DDI occurs when the efficacy or safety of a drug is altered by the concomitant administration of another pharmacological agent. The consequences of a DDI can be either beneficial, if the interaction results in increased therapeutic efficacy or reduced risk of adverse drug reactions (ADRs), or harmful, if it leads to decreased efficacy or increased ADRs of one or more of the administered medications. Based on their mechanisms, DDIs can be classified as either pharmacokinetic or pharmacodynamic. Pharmacokinetic DDIs occur at sites of absorption, distribution, metabolism, or excretion of a drug and/or its metabolite(s) and can be established and quantified by the study of changes in plasma drug concentrations, called therapeutic drug monitoring (TDM). The most important pharmacokinetic DDIs are at the metabolism level; inhibitors decrease drug metabolism and increase plasma concentrations while inducers increase drug metabolism and decrease concentrations. On the other hand, pharmacodynamic DDIs occur at the site of pharmacological action between drugs that have either similar or opposing mechanisms of action. These DDIs are not associated with changes in plasma drug concentrations and are less well-recognized and documented than pharmacokinetic DDIs.

The potential for pharmacokinetic DDIs is an important issue to consider for rational drug prescribing. DDIs can be identified at different times during the development of new drugs. Preclinical characterization of DDIs includes the use of different in vitro methods such as enzyme-based techniques (i.e. purified enzymes, recombinant human enzymes, and human liver microsomes) or cell-based techniques (i.e. liver slices, immortalized cell lines, and primary hepatocytes) and in vivo experimental studies in animal models.[2] These methodologies have become widely used as screening tools to assess and predict metabolic DDIs. The Food and Drug Administration provided recommendations on how and when DDI studies should be conducted during drug development.[3] DDI studies can also be performed in healthy volunteers or patients during the clinical phase of drug development, using a strategy based on the therapeutic indices of drugs, the likelihood of their concurrent use or when metabolic prediction and guidelines for their conduction have been performed. However, knowledge of the pharmacokinetic DDI profile is often incomplete at the time of drug commercialization. There are many reasons for this incomplete knowledge. Some of the most common

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Article highlights

- The SGA literature on DDIs is limited and psychiatric textbooks and drug package inserts provide few recommendations to clinicians on how to manage them.
- A review of the literature on oral SGA TDM studies is integrated with the information on in vitro metabolism studies, case report/series, and prospective studies to provide our best interpretation of what to expect in the average SGA patient taking inducers or inhibitors by providing suggestions of when to use TDM and/or dose SGA corrections.
- Clozapine and risperidone are narrow therapeutic window drugs; adding an inhibitor or discontinuing an inducer may be particularly prone to cause ADRs in clozapine or risperidone patients.
- Quetiapine and lurasidone, which are very sensitive to decreases in plasma concentrations by induction, should not be administered with potent inducers.
- Amisulpride and ziprasidone, which bring about little CYP metabolism, even in conditions of induction, may not need dosages changes in the presence of potent inducers.
- Sertrindole data is limited but prescribing it under TDM control appears a good idea due to (1) its possible narrow therapeutic window with risk for QTc prolongation and (2) being influenced by CYP2D6 genetic polymorphism, CYP2D6 inhibitors, CYP3A4 inhibitors, and CYP3A4 inducers.

This box summarizes key points contained in the article.

are (1) metabolic enzymes, such as the cytochrome P450 (CYP), are specific to species; therefore, animal DDI studies are not very helpful; (2) in vitro studies using human CYPs have a difficult time replicating the complexity of a human organism (e.g. studying the in vitro effect of an inducer such as carbamazepine does not take into account that in vivo carbamazepine metabolism and metabolites may modify its inductive actions); and (3) DDIs with single-dose control studies in healthy volunteers may not reflect clinical practice with long-term treatment, particularly if steady state of the inhibitor or inducer has not been reached. Therefore, careful postmarketing surveillance remains essential for identifying previously unexpected DDIs in populations that often differ from the ones considered in premarketing studies. TDM databases may provide a unique opportunity in this respect.[4]

Psychotropic drugs, including antipsychotic medications, are often involved in DDIs as they are commonly prescribed in combination with other compounds used to treat comorbid psychiatric, neurological, or somatic disorders, for controlling ADRs or to increase a medication response. Currently available antipsychotic medications can be divided into traditional or first-generation antipsychotics (FGAs) and atypical or second-generation antipsychotics (SGAs).[5] In recent years, SGAs have become the mainstream treatment intervention for patients with schizophrenia, bipolar disorder, and other psychotic conditions due to a lower risk for acute and chronic extrapyramidal symptoms and prolactin elevation, as compared to traditional antipsychotics. Moreover, SGAs are frequently used for off-label indications.[5]

The purpose of the present article is to evaluate the role of TDM as a tool to identify and assess pharmacokinetic DDIs affecting SGAs. The different methodological approaches and study designs used to document DDIs will be discussed. In particular, the available retrospective studies based on routinely collected TDM databases that allowed documentation of DDIs involving SGAs will be reviewed.

Box 1. Second-generation antipsychotic drug-drug interactions with nonpsychiatric drugs.

Potent inducers

Rifampicin is a potent inducer with a wide spectrum. To manage patients on rifampicin and an SGA, look at the *Actions to take* column in Table 4, including dose correction factors, in patients taking potent inducers (carbamazepine, phenobarbital, and phenytoin).

Other CYP3A4 mild inducers

Some antiepileptics (clobazam, eslicarbazepine, felbamate, and rufinamide) can be CYP3A4 mild inducers and, as such, can interact with SGAS. They are not listed in Table 4 but described in other articles.[12,69] Look also at Table 4 for actions suggested for high doses of oxcarbazepine (≥1400 4 mg/day) or topiramate (≥400 mg/day). They should apply to clobazam, eslicarbazepine, felbamate, or rufinamide, particularly when co-prescribed in high doses.

The same actions described in Table 4 should apply to SGA patients taking other mild CYP3A4 inducers, such as St. John's wort or some corticosteroids (e.g. dexamethasone or prednisone).

CYP1A2 inducers

Omeprazole is clinically relevant CYP1A2 inducer and appears to increase the metabolism of clozapine or olanzapine. Tobacco smoking is also a CYP1A2 inducer, currently is not definitively established whether omeprazole and smoking have additive effects or omeprazole inductive effects are only evident in nonsmokers.

CYP1A2 inhibitors

Ciprofloxacin is a potent CYP1A2 inhibitor and should not be co-prescribed with clozapine or olanzapine. Antibiotics from the same family that are not CYP1A2 inhibitors and can be co-prescribed with clozapine or olanzapine are described in a prior article.[16]

Caffeine can also inhibit the metabolism of clozapine and olanzapine.[114][1]

Oral contraceptives including estrogens are CYP1A2 inhibitors and can inhibit clozapine metabolism.[16]

Similarly, pregnancy due to elevations in estrogens is expected to decrease clozapine and olanzapine metabolism.[16]

CYP3A4 inhibitors

Ketoconazole, erythromycin, clarithromycin, diltiazem, and grapefruit juice are powerful CYP3A4 inhibitors and should not be administered with SGAs for which metabolism depends on CYP3A4 (aripiprazole, iloperidone, lurasidone, quetiapine, risperidone, and sertindole). If they need to be co-prescribed, SGA TDM is a requirement.

Drugs prescribed for patients infected with HIV

Many drugs prescribed for patients infected with HIV are powerful inducers and inhibitors, or both. Prior articles described their limited available information on DDIs with this type of drug and SGAs.[8,16] If they are co-prescribed with SGAs, SGA TDM is a requirement unless an SGA with low risk for DDIs is selected (e.g. amisulpride or ziprasidone).

Inflammation and severe infection

One peculiar inhibitor that is not a drug but can decrease SGA metabolism. Inflammation and severe infection can release cytokines that can inhibit some CYPs. It is clear that it can happen with CYP1A2 drugs such as clozapine and olanzapine.[115] More recently, it is becoming clearer that other CYPs, including CYP2C19 and possibly CYP3A4, may be inhibited by inflammation.[116] Two risperidone case reports [117] and a retrospective analysis of a TDM base [118] suggested that inflammation inhibits risperidone metabolism. If that is correct, TDM for SGAs for which metabolism depends on CYP3A4 (aripiprazole, iloperidone, lurasidone, quetiapine, risperidone, and sertindole) should be recommended during inflammations or severe infections, as it is recommended for the CYP1A2-dependent SGAs, clozapine and olanzapine. Moreover, an unexpected and unexplained high SGA TDM requires drawing a CRP to rule out undetected inflammation.[119]

CRP: C-reactive protein; DDI: drug-drug interaction; SGA: second-generation antipsychotic; TDM: therapeutic drug monitoring.

[1]Caffeine is a CYP1A2 substrate and appears to have the potential to be a CYP1A2 competitive inhibitor. Typical plasma caffeine concentrations are around 1 mg/mL which is 1000 µg/mL. As caffeine has high affinity for CYP1A2 and is present in relatively high concentrations, it is not surprising that it can behave as a competitive inhibitor of clozapine or olanzapine metabolism.

Articles for this review were obtained from a PubMed search without a time limit. Searches were performed for each of the SGAs. Only articles published in peer-reviewed journals were included, while meeting abstracts were excluded.

2. Pharmacokinetic DDIs of SGAs

SGAs are often prescribed in combination with other medications and this may result in clinically relevant DDIs. Therefore, the use of SGAs with low DDI potential is desirable, especially for elderly patients who are more likely to take many medications. In recent years, a number of comprehensive reviews have been published, describing their pharmacokinetics as well as the clinically relevant SGA pharmacokinetic DDIs.[6–14] The basic SGA pharmacokinetic properties are summarized in Table 1. Many pharmacokinetic SGA DDIs were identified during investigational preclinical and clinical drug development by employing a series of standardized in vitro and in vivo studies with known inhibitors or inducers of drug metabolism.[13] However, clinical studies conducted post-approval allowed detection of other clinically relevant SGA DDIs.

The majority of clinically relevant pharmacokinetic DDIs with SGAs occur as a consequence of drug-induced changes in hepatic metabolism, through inhibition or induction of isoenzymes of the CYP system and, to a lesser extent, the uridine diphosphate glucuronosyltransferase (UGT) system. In recent years, the in vitro characterization of the major drug-metabolizing enzymes, in particular the human CYP system, with identification of substrates, inhibitors, and inducers of different CYP isoforms, has greatly improved the prediction of metabolic DDIs, providing an invaluable resource in helping to anticipate and avoid potential DDIs.[1] In principle, concomitant treatment of a patient with a drug that is a substrate of a distinct CYP enzyme (victim drug) and a known inhibitor or inducer of that enzyme involves the risk of a DDI. The potential occurrence, magnitude, and clinical significance of a metabolic DDI will then depend on a variety of drug-related (i.e. potency and concentration/dose of the inhibitor/inducer, therapeutic index of the victim drug, and its extent of metabolism through the affected enzyme, presence of active metabolites), patient-related (i.e. age, genetic predisposition), and environmental factors (i.e. smoking).[8] Very rarely, clinically relevant DDIs happen with concomitant treatment with drugs metabolized by the same enzyme. This is called competitive inhibition and only happens in very peculiar patient-related circumstances with polytherapy in which the metabolism is compromised and adding an SGA may be the straw that breaks the camel's back.[16] SGAs are not considered clinically relevant inhibitors, except for asenapine, which may be a mild CYP2D6 inhibitor.[14] In spite of that, in rare circumstances, any SGA has the potential to cause a clinically relevant DDI due to competitive inhibition. A few case reports of SGAs decreasing metabolism of other drugs have been published, such as clozapine on tricyclic antidepressants (TCAs) [17] or quetiapine on warfarin.[18–20]

The metabolic enzymes are not only located in the liver but they appear to be highly expressed in the gut, but the role of these intestine enzymes on DDIs is not well-understood. There is definitive agreement in the literature that CYP3A4 is the most important CYP in the gut, moreover it has clinical relevance in the first-past metabolism of drugs metabolized by CYP3A4. UGTs are particularly complex since some of them are only gastrointestinal and not located in the liver (UGT1A7, UGT1A10, and UGT1A18) while some of the hepatic UGTs have also substantial gastrointestinal expression (UGT1A1, UGT1A4, UGT2B7, and UGT2B15).[21] It is not easy to study the contribution of intestinal CYP3A4 or UGTs to DDIs and the authors are not aware of any study relevant for intestinal DDIs with SGAs but do not doubt that intestinal metabolism may be clinically relevant.

Protein-binding displacement DDIs with SGAs are uncommon and unlikely to be clinically significant.[13] DDIs at the level of renal excretion are rare and can be expected to occur

Table 1. Pharmacokinetic parameters of SGAs.

	Bioavailability (%)	Protein binding (%)	Half-life (h)	Metabolism	Active metabolites	Therapeutic reference range in ng/mL (calculation of index)
Amisulpride	43–48	17	12	Minimal hepatic metabolism Renal excretion		100–320 (3.2)
Aripiprazole	87	99	48–68	CYP2D6, CYP3A4	Dehydroaripiprazole	150–500 (3.3)
Asenapine	35	95	1–2	UGT1A4, CYP1A2		2–5 (2.5)
Clozapine	12–81	95	6–33	CYP1A2 (major), CYP2C19, CYP3A4, CYP2D6	Norclozapine[1]	350–600 (1.7)
Iloperidone	96	93	20–24	CYP2D6 (major), CYP3A4	P88,[2] P95	5–10 (2)
Lurasidone	9–19	99	18	CYP3A4	ID-14823	40–120 (3)
Olanzapine	60–80	93	20–70	CYP1A2 (major), UGT1A4, CYP2D6, FMO		20–80 (4)
Paliperidone	28	30	24	Minimal hepatic metabolism Renal excretion		20–60 (3)
Quetiapine	NA	83	5–8	CYP3A4	Norquetiapine[3]	100–500 (5)
Risperidone	68	90	3–24	CYP2D6 (major), CYP3A4	9-hydroxyrisperidone	20–60 (3)
Sertindole	75	99	85–99	CYP2D6, CYP3A4		50–100 (2)
Ziprasidone	60[b]	99	4–10	Aldehyde oxidase (major) CYP3A4		50–200 (4)

CYP: Cytochrome P450; UGT: uridine diphosphate glucuronosyltransferase.
[1]Norclozapine does not appear to have antipsychotic efficacy, but it may contribute to anticholinergic effects and hypersalivation.
[2]It does not cross the blood–brain barrier. It may contribute to peripheral adverse drug reactions.
[3]Some authors suggest that norquetiapine may contribute to quetiapine antidepressant properties, but at this time this is only a hypothesis.
Adapted from [8,14,15].

only with SGAs such as amisulpride and paliperidone, which are eliminated predominantly by the kidneys.[14] In recent years, however, increasing knowledge of the role played by drug transporters in the absorption, distribution, and excretion of a wide variety of drugs including SGAs has suggested that other mechanisms may occasionally be involved.[22] The best known transporter is the P-glycoprotein (P-gp) which is located in the gut, liver, kidney, and blood–brain barrier. Currently, there is no agreement on which SGAs are substrates and inhibitors of P-gp,[23] but it cannot be ruled out that in 5–10 years it may become clear that DDIs at the P-gp (or other transporter) level may be important in SGA DDIs. To make things more complicated, we are not sure whether or not these pharmacokinetic DDIs at the P-gp level manifest with changes at TDM.[23]

3. TDM as a tool for assessing and identifying DDIS

TDM may be defined as the quantification of serum or plasma concentrations of a drug (and its metabolites), but to simplify we will use word 'plasma' for the rest of the article. The goal of TDM is to titrate the dosage per individual patient so that a drug concentration associated with the highest possible probability of response and tolerability and a low risk of toxicity can be obtained.[15] Therefore, TDM is a valuable tool for tailoring the dosage of the prescribed medication(s) to the individual characteristics of a patient. TDM is based on the assumption that there is a relationship between plasma concentrations and clinical effects (efficacy and ADRs).[24] It also assumes that there is a plasma concentration range of the drug which is characterized by maximal effectiveness and maximal safety, the 'therapeutic window or index'. TDM is primarily recommended for drugs with wide interindividual pharmacokinetic variability and narrow therapeutic index.

3.1. SGA TDM

To promote an appropriate use of TDM of psychotropic drugs, the interdisciplinary TDM expert group of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) issued guidelines for TDM in psychiatry in 2004,[25] which were updated in 2011.[15] Even in the absence of clearly defined therapeutic windows for each psychotropic drug, these guidelines reported the so-called therapeutic reference ranges, defined as 'ranges of medication concentrations which specify a lower limit below which a drug induced therapeutic response is relatively unlikely to occur and an upper limit above which tolerability decreases or above which it is relatively unlikely that therapeutic improvement may be still enhanced'.[15]

TDM has been introduced for many drugs in psychiatry including antipsychotics. For many aspects, antipsychotic drugs are ideal candidates for TDM: they show wide interindividual variability of plasma concentrations; they have a relatively high ADR incidence; patients treated with these agents have a relatively high discontinuation rate and adherence is typically low; and finally, they are usually part of a chronic treatment and polypharmacy is obviously common in increased DDI risk.[26] In practice, SGA TDM use is limited. On the other hand, TDM for lithium and TCAs has become an established procedure for dose adjustment. Moreover, lithium and TCAs tend to be considered drugs with narrow therapeutic windows, which tend to be toxic since the lower limit of concentration for efficacy and the upper limit for ADRs tend to be close. The literature does not provide an agreed-upon definition of narrow therapeutic window but drugs such as lithium, phenytoin, carbamazepine, or TCAs tend to have a narrow therapeutic window or index around 2–3 (the concentration of the upper limit of the range is only 2–3 times higher than the concentration of the lower limit). For example, Hiemke et al. [15] describe imipramine's therapeutic range as 100–300 ng/mL. If you divide the upper range by the lower range, the quotient is 3 (300/100 = 3).

Typical indications for SGA TDM are described in Table 2. SGA TDM in routine psychiatric practice is still relatively limited, in spite of its obvious advantages. The lack of interest in TDM displayed by pharmaceutical companies has contributed to the lack of a well-defined relationship between plasma concentrations and clinical effects for many SGAs.[15,25,27–30] For a number of SGAs, metabolites actively contribute to the overall clinical effect of the parent compound. TDM must include the quantification of active metabolites such as 9-hydroxyripseridone (9-OH-R) for risperidone and dehydroaripiprazole for aripiprazole. For clozapine, the clinical relevance of its metabolite norclozapine is not clear since it does not contribute to efficacy, but it may contribute to some ADRs. However, measuring clozapine and norclozapine provides a better idea of the metabolism of clozapine. In the case of risperidone, the ratio of risperidone/9-OH-R is an excellent measure of the CYP2D6 activity (or phenotype).[31]

The AGNP-TDM Consensus Group used various levels of recommendation for the clinical applicability of monitoring plasma SGA concentrations: strongly recommended, recommended, useful, and potentially useful.[15] Those strongly recommended for TDM included three SGAs: clozapine, amisulpride, and olanzapine. The recommended included six

Table 2. Typical indications for using TDM for guidance of antipsychotic medications according to AGNP guidelines.

Dose optimization after initial prescription or after dosage change
Drugs for which TDM is mandatory for safety reasons (e.g. clozapine)
Suspected complete or partial nonadherence (noncompliance) to medication
Lack of clinical improvement under recommended doses
ADRs under recommended doses
Combination treatment with a drug known for its DDI potential or suspected DDI
TDM in pharmacovigilance programs
Relapse prevention under maintenance treatment
Recurrence under adequate doses
Presence of a genetic particularity concerning drug metabolism (genetic deficiency, gene multiplication)
Pregnant or breast-feeding patient
Child and adolescent patients
Elderly patient (>65 years)
Individuals with intellectual disabilities
Patients with pharmacokinetically relevant comorbidities (hepatic or renal insufficiency, cardiovascular disease)
Forensic patients
Switching from an original preparation to a generic form (and vice versa)

ADR: Adverse drug reaction; DDI: drug-drug interaction; SGA: second-generation antipsychotic; TDM: therapeutic drug monitoring.
Adapted from [15].

SGAs: risperidone, paliperidone, aripiprazole, sertindole, ziprasidone, and quetiapine. Iloperidone TDM is considered 'useful' and asenapine TDM had the lowest recommendation of 'potentially useful'. In accordance with the categorization principles of the AGNP-TDM group, TDM may be considered 'useful' for lurasidone.

The therapeutic reference ranges for SGAs as recommended by the TDM group of the AGNP are given in Table 1. These ranges are only to be used as guidelines; exceptions will occur because of patient variables and variability in the psychiatric illness being treated. This table contributes to the literature by adding, for the first time, the therapeutic window index calculation. From these eight SGAs with reasonably well-established TDM (three from the highest recommendation level and three from the second-highest recommendation level), there are four with an index ≤3, clozapine, paliperidone, risperidone, and sertindole compatible with a narrow index, and five with a wide index >3, amisulpride, aripiprazole, olanzapine, ziprasidone, and quetiapine.

3.2. TDM as a tool for identifying DDIs: methodological considerations

Evaluation of potential DDIs has long been advocated as an appropriate indication for TDM.[32] As stated in the previous section, combination treatment with a drug known for its DDI potential or assessment of a suspected pharmacokinetic DDI is a strong indicator for TDM. Therefore, TDM is a valuable tool for adjusting the SGA dosage when a drug combination contains inhibitors or inducers that may modify plasma concentrations of SGAs.[15] In addition, TDM studies, in particular those based on large TDM databases collected under naturalistic conditions, may be particularly useful for detecting DDIs in patients in the 'real world'. Various prerequisites have to be fulfilled for a correct interpretation of TDM data and to provide valid information for documenting DDIs, including pharmacokinetic factors, quality of collected data, and analytical aspects.[4]

3.2.1. Pharmacokinetic factors

TDM is carried out under steady-state conditions. The average steady-state concentration (Css) of a drug administered at a fixed dose and constant dosing interval is provided by the following equation:

$$Css = F \times D/CL \times \tau,$$

where F is the bioavailability of the drug, D the daily dose, CL is the clearance of the compound, and τ is dosing interval.

This formula assumes that the relationship between dose and concentration is stable; pharmacokinetic experts call it 'following linear kinetics'. This means that a doubling of the D is associated with a doubling of the Css and halving of the D is associated with halving of the Css. As a matter of fact, it appears that all SGAs in the therapeutic range probably follow linear kinetics.

The same concept can be simplified for clinicians by ignoring units and normalizing the dose by the concentration at steady state. This is usually represented in the literature as the concentration-to-dose ratio, or C/D ratio. This C/D ratio is a simplified representation of the ability to clear the drug from the body and estimates for inter- or intraindividual differences in metabolism and for dosing needs. Changes in C/D ratio by an order of magnitude of 2 (multiplying or dividing by 2) are probably clinically meaningful.[16] Imagine a patient whose C/D is multiplied by 2 (doubled) due to adding an inhibitor, discontinuing an inducer, or decreasing clearance during pregnancy; this would require halving the SGA dose (a correction factor of 0.5). Imagine a patient whose C/D is multiplied by 0.5 (or divided by 2) due to adding an inducer, discontinuing an inhibitor, or increasing clearance during pregnancy; this would require doubling the SGA dose (a correction factor of 2). Smaller C/D changes are unlikely to be detected above the 'noise' when measuring TDM in the clinical environment. TDM for children is not discussed here because the identified TDM studies were in adults. In small children, the C/D ratio needs to be corrected by weight since dosing is usually guided by weight.

3.2.2. Quality of collected data

The interpretation of TDM data requires a certain quality of data which also applies to DDI studies. The TDM request form should include the amount of information necessary for proper data interpretation. In addition to information on gender, age, bodyweight, diagnosis, renal or hepatic diseases, smoking, and drinking habits, a rigorous documentation of posology, dosing schedule and time interval since introduction, and dose adjustment or discontinuation for the drugs under investigation should be reported. A full medication history for the week preceding the start of drug use may also be required. It has been suggested that this information should be coupled with data on phenotype and genotype to allow evaluation of the pharmacogenetic and other causative factors altering drug metabolism.[33] Pharmacogenetic testing and TDM can definitely provide complementary information.[34] For CYP2D6 and CYP2C19 genotyping, some subjects are poor metabolizers (PMs) and do not have active isoenzyme; others are ultrarapid metabolizers (UMs) who have too much of the isoenzyme due to a duplication (or more) for CYP2D6 or a mutation that causes too much expression for CYP2C19.[35] These subjects can be called genetic PMs and UMs, respectively.[36] DDIs with inhibitors can make a normal subject look like a PM; DDIs with inducers can make subjects look like a UM. These can be called phenotypical PMs and UMs.[36] As a matter of fact, in the clinical environment, these phenotypical PMs and UMs can be frequent, as a risperidone TDM study demonstrated.[37]

Blood samples must be taken when steady-state conditions have been reached (i.e. after at least five half-lives have already elapsed after the last dose titration [32]). For the majority of oral SGAs, waiting 1 week after any dose change is a safe estimate for reaching steady state, but aripiprazole probably requires 2 weeks after the last dose change, due to its long steady state. When collecting TDM data on SGA DDIs, it is also important to collect samples that account for the inhibitor or inducer and its effects on the SGA TDM has reached steady-state. This review focuses only on oral SGAs,

but long-acting SGAs require a very long time to get to steady state. Anyway, we have found only one TDM study on a long-acting SGA.[38]

The timing of blood samples taken with respect to the last drug dose administered is also critical. With regard to this, TDM deals with trough levels and blood samples are generally withdrawn 12 h after the last intake of the drug, or in the morning immediately before the first dose of the day is administered. When SGAs have a long half-life such that the drug can be administered once a day (aripiprazole, clozapine, risperidone, and paliperidone), there are relatively small variations throughout the day and between trough and peak concentrations. When SGAs have a very short half-life, as with quetiapine and ziprasidone, there are very large variations throughout the day and between trough and peak concentrations. In the case of quetiapine, peak concentrations are almost 10 times higher than in the trough,[39] making TDM more complicated to interpret since variations in pattern of administration (twice versus three or more times a day) and time to last drug intake may have relevant effects on trough concentrations.

Ideally, repeated measurements over time should be obtained to increase the validity of results and to allow a better assessment of the relationship between dose, duration of exposure, and DDI magnitude.[4]

3.2.3. Analytical aspects

The logical prerequisite for any effective TDM practice is the availability of selective and sensitive analytical methods for the quantitative evaluation of drugs and their metabolites.[15] This is especially important for psychoactive drugs as their plasma concentrations are low and patients are frequently co-medicated with other drugs, which may interfere with the assay. In this respect, HPLC with fluorimetric detection, with coulometric detection, or UV detection and HPLC/MS were applied in analysis of SGAs.[40] Methods must be validated by demonstrating that the specific assay used for quantitative measurement of the analytes in a given biological matrix is reliable and reproducible for the intended use. Fundamental parameters for validation include (1) accuracy, (2) precision, (3) selectivity, (4) sensitivity, (5) reproducibility, and (6) stability.

Ideally, the laboratory should not only measure the drug but also its active metabolites (i.e. risperidone plus 9-OH-R or aripiprazole plus dehydroaripiprazole). For some SGAs, determination of metabolites that do not contribute to the overall clinical effect (i.e. norclozapine) may be useful to check the adherence of the patient, to obtain information on his/her capacity to metabolize drugs, or to interpret DDIs when the medications that are involved act as enzyme inhibitors or inducers.

4. TDM DDI studies with SGAs

During the past 20 years, many pharmacokinetic DDIs affecting SGAs have been suspected, confirmed, and assessed by using TDM databases. Different methodologies and study designs have been used in TDM-based investigations, including case reports or case series, prospective studies, and retrospective evaluation of TDM databases.[4]

4.1. Case reports or case series

Case reports or case series play an important role as an alert system for suspected DDIs.[4] They are simple and cost-effective methods to generate hypotheses which in turn inform the basis of studies on a larger scale. TDM has an important role in the identification of suspected DDIs because of the variety of the co-medication circumstances covered, including patients on chronic pharmacotherapy whose plasma drug levels are measured before, during, and after the use of a potentially interacting drug. However, single reports of pharmacokinetic DDIs need to be confirmed by further reports or large-scale studies before considered to be reliable, due to a lack of generalizability. Examples of clinically relevant DDIs involving SGAs and identified by case reports or case series are given in Table 3.[41–58]

4.2. Prospective studies

As outlined above, findings from single pharmacokinetic DDI case reports require consolidation. One of the best ways to confirm such findings or otherwise study them is through prospective on-and-off co-medication studies.[4] Such studies are carried out in patient cohorts observed before, during, and after exposure to drugs potentially interacting with currently prescribed drugs. These prospective studies are similar to the DDI studies carried out during the drug development process [3] in that patient selection is rigorous and drug exposure is controlled for. A main difference between the two types of studies is that in prospective studies outside of the drug development context, only drug concentrations during steady state are measured as opposed to all pharmacokinetic parameters. Steady-state drug levels are used for intraindividual comparisons, with each patient acting as his/her own control. This prospective experimental study design plays an important role in assessing DDIs in a causal perspective.

Different SGA DDIs detected through case reports gave rise to prospective studies to verify the initial finding and to quantify the magnitude of inhibitory or inducing properties of responsible drugs. Examples of DDIs that were studied prospectively include those between fluvoxamine and clozapine,[59] fluoxetine and clozapine,[60] carbamazepine and risperidone,[61] paroxetine and risperidone,[62,63] carbamazepine and aripiprazole,[64] and paroxetine and aripiprazole.[65] Some of these studies allowed investigation of a dose–effect relationship.[63,65]

A recent important study on carbamazepine and paliperidone [66] provides one of the best examples of the need for prospective DDI studies by independent investigators in order to improve clinical practice. The marketer considered paliperidone metabolism by CYP to be irrelevant for clinical purposes.[67] When the company studied adding carbamazepine to paliperidone, the carbamazepine treatment was subtherapeutic (400 mg/day) and too short (3 weeks) to cause maximal induction. In these circumstances, carbamazepine only decreased by 37% the paliperidone area under the curve.[68] For years, based on experience with risperidone, it has been hypothesized that paliperidone may be quite similarly susceptible to induction by a dramatic increase in percentage

Table 3. DDIs identified by TDM in single cases.

Inhibitory or inducing drug	Victim drug	Effect	Suggested mechanism	Reference
Caffeine	Clozapine	Decreased plasma clozapine concentrations after caffeine discontinuation	Inhibition of CYP1A2	Odom-White and de Leon, 1996 [41]
Phenobarbital	Clozapine	Elevated plasma clozapine concentrations after phenobarbital discontinuation	Induction of CYP1A2 and CYP3A4	Lane et al., 1998 [42]
Fluvoxamine	Clozapine	Increase of plasma clozapine concentration, ADRs, improved tolerability after dose reduction	Inhibition of CYP1A2 and CYP219	Hiemke et al., 1994 [43] Szegedi et al., 1995 [44]
Ciprofloxacin	Clozapine	Increase of clozapine concentrations	Inhibition of CYP1A2	Markowitz et al., 1997 [45] Sanbhi et al., 2007 [46] Brouwers et al., 2009 [47]
Erythromycin	Clozapine	Increase of clozapine concentrations associated with seizures	Inhibition of CYP3A4	Funderberg et al., 1994 [48]
Rifampicin	Clozapine	Decrease of clozapine concentrations	Induction of CYP1A2 and CYP3A4	Joos et al., 1998 [49]
Omeprazole	Clozapine	Decrease of plasma clozapine concentrations	Induction of CYP1A2	Frick et al., 2008 [50]
Fluoxetine	Risperidone	Elevated plasma concentrations of risperidone active moiety with ADRs	Inhibition if CYP2D6 and CYP3A4	Bork et al., 1999 [51]
Carbamazepine	Risperidone	Decrease of risperidone plasma concentrations associated with exacerbation of psychotic symptoms	Induction of CYP3A4	de Leon and Bork, 1997 [52] Spina et al., 2001 [53]
Ciprofloxacin	Olanzapine	Increase of plasma olanzapine concentrations	Inhibition of CYP1A2	Markovitz and Devane, 1999 [54]
Carbamazepine	Olanzapine	Decrease of olanzapine plasma concentrations	Induction of CYP1A2 and UGT	Licht et al., 2000 [55]
Atazanavir, Ritonavir	Quetiapine	Increase of quetiapine concentrations with associated ADRs	Inhibition of CYP3A4	Pollack et al., 2009 [56]
Oxcarbazepine	Quetiapine	Decrease of quetiapine plasma concentrations and lack of efficacy	Induction of CYP3A4	McGrane et al., 2015 [57]
Darunavir, Ritonavir	Aripiprazole	Increase of serum aripiprazole concentrations	Inhibition of CYP2D6 and CYP3A4	Aung et al., 2010 [58]

ADRs: Adverse dug reaction; CYP: cytochrome P450.

metabolized under induction.[67] Yasui-Furakori et al. [66] demonstrated that 600 mg/day of carbamazepine for 2–4 weeks was associated with an average reduction in plasma paliperidone concentrations to one-third. This will require multiplying the paliperidone dose by 3 in these patients. It is possible that an even higher paliperidone correction factor will be needed in patients taking higher carbamazepine doses or for longer periods of time.[69]

4.3. Retrospective evaluation of TDM databases

The availability of large TDM databases may allow retrospective evaluation of DDIs. This may prove useful when case reports have documented severe ADRs by a drug combination and, therefore, prospective studies can be ethically problematic. Inter- and intraindividual comparisons of concentrations obtained on monotherapy and while on co-medication have demonstrated its value for documenting DDIs.[4] In recent years, many studies based on retrospective analysis of TDM databases have investigated SGA pharmacokinetic DDIs. In general, the aim of these studies was to examine the contribution of various factors such as age, gender, smoking, and co-medication to the large interpatient variability of SGA plasma concentrations. In the following section, for each SGA, the part of these investigations specifically addressing the impact of concomitant treatment will be discussed.

4.3.1. Clozapine

Clozapine is converted by CYP1A2 and CYP3A4 to norclozapine, which has limited pharmacological activity, and by CYP3A4 to clozapine-N-oxide.[10] More recently, a role for CYP2C19 has been suggested.[70] Plasma concentrations of clozapine may significantly increase in combination with CYP1A2 inhibitors such as fluvoxamine and ciprofloxacin, but may decrease following administration of broad-spectrum CYP inducers such as carbamazepine.[8–10,13] Clozapine TDM may be of clinical value for dose adaption when handling DDIs.[71]

Jerling et al. [72] performed the first retrospective TDM study to detect and quantify SGA DDIs. They examined a large routine TDM database of clozapine performed during the period 1989–1992 and included 229 samples from 168 patients. Subjects were divided into four groups: clozapine monotherapy, co-medication with benzodiazepines, co-medication with CYP2D6-inhibitors, and co-medication with carbamazepine. Patients with carbamazepine had significantly lower C/D of clozapine than all the other groups and the ratio was inversely correlated to the daily carbamazepine dosage. In this respect, in eight patients clozapine was measured both in the absence and in the presence of carbamazepine. All patients had a lower C/D ratio when on carbamazepine than when off this drug. Moreover, in four patients co-medicated with fluvoxamine, C/D ratios of clozapine were 5–10 times higher than those of the monotherapy group. This was the first documentation of the potent inhibitory effect of fluvoxamine on clozapine metabolism and was subsequently confirmed by formal DDI studies.[59,73]

Diaz et al. [74] conducted a study to evaluate the DDI effect size on steady-state plasma concentrations of clozapine, adjusting for potentially confounding factors known to influence clozapine metabolism such as smoking. The estimation was performed by using a mixed model,[75] along with a combination of unpublished data from patients under clinical

TDM and data from previously published studies of phenobarbital,[76] valproic acid,[77] fluoxetine,[60] paroxetine and sertraline,[78] citalopram, [79] and reboxetine.[80] The analysis included a total of 415 steady-state trough plasma clozapine concentrations from 255 patients. After adjusting for clozapine dose and other potential confounding variables, total plasma clozapine concentrations in patients taking fluoxetine, fluvoxamine, or paroxetine were higher than those in patients on clozapine monotherapy by 42%, 263%, and 30%, respectively. Plasma clozapine concentrations in patients taking phenobarbital were 28% lower than those in patients receiving clozapine alone. The effects of valproic acid on plasma clozapine concentrations were modified by smoking. In this respect, plasma clozapine concentrations in nonsmokers who were taking valproic acid were 16% higher than those in nonsmokers on clozapine monotherapy; in contrast, plasma clozapine concentrations in smokers who were taking valproate were 22% lower than those in smokers who were not taking valproate. Thus, valproic acid may inhibit clozapine metabolism in nonsmokers, whereas it may induce clozapine metabolism in smokers. The effect sizes allowed the computation of clozapine dose-correction factors for phenobarbital, 1.4 [95% confidence interval, CI, (1.1, 1.7)]; paroxetine, 0.77 (0.67, 0.89); fluoxetine, 0.70 (0.64, 0.78); fluvoxamine, 0.28 (0.22, 0.35); and valproic acid [0.86 (0.75, 1.0) in nonsmokers, and 1.3 (0.96, 1.73) in smokers]. Sertraline, reboxetine, and citalopram had no significant effects on plasma clozapine concentrations.

4.3.2. Risperidone

Risperidone is primarily metabolized by CYP2D6 and, to a lesser extent, CYP3A4 to form the pharmacologically active 9-OH-R or paliperidone.[10] It is well documented that concomitantly administered medications that inhibit CYP2D6 or CYP3A4 or induce CYP3A4 may affect plasma concentrations of risperidone, 9-OH-R, and/or active moiety.[8–10,13] Based on this, TDM of risperidone may be beneficial in managing DDIs.[81]

C/D ratios of risperidone and 9-OH-R in 218 patients were associated with the number of concomitantly used substrates or inhibitors of CYP2D6.[82] The C/D ratios of risperidone in patients with 0, 1, and >1 CYP2D6 inhibitors were 2.6, 8.5, and 17 nmol/L/mg, respectively (corresponding to 1, 3.5, and 7 ng/mL/mg, respectively). Differences between the groups were highly significant ($p < 0.001$). All patients with >1 CYP2D6 inhibitors were administered at least one potent CYP2D6 inhibitor, namely fluoxetine, paroxetine, thioridazine, and/or levomepromazine. The C/D ratios of the active moiety (risperidone + 9-OH-R) in patients with 0, 1, and >1 concomitant CYP2D6 inhibitors were 17, 24, and 30 nmol/L/mg (7, 10, and 12.5 ng/mL/mg), respectively ($p = 0.001$), which was explained by higher levels of risperidone without any change in the levels of 9-OH-R. Concomitant use of one or several drugs recognized as substrates for CYP2D6, without any proven inhibitory effect, had no apparent influence on the levels of risperidone or 9-OH-R, suggesting that the DDI risk between different substrates of CYP2D6 is low when used in therapeutic doses. These results indicated that an increase in the number of concomitant inhibitors may be associated with lower CYP2D6 activity. An indication for risperidone TDM should, therefore, include concomitant medication with established CYP inhibitors.

Risperidone TDM plus genotyping of several genes, including CYP2D6, was studied in 277 US patients.[83] The plasma risperidone/9-OH-R ratio and the total concentration-to-dose ratio as the C/D ratio were studied. The normal C/D ratio was 7. Twice the C/D ratio (>14) was considered indicative of diminished risperidone clearance, while half the C/D ratio (<3.5) was considered indicative of increased risperidone clearance. Almost all CYP2D6 PMs had an inverted risperidone/9-OH-R ratio (>1). After controlling for confounders, taking CYP inhibitors was strongly associated with a C/D ratio >14 (odds ratio = 8.2; 95% confidence interval [CI] = 2.0–32.7), indicating diminished risperidone elimination. After controlling for confounders, taking CYP3A inducers was significantly associated with a C/D ratio <3.5 (OR = 41.8; CI = 12.7–138), indicating increased risperidone elimination. In a linear regression of the total concentration, after controlling for potential confounding variables, patients who were taking CYP3A inducers had 59% lower total concentrations than those in patients who were not and patients who were taking CYP inhibitors had 27% higher total concentrations than those in patients who were not. Female patients had 28% higher total concentrations than male patients.

4.3.3. Olanzapine

The major metabolic pathways of olanzapine include direct N-glucuronidation, mediated by UGT1A4, and N-demethylation, mediated by CYP1A2.[10] Minor routes of olanzapine biotransformation include N-oxidation, catalyzed by the flavin-containing mono-oxygenase-3 system, and 2-hydroxylation, metabolized by CYP2D6. Concomitant administration of other compounds acting as inhibitors or inducers of CYP or UGT enzymes involved in olanzapine metabolism may affect olanzapine TDM with potential clinical implications.[8–10,13] Therefore, olanzapine TDM may be useful in patients under polytherapy.[84]

Olesen and Linnet [85] described steady-state olanzapine TDM in a relatively small sample of 56 psychiatric patients under routine conditions. Patients were divided into four groups: group 1 consisted of 22 patients on olanzapine monotherapy, group 2 included 15 patients co-medicated with drugs not known to interfere with CYP2D6, group 3 consisted of 14 patients treated with medications acting as inhibitors or substrates for CYP2D6, and group 4 included 5 patients treated with carbamazepine, a well-known broad-spectrum enzyme inducer. By pooling data from groups 2 and 3, co-medication was found to increase the median C/D of olanzapine by 40% as compared to group 1 ($p < 0.05$). On the other hand, patients on carbamazepine co-medication had a median C/D of olanzapine 36% lower than those on monotherapy ($p < 0.05$). In a subsequent study, the same authors [86] measured both free and glucuronidated olanzapine in psychiatric patients referred to routine TDM of olanzapine. The median C/Ds of free and glucuronidated olanzapine in 30 psychiatric patients in monotherapy were 5.8 and 2.2 nmol/L/mg, respectively (corresponding to 1.8 and 0.7 ng/mL/mg, respectively). The corresponding values in 15 patients co-medicated with carbamazepine were 3.6 and 3.1 nmol/L/mg (1.1 and 1, ng/mL/mg, respectively). The median C/D of free

olanzapine in the carbamazepine group was 38% lower than that of the monotherapy group ($p < 0.01$, confirming that carbamazepine may stimulate the biotransformation of olanzapine, presumably by inducing both CYP1A2 and UGT1A4.

Weigmann et al. [87] used olanzapine TDM data to study the potential DDIs with fluvoxamine and sertraline. Patients co-medicated with fluvoxamine ($n = 10$) had C/D ratios of olanzapine 2.3-fold higher than those on olanzapine monotherapy ($n = 124$). No significant difference in olanzapine C/D ratios was observed between patients receiving additional sertraline ($n = 21$) and the olanzapine group. This indicated that fluvoxamine inhibits the metabolism of olanzapine, probably due to CYP1A2 inhibition, whereas sertraline is unlikely to interfere with the metabolism of olanzapine.

A large Swedish TDM database of olanzapine and its metabolite N-desmethylolanzapine, including a final sample of 194 patients, documented that patients co-medicated with carbamazepine had a median C/D ratio of olanzapine 71% lower than patients on olanzapine monotherapy.[88] Olanzapine TDM data were also investigated by Gex-Fabry et al.[89] The study included 250 patients, with daily doses ranging from 2.5 to 30 mg. In the whole sample, multiple regression analysis of the C/D ratio of olanzapine revealed significant effects of co-medication with fluvoxamine (+74%, $p < 0.001$), paroxetine, fluoxetine, or sertraline (considered together, +32%, $p < 0.05$), venlafaxine (+27%, $p < 0.05$), and inducers of CYPs (−40%, $p < 0.001$).

Botts et al. [90] estimated the DDI effect size on steady-state olanzapine TDM, adjusting for potentially confounding factors known to influence olanzapine metabolism, such as smoking. The evaluation was performed by using a mixed model [75] and included data from a series of previously published studies of lamotrigine,[91] oxcarbazepine,[92] topiramate,[93] mirtazapine,[94] and unpublished data from patients under clinical TDM. The total sample included 163 patients who provided a total of 360 olanzapine concentrations (1–11 measures per patient). Concomitant carbamazepine or lamotrigine use was found to have significant effects on median plasma olanzapine concentrations. The effects of lamotrigine on plasma olanzapine concentrations were influenced by smoking. Lamotrigine behaved as an olanzapine inhibitor in smokers, increasing the C/D ratio by 35%, whereas it caused a mild nonsignificant 11% decrease in olanzapine C/D ratio in nonsmokers. Concomitant use of mirtazapine, valproic acid, topiramate, lorazepam, citalopram, or oxcarbazepine did not significantly affect olanzapine concentrations.

Haslemo et al. [95] used data from a routine TDM service to investigate the potential interaction between an ethinylestradiol-containing contraceptive (ECC) and olanzapine. The study included 149 patients of which 10 received ECC and 10 received progestogen-based contraceptives (PBC). In users of ECC, there were no differences in serum concentrations of olanzapine, but significantly lower concentrations of the CYP1A2-mediated metabolite *N*-desmethylolanzapine compared with users of PBC ($p = 0.019$) and noncontraceptive users ($p = 0.012$). Haslemo et al. [96] performed a study to investigate the impact of various antiepileptics on a large-scale sample of olanzapine TDM material (598 serum samples from 450 patients). Concomitant administration with valproic acid was found to significantly decrease serum concentration of olanzapine to an extent comparable to that of cigarette smoking. Significantly lowered C/D ratios of olanzapine were observed in patients co-medicated with valproic acid ($n = 92$, −32%, $p < 0.001$), valproic acid + lamotrigine ($n = 7$, −31%, $p < 0.01$), and carbamazepine ($n = 8$, −50%, $p < 0.001$) compared with controls ($n = 205$). On the other hand, C/D ratios of olanzapine did not differ between patients treated with lamotrigine ($n = 110$) and the control group.

4.3.4. Quetiapine

Quetiapine is metabolized almost exclusively by CYP3A4 with some additional contribution from CYP2D6.[10] Therefore, co-administration of inhibitors or inducers of CYP3A4 may interfere with its elimination, thereby resulting in potentially significant pharmacokinetic DDIs.[8–10,13]

Hasselstrom and Linnet [97] recorded serum concentrations of quetiapine in 62 psychiatric patients under routine conditions. Patients were divided into various groups according to concomitant treatment. Patients co-medicated with CYP3A4 inhibitors ($n = 38$) had a median quetiapine C/D value of 0.48 nmol/L/mg (0.18 ng/mL/mg), which was 70% higher than the median C/D value of 0.28 nmol/L/mg (0.11 ng/mL/mg) in the monotherapy group ($n = 8$) and the corresponding value of 0.23 nmol/L/mg (0.09 ng/mL/mg) in patients receiving drugs metabolized by CYP2D6 ($n = 10$). The two patients treated with the CYP3A4-inducer carbamazepine had the lowest quetiapine C/D values, 0.02 and 0.04 nmol/L/mg (0.008 and 0.016 ng/mL/mg).

A TDM study of 96 patients investigated the effect of various factors including co-medications on quetiapine plasma concentrations.[98] Quetiapine C/D ratios were 77% higher ($p = 0.016$ in patients co-medicated with valproate ($n = 9$) as compared to those not receiving valproate. Based on this finding, the authors suggested a CYP3A4-mediated inhibition of quetiapine metabolism by valproate.

The effect of various co-medications on the serum concentrations of quetiapine was investigated by using data from a large routine TDM service, 2001–2004, including 2111 samples from 1179 patients.[99] Concomitant treatment with fluvoxamine ($n = 11$) and clozapine ($n = 70$) significantly increased ($p < 0.001$) the quetiapine C/D ratio by 159% and 82%, respectively. By contrast, co-administration with carbamazepine ($n = 39$) significantly decreased ($p < 0.001$) quetiapine C/D ratio by 86%. Co-medication with lamotrigine ($n = 147$) was also associated with a slight, but significant, 17% decrease ($p < 0.05$) in quetiapine C/D ratio. In contrast to Aichhorn et al.,[98] no relevant changes in quetiapine concentrations were observed in patients receiving valproate ($n = 237$).

Data from another routine TDM service, 2006–2007, including 138 samples from 87 psychiatric patients were used to investigate the effect of concomitant treatment with various antiepileptic drugs on steady-state plasma concentrations of quetiapine.[100] C/D ratio values of quetiapine were significantly lower, by approximately 75% ($p < 0.001$), in the carbamazepine group ($n = 6$) as compared to patients on quetiapine monotherapy ($n = 35$). No differences in quetiapine C/D values were found between patients co-medicated with

valproate (N = 19), lamotrigine (N = 16), topiramate (n = 6), oxcarbazepine (n = 5) and patients on quetiapine alone.

Andersson et al. [101] used data from a Swedish TDM program to investigate the possible DDI between lamotrigine and quetiapine. Patients co-medicated with lamotrigine (n = 22) had a 58% lower quetiapine C/D ratio as compared to 22 controls under quetiapine monotherapy. Based on these findings, the authors proposed that lamotrigine may reduce quetiapine concentrations, possibly by inducing glucuronidation.

A large TDM database including 927 samples from 601 subjects was used to study the pharmacokinetic variability of quetiapine and its active metabolite N-desalkylquetiapine in psychiatric patients.[102] In three patients co-medicated with potent CYP3A4 inducers such as carbamazepine (n = 2) and phenobarbital (n = 1), the C/D ratios of quetiapine and N-desalkylquetiapine were on average 77% and 11% lower than the mean C/D ratio in the study population.

4.3.5. Aripiprazole

Aripiprazole is metabolized by CYP2D6 and CYP3A4 to dehydroaripiprazole and other metabolites.[10] Plasma concentrations are significantly affected by co-medication with inhibitors or inducers of CYP3A4.[8–10,13]

Molden et al. [103] investigated the pharmacokinetic variability of aripiprazole and its active metabolite dehydroaripiprazole on the basis of 155 TDM samples from 118 psychiatric patients receiving therapeutic doses of aripiprazole (10–30 mg/day). The mean C/D ratios of aripiprazole, dehydroaripiprazole, and their sum in the three patients who were prescribed potent CYP2D6 inhibitors (paroxetine or fluoxetine) did not differ from the median C/D ratio in the whole population.

The effects of co-medications on the serum concentrations of aripiprazole were studied in a relatively small sample of 81 patients from a routine TDM service.[104] Co-medication with the CYP3A4 inducer carbamazepine (n = 1) lowered the C/D ratio of aripiprazole by 88%. Concomitant treatment with CYP2D6 inhibitors (levomepromazine and fluoxetine) resulted in a mean C/D ratio 44% higher than in the monotherapy group. Subjects co-medicated with valproate had a 24% lower mean C/D ratio of aripiprazole than in patients on monotherapy, while subjects co-medicated with lamotrigine, citalopram/escitalopram, and lithium had mean C/D ratios 51%, 39%, and 34% higher than the monotherapy group. Dehydroaripiprazole, the active metabolite of aripiprazole, was not measured in samples included in this study.

Waade et al. [105] evaluated the impact of various co-medications on aripiprazole and dehydroaripiprazole in a large TDM database including 361 samples from 223 psychiatric patients. Co-administration with CYP3A4 inducers (carbamazepine, phenobarbital, and phenytoin) resulted in approximately 60% lower mean C/D ratios of aripiprazole, dehydroaripiprazole, and their sum as compared with the monotherapy group ($p < 0.05$, $p < 0.01$, and $p < 0.05$, respectively). Co-medication with CYP2D6 inhibitors (fluoxetine and paroxetine) was associated with a 45% higher mean C/D ratio of aripiprazole compared with monotherapy controls ($p < 0.05$), while the mean C/D ratio of dehydroaripiprazole was unchanged. Concomitant administration of escitalopram, olanzapine, or lamotrigine resulted in slight, but statistically significant, changes in aripiprazole systemic exposure. Conversely, concomitant intake of the other antidepressants such as mirtazapine, sertraline or venlafaxine, or other antipsychotics including clozapine, risperidone, or quetiapine did not affect the pharmacokinetics of aripiprazole.

4.3.6. Ziprasidone

Ziprasidone is metabolized primarily by an aldehyde oxidase and to some extent by CYP3A4.[10] The pharmacokinetic DDI profile of ziprasidone has been poorly investigated. The interindividual variability of steady-state serum concentrations of ziprasidone and its active metabolite S-methyl-dihydroziprasidone were investigated by using routine TDM data from a cohort of 370 patients treated with ziprasidone, January 2001–December 2004.[106] No differences in C/D ratios of ziprasidone or its active metabolite were found between patients on ziprasidone monotherapy (10%) and the remaining subjects receiving concomitant medication. Due to the small number of patients in each group, it was not possible to evaluate the impact of inducers (n = 3) or inhibitors (n = 3) of CYP3A4 on ziprasidone TDM.

Vogel et al. [107] performed a retrospective analysis of data from a ziprasidone TDM database. The total sample included 463 patients treated with ziprasidone at doses ranging between 20 and 320 mg/day. Pharmacokinetic DDIs with co-medication played a minor role. The C/D ratios of ziprasidone did not differ significantly between patients without (n = 115) and with co-medication (n = 348). Among the multiple drugs that were taken as co-medication, there was a trend showing that carbamazepine decreased ziprasidone concentration. This was in agreement with earlier findings from a formal kinetic study in healthy subjects suggesting that carbamazepine may be a mild inducer of ziprasidone metabolism by increasing CYP3A4 metabolism.[108]

4.3.7. Amisulpride

Amisulpride is largely excreted unchanged in the urine with less than 5% of a dose undergoing hepatic metabolism. Bowskill et al. [109] investigated the effect of dose and other factors on plasma amisulpride concentrations under routine conditions. The study included 296 samples from 196 psychiatric patients. There was no significant difference in either the mean dose or the mean plasma amisulpride concentration between patients co-medicated with clozapine (n = 16) and those in whom clozapine co-prescription was not recorded ($p > 0.1$ in both cases).

4.3.8. Asenapine, iloperidone, lurasidone, paliperidone, and sertindole

We found no TDM database studies for the new antipsychotics asenapine, iloperidone, lurasidone, paliperidone, and sertindole.

5. Conclusion

5.1. Article conclusions

This review article of SGA TDM has sought to contribute increased knowledge of DDIs caused by inhibitors and inducers of SGA metabolism. Unfortunately, psychiatric textbooks

and, more importantly, drug package inserts (or prescribing information) are not good sources for learning about DDI. Drug package inserts (1) do not give easy instructions on how to correct for DDI effects [110] and (2) frequently use DDI single-dose studies instead of steady-state conditions to provide suggestions.[111]

To understand the clinical relevance of DDIs on ADRs, the concept of therapeutic window is important.[37] Based on TDM ranges, clozapine, paliperidone, and risperidone may be narrow therapeutic window drugs and after adding an inhibitor or discontinuing an inducer, they may be particularly prone to cause ADRs. One should expect that high clozapine or risperidone plasma concentrations may be associated with any of the ADRs that are dose-related. Although paliperidone may be a narrow therapeutic drug, it appears that the effects of CYP inhibitors on paliperidone TDM are limited; therefore, adding a CYP inhibitor to paliperidone is not likely to cause ADRs. On the other hand, discontinuing a powerful CYP inducer, such as carbamazepine, phenobarbital, or phenytoin, is expected to increase the risk of dose-related paliperidone ADRs. Amisulpride, aripiprazole, olanzapine, ziprasidone, and quetiapine are probably wider therapeutic window drugs. This means that adding an inhibitor or discontinuing an inducer is much less likely to cause ADRs than in the narrower window SGAs.

To understand the clinical relevance of DDIs on lack of efficacy after adding an inducer, the most important fact is the size effects of the decrease on TDM under maximum induction.[69] Two SGAs, quetiapine and lurasidone, which are mainly metabolized by CYP3A4, are very sensitive to induction and should not be administered with potent inducers such as carbamazepine, phenytoin, or phenobarbital. Quetiapine and lurasidone may also be rather sensitive to induction by CYP3A4 mild inducers, such as oxcarbazepine and topiramate.[69] Two SGAs, amisulpride and ziprasidone, which have little CYP metabolism even in conditions of induction, may not need dosage changes in the presence of potent inducers. The other SGAs, aripiprazole, clozapine, iloperidone, olanzapine, paliperidone, and risperidone, are moderately sensitive to potent inducers (Table 4). There is limited data on asenapine, but the authors would not be surprised if asenapine is found to be moderately sensitive to induction.[69]

Table 4 integrates TDM studies with the information on in vitro metabolism studies, case report/series, and prospective studies to provide our best interpretation of what to expect in the average patient after adding psychotropic drugs with inducing or inhibitory properties. This will provide some orientation to clinicians with no TDM access and may also encourage clinicians to further study TDM. Some of the SGAs have almost no data regarding their metabolism during co-prescription with inducers and inhibitors.

We need to acknowledge that the TDM studies described in this article and our Table 4 are hampered because they focus on the average patient. Many patients, though, are not average. For genetic, environmental, or personal reasons, some patients may be more sensitive to inhibition or induction. Some patients appear to be very sensitive to inducers.[23] For example, in a male smoker valproate behaved as a powerful inducer of clozapine metabolism, in a dose-related way.[112] TDM results after combining carbamazepine with risperidone and (1) a CYP2D6 PM genotype [53,113] or (2) a potent CYP2D6 inhibitor that can cause a PM phenotype have been described.[113] More studies combining CYP genotype with TDM in patients taking inducers or inhibitors are important. As an example, although it has never been studied with risperidone TDM, CYP2D6 PMs should have little sensitivity to inhibition by paroxetine, a relatively specific CYP2D6 inhibitor, because CYP2D6 PMs have no CYP2D6 activity, but they may be sensitive to fluoxetine, which is not only a powerful CYP2D6 inhibitor but a mild/moderate CYP3A4 inhibitor.

Many DDIs with nonpsychiatric drugs have never been systematically studied for SGAs in TDM studies and clinicians may be lucky if they find published case reports. However, we know, based on pharmacokinetic mechanisms, that many of these DDIs are undoubtedly occurring in the clinical environment.[8–14,16] DDIs with nonpsychiatric drugs (and inflammation) and TDM recommendations are described in Box 1. [8,12,16,69,114–119]

6. Expert opinion

In spite of the very limited effort of pharmaceutical companies on SGA TDM and DDIs, the integration of TDM DDI studies with in vitro metabolism studies, case report/series, and prospective studies provides some understanding of SGA TDM (Table 4). TDM knowledge for clozapine and olanzapine is relatively sophisticated and TDM is strongly recommended. [15] Those readers interested in using C/D ratios to interpret clozapine DDIs are referred to another article.[35] Olanzapine C/D ratios can be used to describe olanzapine DDIs with inducers and inhibitors,[90] but more studies are needed to establish the range of normal and abnormal values. Olanzapine TDM studies exploring possibility that lamotrigine effects are influenced by smoking and that is an inhibitor of olanzapine metabolism in smokers [90] are needed. Amisulpride appears to have little potential for DDIs, so in that SGA, TDM may have more benefit related to issues other than DDIs.

There are six SGAs in which TDM is recommended: sertindole, risperidone, paliperidone, aripiprazole, quetiapine, and ziprasidone.[15] Sertindole data is limited but prescribing it under TDM control appears a good idea due to (1) its possible narrow therapeutic window with risk for QTc prolongation and (2) being influenced by CYP2D6 genetic polymorphism, CYP2D6 inhibitor, CYP3A4 inhibitors, and CYP3A4 inducers. Risperidone TDM is the best understood of them and, as it may be a narrow-therapeutic drug, we highly recommend (Table 4) risperidone TDM in patients taking inducers or inhibitors, and those with an inflammation.[118] Those readers interested in learning about using risperidone/9-OH-R ratio and the total C/D ratio to interpret risperidone DDIs are referred to another article.[35] There are no paliperidone TDM studies exploring DDI but a recent prospective DDI study [66] suggested that it will be particularly important to complete them in patients taking inducers such as carbamazepine, which appears to be a potent inducer of CYP3A4 and P-gp. More aripiprazole TDM studies are needed to explore the

Table 4. Provisional SGA dose correction factors during DDIs with psychotropic drugs with inhibitory and inducing properties based on the limited available information from TDM and other sources.

SGA	Other psychotropic drugs (inducers or inhibitors)	Actions to take
CYP1A2 SGA	Potent inducers: carbamazepine, phenytoin, or Phenobarbital	1) Correction dose factor: Clozapine: 1.5–2. Olanzapine: 2–3
Clozapine		2) TDM is strongly recommended.
Olanzapine		3) In some countries, carbamazepine is not recommended since it is also associated with agranulocytosis.
	High dose mild inducers: oxcarbazepine (≥1200 mg/day) or topiramate (≥400 mg/day)	1) Not well studied. 2) TDM is strongly recommended.
	Valproate: possible mild inhibitor and/or mild inducer	1) Not well studied. 2) TDM is strongly recommended.
	Other SSRIs or other second-generation antidepressants no listed below	1) No need for dose change 2) TDM can help to verify that.
	Mild inhibitors: fluoxetine or paroxetine	1) Not relevant. 2) TDM if ADRs.
	TCAs	Risky without TDM for both (SGA and TCA).
	Potent inhibitor: fluvoxamine	1) Correction dose factor: Clozapine 0.1–0.2. Olanzapine:0.3–0.5
		2) Very risky without TDM.
CYP3A4	Potent inducers: carbamazepine, phenytoin, or Phenobarbital	Do not use (Correction factor ≥5).
Lurasidone	High dose mild inducers: oxcarbazepine (≥1200 mg/day) or topiramate (≥400 mg/day)	Do not use unless access to TDM.
Quetiapine	Other antidepressants no listed below	No need for dose change.
	Mild/moderate CYP3A4 inhibitors not well studied: fluoxetine or fluvoxamine	1) No need for dose change. 2) Consider TDM if accessible.
CYP2D6/CYP3A	Potent inducers: carbamazepine, phenytoin, or Phenobarbital	1) Correction dose factor: 0.5. 2) Use TDM if accessible.
Aripiprazole	High dose mild inducers: oxcarbazepine (≥1200 mg/day) or topiramate (≥400 mg/day)	1) Not well studied. 2) Use TDM if accessible.
Iloperiodone		
Risperidone	Other[2] SSRIs or other[2] second-generation antidepressants	No need for dose change.
Sertindole (always TDM)[1]	Mild CYP2D6 inhibitors: fluvoxamine or high dose sertraline	1) Not well studied. 2) Use TDM if accessible.
	Moderate CYP2D6 inhibitors: bupropion, duloxetine, or TCAs	1) Not well studied. 2) Use TDM if accessible.
	Potent CYP2D6 inhibitor: paroxetine	1) Correction dose factor: 0.5. 2) Use TDM if accessible.
	Fluoxetine (CYP2D6 and some CYP3A4 inhibition) or CYP2D6 PM and some CYP3A4 inhibition	1) Correction dose factor: 0.25. 2) Use TDM if accessible.
Only Aripiprazole	Valproate: possible inducer	1) Correction dose factor: 1.25. 2) Consider TDM.
Aldehyde oxidase (CYP3A4)	Potent inducers: carbamazepine, phenytoin, or phenobarbital	1) No need for dose change (Very small correction factor 1.33) 2) TDM can help to verify that.
Ziprasidone	Mild/moderate CYP3A4 inhibitors not well studied: fluoxetine or fluvoxamine	1) No need for dose change.2) TDM can help to verify that.
UGT1A4 & CYP1A2	Potent inducers: carbamazepine, phenytoin or Phenobarbital	Not well studied. TDM is strongly recommended.
Asenapine	High dose mild inducers: oxcarbazepine (≥1200 mg/day) or topiramate (≥400 mg/day)	Not well studied. Consider TDM.
	Valproate: possible inhibitor	Not well studied. Consider TDM.
	Inhibitor: fluvoxamine	Correction dose factor: 0.5–0.75.TDM is strongly recommended.
	Antidepressant metabolized by CYP2D6[3]: paroxetine, TCAs, or venlafaxine	Do not use (consider ↓ dose or TDM for antidepressant).
	Other[2] antidepressants	No need for dose change.
Renally excreted	Potent inducers: carbamazepine, phenytoin, or Phenobarbital	No need for dose change (TDM can help to verify that).
Amisulpride	SSRIs and other CYP inhibitors	No need for dose change (TDM can help to verify that).
Paliperidone	Potent inducers: carbamazepine, phenytoin, or Phenobarbital	Correction dose factor: 3. TDM is strongly recommended.
	High dose mild inducers: oxcarbazepine (≥1200 mg/day) or topiramate (≥400 mg/day)	Not well studied. TDM is strongly recommended.
	Valproate: inhibitor	Correction dose factor: 0.5. TDM is strongly recommended.
	Antidepressant are not likely to be inhibitors but not well studied.	No need for dose change. Consider TDM if ADRs.

ADRs: Adverse dug reaction; CYP: cytochrome P450; DDI: drug-drug interaction; SGA: second-generation antipsychotic; SSRI: selective serotonin reuptake inhibitor; TDM: therapeutic drug monitoring.

[1]Sertindole is metabolized by CYP2D6 and CYP3A4. There is no TDM data on the effects of CYP2D6 genetic polymorphism, CYP2D6 inhibitor, CYP3A4 inhibitors, or CYP3A4 inducers. Based on pharmacological mechanism knowledge, it appears reasonable that dose correction factors from other antipsychotics metabolized in same way may apply to sertindole too. Due to this lack of data and its possible narrow therapeutic window with risk for QTc prolongation, it appears reasonable to always prescribe sertindole under TDM control.

[2]Others refer to other antidepressants not listed in the lines above for that specific SGA.

[3]Asenapine is a mild CYP2D6 inhibitor.

effect of inducers and inhibitors, including valproate, which may be a mild inducer.[120] Quetiapine is probably the SGA with the widest therapeutic index, so DDIs with inhibitors may not be very relevant clinically, but the studies by the pharmaceutical company and TDM suggest that it is very sensitive to potent inducers. This is why we recommend against quetiapine co-prescription with carbamazepine, phenobarbital, or phenytoin (Table 4). A recent case report [57] indicates that quetiapine TDM studies in patients taking mild CYP3A4 inducers, such as oxcarbazepine, may be very important, since mild inducers may cause clinically relevant decreases in plasma quetiapine concentrations and lack of efficacy. Quetiapine TDM studies exploring possibility that lamotrigine may be a mild inducer [99] and valproate a mild inhibitor [98] are needed paying particular attention to the variability associated with quetiapine's short half-life. According to our pharmacological knowledge, ziprasidone may have little risk of clinically relevant DDIs with inhibitors and inducers, but it would be important to have a good number of TDM studies indicating that this is true in the clinical environment.

It is unfortunate that we have such limited available evidence for iloperidone, asenapine, and lurasidone. More TDM

iloperidone studies are needed to verify that its profile for DDI is similar to risperidone and aripiprazole, drugs also metabolized by CYP2D6 and CYP3A4. Asenapine's unusual metabolism by UGT1A4 and CYP1A2 makes it difficult to make predictions about DDIs. Table 4 is full of uncertainty about asenapine DDIs since we do not know any other drug with a similar metabolic profile that we can use as a model for making predictions. Asenapine TDM studies are desperately needed to establish the clinical relevance of DDIs with inducers and inhibitors, including carbamazepine and valproate, drugs likely to be co-prescribed in patients with bipolar disorder. Table 4 indicates that lurasidone DDIs may follow the same pattern than quetiapine DDI. This is why we recommend against the co-prescription of potent inducers such as carbamazepine, phenobarbital, or phenytoin with lurasidone (Table 4). Lurasidone TDM studies with mild inducers, such as oxcarbazepine or topiramate, are urgently needed since we suspect they may be associated with significant decreases in plasma lurasidone concentrations and lack of efficacy.

DDI descriptions in the package inserts (or prescribing information) are usually not designed to provide easy helps for clinicians in correcting pharmacokinetic DDIs. Independent investigators have no easy access for funding to conduct prospective DDI studies using clinically relevant doses of inducers and inhibitors to orient clinicians. The main goal of Table 4 is to provide provisional guidance for SGA dosing of average patients who are taking clinically-relevant inducers or inhibitors

Table 4 has also a secondary goal. Clinicians frequently co-prescribe antidepressants or antiepileptic/mood stabilizers with SGAs. Thousands of patients all over the Western countries take these combinations. Clinicians using these combinations, after reading our Table 4, may be encouraged to publish case reports/series to demonstrate whether or not our dose indications are correct for their patients. Pharmacokinetic researchers with interest in SGA TDM can use Table 4 to explore which DDIs may be important to study in prospective and retrospective ways using large TDM databases.

Progress in the next few years, if this TDM research agenda for SGA DDIs is followed, should also be accompanied by better continuous medical education on DDIs and improvements in psychopharmacology textbooks. Then clinicians can begin paying more attention to DDIs with inducers and inhibitors in patients taking SGAs.

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