

# Drug–Drug Interactions Associated with Second-Generation Antipsychotics: Considerations for Clinicians and Patients

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**ABSTRACT ~ Objectives:** While not always clinically significant, patients with schizophrenia may be at risk for drug–drug interactions (DDIs) with second-generation antipsychotics. Second-generation antipsychotics are increasingly being used in a broader population of patients and, therefore, for those with comorbid illnesses, adjunctive treatments, or other diagnoses, the clinical significance of DDIs is increasing. This paper reviews currently available data concerning DDIs that occur between second generation antipsychotics, and other medications or substances, when metabolized by the cytochrome P-450 (CYP) family of enzymes. This review will assess the clinical relevance of these interactions for physicians and patients with schizophrenia. **Methods:** EMBASE and MEDLINE searches were conducted (no date restrictions) using the keywords “drug–drug interactions,” “atypical antipsychotics,” “olanzapine,” “ziprasidone,” “quetiapine,” “risperidone,” “aripiprazole,” “clozapine,” “asenapine,” “bifeprunox,” and “paliperidone.” **Principal observations:** Second-generation antipsychotics are primarily metabolized by CYP enzymes. When coadministered with inducers or inhibitors (psychotropic or non-psychotropic medications or substances) of CYP enzymes, antipsychotic plasma levels may be reduced or increased, respectively, as a result of DDIs. This can result in a reduced effectiveness of the antipsychotic, or an increased risk of adverse events, respectively. Drugs with a less clinically significant risk for DDIs are a more reliable treatment option for patients in whom drug plasma levels may fluctuate. **Conclusion:** Some of the currently available second-generation antipsychotics have a higher potential for DDIs. Agents with a reduced liability for DDIs may be safer treatments as the systemic drug concentration is less likely to seriously increase/decrease when other medications are knowingly or inadvertently co-prescribed or hepatic problems and drug abuse is present. *Psychopharmacology Bulletin. 2007;40(1):77-97.*

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## INTRODUCTION

### *Profiling Patients with Schizophrenia*

Patients with schizophrenia are highly likely to have comorbid medical and other psychiatric conditions (comorbidities),<sup>1</sup> often requiring multiple psychotropic or nonpsychotropic medications. Studies have shown that patients with schizophrenia are at an elevated risk of anxiety disorders, depression, cardiovascular disease, diabetes, hypertriglyceridemia, and infection with human immunodeficiency virus (HIV) and hepatitis C, thereby increasing the likelihood of polypharmacy.<sup>2-4</sup> This risk of a comorbid medical diagnosis is further raised in certain populations with schizophrenia, such as the elderly, who are consequently more likely to be receiving concomitant therapy.<sup>5,6</sup> Second-generation antipsychotics are now generally accepted as the first-line treatment for patients with schizophrenia; however, psychotropic polypharmacy is widely used either justifiably to treat comorbid conditions or, in some cases, due to poor prescribing practices.<sup>7-9</sup> Specifically, antipsychotic polypharmacy (a combination of two or more antipsychotics) and pharmacological add-on therapy with benzodiazepines, antidepressants, and mood stabilizers are increasingly being used in patients with schizophrenia to treat various aspects of their illness.<sup>8,10</sup>

In addition to medical comorbidities, it has also been shown that patients with schizophrenia are more likely to have comorbid substance abuse, such as alcohol, cannabis, cocaine, or nicotine dependence.<sup>11-13</sup> For example, results from a meta-analysis have demonstrated that, compared with the general population, patients with schizophrenia are more likely to start smoking, be heavy smokers, have high nicotine dependence, and be less likely to stop smoking.<sup>14</sup> The risk of comorbid substance abuse is generally greater in younger populations.<sup>5</sup> Patients with a dual diagnosis of schizophrenia and substance abuse are at particular risk for hepatic impairment; for example, alcohol abuse has been known for a some time to be associated with detrimental effects on the liver,<sup>15</sup> which can result in a decrease in drug metabolism activity,<sup>16</sup> and intravenous drug use can expose patients to hepatitis C and HIV infections and, therefore, increase the risk of hepatic disease.<sup>17</sup> Hepatitis C has also been shown to reduce hepatic metabolic activity and, thus, drug clearance in this patient population. Moreover, recently published consensus recommendations for patients with schizophrenia and substance abuse point out that it is with this population and especially dual diagnosis patients with medical comorbidities that drug interaction concerns are critical.<sup>18</sup> Comorbid substance abuse is, therefore, an important consideration in the development of a treatment regimen, since in addition to intrinsic deleterious effects on health and relationships, substance abuse

can reduce adherence, efficacy of medication, and the optimal clinical outcome that patients could otherwise expect from their schizophrenia treatment.<sup>16,19-22</sup>

### *Drug-Drug Interactions*

With the increasing use of polypharmacy to treat psychiatric and non-psychiatric comorbid medical conditions, and the prevalence of substance abuse,<sup>23</sup> the potential for drug-drug interactions (DDIs) is becoming an important consideration in the treatment of patients with schizophrenia.<sup>8,24-26</sup> DDIs are of clinical relevance when they impact on drug metabolism.

Drug metabolism is the method by which drugs are deactivated and excreted from the body; drug metabolism may also be the method by which the drug becomes activated to the potent metabolite.<sup>27,28</sup> Drugs can be metabolized by a variety of sequential or competitive processes<sup>29</sup>: Phase I reactions, usually involving oxidation, reduction, or hydrolysis, convert the parent compound into a more hydrophilic species, facilitating renal excretion<sup>24,25</sup>; Phase II reactions involving glucuronidation, sulfation, acetylation, and methylation generally produce inactive metabolites.<sup>25</sup> Oxidation is among the most important of the Phase I reactions and is mediated by the cytochrome P-450 (CYP) enzymes, a superfamily of microsomal drug-metabolizing enzymes.<sup>25,29</sup> CYP enzymes play the major role in the metabolism of most second-generation antipsychotics.<sup>26</sup>

A more recently identified pathway for potential drug interactions involves the drug transporter, P-glycoprotein. This protein influences drug distribution across the blood-brain barrier by actively extruding drugs into the neural capillaries. Many medications have recently been identified as substrates or inhibitors that may compete for the bioavailability of antipsychotic medications.<sup>30-32</sup> The extent of antipsychotic involvement through this pathway is yet to be fully elucidated, thus, drug interaction data involving this pathway will not be reported in this review.

DDIs can occur when a drug either inhibits (competitively or non-competitively) or induces the same CYP enzyme that is used to metabolize another drug. Inhibitors reduce the activity of metabolic enzymes and inducers increase the production of metabolic enzymes and, consequently, the rate of metabolism.<sup>33</sup> Second-generation antipsychotics appear not to induce or inhibit metabolic enzymes themselves but their metabolism can be affected by other drugs that use the same metabolic pathways.<sup>26</sup> This can lead to elevated or diminished plasma levels of drugs in the systemic circulation,<sup>25</sup> which may either reduce the therapeutic benefit patients receive from treatment or increase the risk of adverse events, respectively.<sup>29,33</sup> As such, DDIs may increase or decrease

the potency of administered therapies or lead to potentially serious/life-threatening adverse events.<sup>29,34</sup> There are some data which indicate that DDIs resulting in increased plasma levels of antipsychotic drug can lead to acute toxicity due to immediate effects on brain receptors. This acute toxicity can be manifested as side effects such as extrapyramidal side effects and tardive dyskinesia. Nonetheless, chronic toxicity can also occur because of DDIs. For example, there is a case report of a patient with schizophrenia treated with risperidone who exhibited rhabdomyolysis when prescribed simvastatin for hyperlipidemia simultaneously.<sup>35</sup> It was concluded that interactions with the CYP enzyme system rapidly elevated drug plasma levels, leading to the muscle toxicity. The liver is an important organ involved in key steps of lipid metabolism. As such, the chronic effects of DDIs may also include side effects associated with the dysregulation of lipid metabolism. However, there is little data regarding this at present and the area requires extensive further investigation. DDI interactions can be particularly relevant to certain populations, such as the elderly, who may be intrinsically more susceptible to adverse events due to reduced drug clearance rates.<sup>16,28,36</sup> Furthermore, as a majority of second generation antipsychotics are metabolized in the liver, patients with hepatic impairment (and thus, reduced drug clearance) are at a higher risk of adverse events from DDIs with these agents.<sup>16,28</sup>

The objective of this paper is to review currently available data concerning DDIs that occur between second generation antipsychotics, and other medications or substances, when metabolized by the CYP family of enzymes. This review will assess the clinical relevance of these interactions for physicians and patients with schizophrenia.

## METHODS

EMBASE and MEDLINE searches were conducted (no date restrictions) for primary and review papers detailing second generation antipsychotic DDIs. Abstracts from congresses June 2004 to June 2006 were also reviewed. Keywords used in the search included: "drug-drug interactions," "atypical antipsychotics," "olanzapine," "ziprasidone," "quetiapine," "risperidone," "aripiprazole," "clozapine," "asenapine," "bifeprunox," and "paliperidone." Abstracts and papers examining clinically relevant DDIs involving the CYP family of enzymes were reviewed and are discussed here.

## RESULTS

There are several important CYP enzymes involved in second-generation antipsychotic metabolism, which are CYP3A4, CYP2D6, and CYP1A2.<sup>26,29</sup> All three of these CYP enzymes can be both inhibited and induced, inferring the potential for DDIs with the different

second-generation antipsychotics that are discussed later in this review and summarized in Table 1.<sup>24-26,28,37-45</sup> The induction of CYP2D6 appears to have a lower clinical significance than induction of CYP3A or CYP1A2.<sup>26</sup> However, inhibition of any of these pathways could lead to increased plasma concentrations and resulting in side effects.

CYP3A enzymes are potentially the most important of the CYP enzymes, since they may be involved in the metabolism of up to 50%

TABLE 1

**KEY CYTOCHROME P-450 ENZYMES INVOLVED IN THE METABOLISM OF SECOND GENERATION ANTIPSYCHOTICS**<sup>24-26,28,37,38,40-45,55</sup>

SECOND-GENERATION ANTIPSYCHOTIC	KEY METABOLIZING CYTOCHROME P-450 ENZYMES		DRUGS/SUBSTANCES POTENTIALLY LEADING TO CLINICALLY RELEVANT METABOLIC INTERACTIONS UPON COADMINISTRATION	
			INDUCERS	INHIBITORS
Risperidone	Major	CYP2D6 CYP3A4	Carbamazepine, rifampin	Fluoxetine, paroxetine, thioridazine, reboxetine, grapefruit juice, fluvoxamine, ketoconazole, erythromycin
Olanzapine	Minor	-		
	Major	CYP1A2	Carbamazepine, smoking, omeprazole	Caffeine, fluvoxamine, ciprofloxacin, norfloxacin, fluoxetine, methotrimeprazine, nortriptyline
Quetiapine	Minor	CYP2D6		
	Major	CYP3A4	Thioridazine, phenytoin, rifampin	Divalproex, ketaconazole, cimetidine, fluoxetine, grapefruit juice, protease inhibitors, erythromycin, nefazadone
Ziprasidone <sup>a</sup>	Minor	CYP2D6		
	Major	-	Carbamazepine	Ketaconazole, grapefruit juice
	Minor	CYP3A4 CYP1A2		
Aripiprazole	Major	CYP2D6 CYP3A4	Carbamazepine, rifampin	Ketaconazole, grapefruit juice, fluoxetine, erythromycin
	Minor	-		
Clozapine	Major	CYP1A2 CYP3A4	Carbamazepine, smoking, omeprazole, rifampin	Caffeine, fluvoxamine, ciprofloxacin, norfloxacin, fluoxetine, methotrimeprazine, nortriptyline, erythromycin
	Minor	CYP2D6		
Paliperidone ER <sup>b,c</sup>	Major	-	-	-
	Minor	-		
Asenapine <sup>c</sup>			No details yet available	
Bifeprunox <sup>c</sup>			No details yet available	

CYP, cytochrome P-450; ER, extended release.

<sup>a</sup>Less than one-third of ziprasidone metabolic clearance is mediated by CYP-catalyzed oxidation; approximately two-thirds occurs via reduction by aldehyde oxidase.

<sup>b</sup>The liver does not appear to play a major role in paliperidone ER metabolism and, consequently, neither do the CYP enzymes.

<sup>c</sup>There is currently no clinical data available regarding clinically relevant drug-drug interactions for administration of paliperidone ER, asenapine, or bifeprunox.

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of drugs that are metabolized by oxidation. They also account for ~50% of all the cytochrome P450 enzymes present in the liver.<sup>29</sup> With regards to the second-generation antipsychotics, CYP3A enzymes provide a major metabolic pathway for quetiapine and a minor one for ziprasidone, risperidone, and aripiprazole. Grapefruit juice inhibits CYP3A4 and, as such, is contraindicated when taking any drugs that are metabolized by this enzyme.<sup>29</sup> Other potent CYP3A4 inhibitors include erythromycin,<sup>47</sup> ketoconazole,<sup>47</sup> fluvoxamine,<sup>48</sup> and nefazodone.<sup>47</sup> Drugs such as rifampin and modafinil, and some anticonvulsants, which are also potent CYP3A inducers, can also reduce the plasma concentrations of certain CYP3A4-metabolized drugs, leading to ineffective treatment at previously efficacious doses.<sup>29</sup>

Polymorphisms are another clinically important consideration with respect to DDIs, due to adverse reactions in people with a poor metabolism or lack of efficacy in people who are ultrarapid metabolizers.<sup>29</sup> CYP3A enzymes appear to have a low potential for individual polymorphisms, possibly because multiple genes are responsible for their regulation.<sup>29</sup> Conversely, 76 polymorphisms of CYP2D6, a major metabolic pathway for risperidone and aripiprazole, have been discovered, many of which reduce enzyme activity. Around 7% of Caucasians are poor metabolizers and 1–7% are ultrarapid metabolizers; generally, the proportion of poor metabolizers in other populations is 1–3%, and up to 25% of North African and Middle Eastern populations are ultrarapid metabolizers.<sup>16,26,49</sup> These polymorphisms are important as they increase the likelihood of adverse reactions in patients with poor metabolism where plasma levels of active (parent) drugs may surpass the therapeutic window.

Metabolism by CYP1A2 is a major metabolic pathway for olanzapine and clozapine and is induced by cigarettes and inhibited by caffeine.<sup>50</sup> This enzyme is also prone to individual polymorphisms and may be involved in the metabolism of female sexual hormones, potentially leading to naturally lower CYP1A2 activity in women compared with men.<sup>51</sup>

### *Cytochrome Metabolism and Drug-Drug Interactions with Second-Generation Antipsychotics*

**Risperidone.** CYP2D6 accounts for a significant portion of risperidone metabolism, primarily to the active metabolite 9-hydroxyrisperidone,<sup>49,52–54</sup> with CYP3A4 also playing a less major role.<sup>49,52</sup> Following metabolism to the active metabolite, risperidone/9-hydroxyrisperidone is then cleared by renal excretion and further oxidation.<sup>28</sup>

Plasma levels of risperidone and 9-hydroxyrisperidone (the major metabolite) account for the total activity of this drug (active moiety).<sup>53</sup> The ratio between these two compounds characterizes CYP2D6

activity<sup>52</sup> and patients with known CYP2D6 deficiencies should be monitored if receiving risperidone<sup>52</sup>—around 7% of Caucasians have a genetically impaired CYP2D6 activity (poor metabolizers).<sup>16,49</sup> Additionally, age and renal impairment have also been shown to impact on clearance of the active moiety.<sup>28</sup>

If any drugs known to induce (carbamazepine) or inhibit (ketaconazole) CYP2D6 or CYP3A4 are coadministered with risperidone, patients will need their medication regulated to ensure safe, and effective doses are used.<sup>26</sup> Carbamazepine has been shown to markedly decrease mean risperidone plasma levels and those of the active metabolite, 9-hydroxyrisperidone.<sup>55</sup> Such decreases can have important clinical implications, as revealed in the case report of a patient who experienced an acute exacerbation of psychotic symptoms when carbamazepine was combined with their risperidone treatment.<sup>46</sup>

Fluoxetine and paroxetine have been shown to inhibit risperidone, potentially leading to toxic plasma levels of risperidone.<sup>24,39,40</sup> Fluoxetine is a potent inhibitor of CYP2D6 and to a lesser extent CYP3A4, and has been shown to increase the levels of active risperidone moiety (risperidone and 9-hydroxyrisperidone) by 75%, which can lead to Parkinsonism in severe cases.<sup>40</sup> The mean risperidone/9-hydroxyrisperidone ratio is also increased, indicating that fluoxetine inhibits the conversion of risperidone to its major metabolite.<sup>40</sup> Similar observations have been seen with coadministration of paroxetine and risperidone.<sup>39</sup> Thioridazine and reboxetine have also been shown to slightly inhibit risperidone, potentially due to the same CYP2D6 inhibition, although the reboxetine interaction has been noted as unlikely to reach clinical significance.<sup>56-59</sup>

**Olanzapine.** CYP1A2 appears to be the dominant enzyme in the metabolism of olanzapine, with CYP2D6 also playing a minor role.<sup>25,60</sup> Additionally, *N*-glucuronidation (Phase II) contributes to the elimination of olanzapine when the CYP pathways are inhibited, thus offering an alternative elimination pathway.

Drugs that induce (nicotine, carbamazepine) or inhibit (fluvoxamine, ciprofloxacin) CYP1A2 activity may increase or decrease olanzapine clearance, respectively.<sup>28</sup> There may also be an ethnic- and age-related variation that plays a role in olanzapine clearance via the CYP1A2 pathway, as Japanese and elderly patients have been shown to have reduced metabolism.<sup>16</sup> However, individual factors impacting most heavily on the oxidative metabolism of olanzapine are gender (females tend to have lower CYP1A2 activity) and smoking status. These attributes present individually may not require adjustments of the administered dose of olanzapine but, if present together, require careful surveillance (i.e. female non-smokers have a lower oxidative metabolism) and, potentially, adjustment of drug dose.<sup>25,51,60</sup>

Drugs that induce CYP1A2 can lead to decreased olanzapine plasma levels. Increased consumption of cigarettes has also been shown to reduce plasma levels by up to 30% of olanzapine, as heavy smoking induces CYP1A2.<sup>20,28,50,60,61</sup> If a patient receiving olanzapine ceases smoking, the plasma levels of olanzapine would increase and may lead to adverse events if not regulated.<sup>62</sup> Carbamazepine is also a CYP1A2 inducer and has been shown to significantly decrease the maximum concentration ( $C_{max}$ ) area under the concentration-time curve (AUC) and elimination half-life of olanzapine, while also significantly increasing the clearance and volume of distribution. Consequently, patients coadministered carbamazepine and olanzapine will demonstrate decreased olanzapine plasma levels compared with patients administered olanzapine alone, and will require higher doses to achieve effective therapeutic outcomes.<sup>60,63</sup> Char-grilled meat<sup>64</sup> and omeprazole,<sup>38</sup> which is available over the counter, also induce the metabolism of medications through the CYP1A2.

CYP1A2 inhibitors, such as caffeine, can lead to increased olanzapine plasma levels. Caffeine is highly dependant on CYP1A2 for metabolism and, as such, caffeine-intake vary dramatically, olanzapine plasma levels may fluctuate substantially.<sup>50</sup> Fluvoxamine, ciprofloxacin, and norfloxacin are also CYP1A2 inhibitors and, thus, can decrease olanzapine metabolism, leading to increased olanzapine plasma levels.<sup>37,60,65</sup> In a study by Wang et al., fluvoxamine (100 mg/day) increased the  $AUC_{(0-t)}$  and  $AUC_{(0-\infty)}$  by 68% and 78%, respectively, and also reduced the elimination rate (40%) and total body clearance (42%) of olanzapine (10 mg),<sup>65</sup> which has also been demonstrated in other studies.<sup>66</sup> Additionally, CYP2D6 inhibitors (methotrimeprazine, nortriptyline, and fluoxetine) may also reduce olanzapine clearance, although this is not thought to be to a clinically significant level.<sup>28,60,67</sup> However, if combined with intrinsic oxidative metabolism deficiencies (polymorphisms, gender, and age), such interactions could become clinically relevant.<sup>67</sup> Higher plasma levels of olanzapine have been associated with an increase in anticholinergic side effects<sup>68</sup> and prolonged QT interval.<sup>69</sup>

Olanzapine itself has also been noted to inhibit other drugs, although this is not thought to be clinically relevant. Olanzapine competitively inhibits (CYP2D6) bufuralol<sup>70</sup> and non-competitively inhibits (CYP2C9) tolbutamide metabolism.<sup>70</sup> Non-competitive inhibition of CYP2C19-mediated metabolism is also seen with olanzapine.<sup>70</sup> However, olanzapine inhibition of substrates metabolized by CYP3A, CYP2D6, CYP2C9, and CYP2C19 has been shown to only affect plasma levels by <0.3% and, consequently, not to be of clinical significance.<sup>70</sup> Finally, olanzapine treatment with divalproex has been associated with more elevations of hepatic enzymes than with either

treatment alone,<sup>71</sup> and orthostatic changes may occur when olanzapine and diazepam or alcohol are coadministered.<sup>60</sup>

**Quetiapine.** Quetiapine is predominantly metabolized by CYP3A4<sup>72,73</sup> and, as such, clearance of quetiapine will be affected by inducers (phenytoin) or inhibitors (ketoconazole, fluoxetine) of this enzyme.<sup>28</sup> Additionally, there is limited evidence that age may be an important factor in influencing quetiapine clearance, although this information is conflicting and inconclusive.<sup>16,28</sup>

Any drugs coadministered with quetiapine that are CYP3A4 inhibitors may lead to increased quetiapine plasma levels. Protease inhibitors (ritonavir, indinavir, and atazanavir) are potent CYP3A4 inhibitors, as are antifungal agents (ketoconazole), macrolides (troleandomycin, erythromycin), and nefazadone.<sup>25,37</sup> Coadministration of cimetidine or fluoxetine with quetiapine may cause a slight increase in mean quetiapine plasma levels, although this does not appear to be clinically significant.<sup>72,74</sup> In a study by Potkin et al., coadministration of quetiapine with fluoxetine led to an increase in  $AUC_{0-12\text{ h}}$  of 12% and  $C_{\text{max}}$  of 26%; these increases were deemed statistically significant, although not clinically significant, and resulted in no adverse events.<sup>74</sup>

Any potent CYP3A4 inducer that is coadministered with quetiapine may result in an increased dose of quetiapine being required to achieve the original desired therapeutic effect. Phenytoin, a potent CYP3A4 inducer, markedly decreases mean plasma levels of quetiapine and, consequently, decreases the therapeutic benefit.<sup>25,73</sup> Thioridazine also significantly increases the oral clearance of quetiapine and, consequently, doses of quetiapine may need to be increased during coadministration with thioridazine to achieve the necessary control of psychotic symptoms.<sup>75</sup>

**Ziprasidone.** Cytosolic aldehyde oxidase mediates the predominant ziprasidone metabolism reactive pathway and CYP3A4 is responsible for two alternative minor oxidation pathways.<sup>26,28,76</sup> Aldehyde oxidase activity does not appear to be altered when drugs or xenobiotics are coadministered<sup>76</sup> and, as CYP3A4 only mediates one-third of metabolism, the likelihood of interaction with CYP3A4 inhibitors/substrates is low.<sup>76</sup> However, coadministration of ziprasidone with potent CYP3A4 inhibitors is inadvisable as this may lead to clinically significant increased plasma levels of the drug. Another important consideration is that the bioavailability of ziprasidone is affected by food and should be given with meals to increase availability of ziprasidone.<sup>77</sup>

Coadministration of ketoconazole and ziprasidone has been shown to lead to modest increases in mean ziprasidone plasma levels. Mean ziprasidone  $AUC_{(0-\infty)}$  increased by 33% and  $C_{\text{max}}$  by 34% which, while statistically significant, were not considered to be clinically significant.<sup>28,78</sup> Conversely, induction of CYP3A4 with carbamazepine has

been shown to lead to around a 36% reduction in steady state exposure to ziprasidone, which again, was not thought to be clinically relevant.<sup>28,79</sup> Plasma level increases with ziprasidone may potentially lead to prolongation of the QTc interval. While this has not been routinely observed in clinical practice, it is a risk and thus CYP3A4 inhibitors and competitive substrates should be used with caution during ziprasidone administration.<sup>80</sup> Likewise, it is contraindicated to utilize other agents (e.g., chlorpromazine, droperidol, pimozide, quinidine, sotalol, and pentamidine), which may prolong the QTc interval.

**Aripiprazole.** Aripiprazole, a new second-generation antipsychotic, is a substrate of both CYP3A4 and CYP2D6 and, as such, there is a potential for other drugs to affect its metabolism.<sup>81</sup> Potent CYP2D6 inducers, such as carbamazepine, will most likely reduce mean plasma levels of aripiprazole, and CYP2D6 inhibitors, such as fluoxetine, are likely to increase mean aripiprazole plasma levels, although the clinical relevance of these interactions is unknown. Nonetheless, the prescribing information recommends that when CYP2D6 and 3A4 inhibitors are used concomitantly, aripiprazole should be reduced to one-half of its normal dose. Also, if CYP3A4 inducers are employed, the dose of aripiprazole should be doubled (to 20–30 mg).<sup>82</sup>

#### *Cytochrome Metabolism and Drug-Drug Interactions with the Second-Line Antipsychotic Agent—Clozapine*

Clozapine was the first atypical agent released<sup>25</sup> although it is considered a second-line agent, with consensus guidelines recommending a trial of three atypical agents before switching to clozapine.<sup>83</sup> Although clozapine is considered to have superior efficacy to other second-generation antipsychotic agents, its use is limited due to a risk of agranulocytosis and dose-dependent seizures.<sup>84</sup> Nonetheless, clozapine is still considered the agent of choice in refractory patients.

Clozapine displays a similar metabolic profile to that of olanzapine, being mainly metabolized by CYP1A2 to desmethylclozapine<sup>25</sup> and is, therefore, subject to similar drug-drug interactions by inhibitors of the isozyme, such as caffeine and fluvoxamine<sup>25</sup> as discussed earlier in this paper. The resulting elevated clozapine levels have been associated with side effects, including somnolence, ataxia, and hypotension.<sup>25</sup> As with olanzapine, the effect of smoking on clozapine metabolism has been noted. One study has demonstrated that clozapine and demethylclozapine concentrations were ~40% lower in smokers compared to the non-smoking group because of the increased metabolism of clozapine due to the induction of CYP1A2 by nicotine.<sup>85</sup> There is also evidence that up to 45% of the hepatic metabolism of clozapine may be performed by CYP3A4,<sup>84</sup> and there are reports of an increase in serum clozapine

levels when patients were simultaneously treated with erythromycin, an inhibitor of the CYP3A family.<sup>25</sup>

One concerning factor associated with clozapine use is a more narrow therapeutic range. The upper limit for plasma concentrations has not been defined, however, side effect rates have been reported to double at higher plasma concentrations. For example, the risk of seizures increases at higher plasma levels and toxicity at very high levels has occurred. It is noteworthy that levels at minimum should be 350 ng/mL<sup>84</sup> for optimal efficacy but the risk for DDIs increases at higher levels in patients receiving concomitant medications and this increases the potential for side effects.

### *Antipsychotic Agents in Development*

There are several antipsychotic agents that are currently in Phase III development for the treatment of schizophrenia. These include asenapine, bifeprunox, and paliperidone extended-release (ER) tablets.

Paliperidone ER is an investigational psychotropic drug, delivered using OROS<sup>®</sup> (Osmotic-controlled Release Oral delivery System) technology, which has demonstrated efficacy and tolerability in the treatment of schizophrenia.<sup>86-88</sup> Early data suggest that ~60% of paliperidone ER is excreted unmetabolized in the urine.<sup>89</sup> Of four urinary metabolites identified, none accounted for >6.5% of the total dose. The four identified metabolic routes were dealkylation, dehydrogenation, benzisoxazole scission, and hydroxylation. These data suggest that metabolism, either CYP- or otherwise mediated, does not play a significant role in the excretion of paliperidone ER and, as such, the systemic plasma level of paliperidone ER is unlikely to be affected by metabolic interactions. Thus, this agent may represent an advantageous treatment in patients with compromised liver activity from HIV, hepatitis or substance abuse.

Asenapine and bifeprunox are also in development for the treatment of patients with schizophrenia. Asenapine has a high affinity for serotonin, dopamine, and noradrenalin receptors and is anticipated to be useful to improve cognitive symptoms.<sup>90</sup> Bifeprunox is a partial D<sub>2</sub>-receptor agonist and is expected to be an effective compound against negative and positive symptoms of schizophrenia.<sup>91</sup> Using the search parameters detailed in the methods section no reports of the metabolic pathways or potential for DDIs for either of these agents were identified.

## DISCUSSION

The metabolism of second-generation antipsychotics appears to be reasonably well understood. Knowledge of the CYP isoenzyme responsible for the metabolism of each specific second-generation antipsychotic can

## DRUG-DRUG INTERACTIONS AND ANTIPSYCHOTICS

TABLE 2

## CLINICALLY RELEVANT DRUG-DRUG INTERACTIONS AS REPORTED IN SECOND-GENERATION ANTIPSYCHOTIC PRESCRIBING INFORMATION

SECOND-GENERATION  
ANTIPSYCHOTICPACKAGE INSERT INFORMATION<sup>a</sup>Risperidone<sup>43</sup>

Caution should be taken when risperidone is taken in combination with other centrally acting drugs and alcohol. Risperidone may enhance the hypotensive effects of other agents with this potential. Risperidone may antagonize the effects of levodopa and dopamine agonists. Chronic administration of clozapine with risperidone may decrease the clearance of risperidone. CYP2D6 (e.g. phenytoin, rifampin, and phenobarbital) inducers may increase risperidone clearance and, consequently, decrease maximum concentration. CYP2D6 inhibitors may reduce risperidone clearance and, consequently, increase the maximum concentration. Coadministration of risperidone and carbamazepine reduces the maximum plasma concentration of risperidone. Fluoxetine and paroxetine increase the plasma concentration of risperidone.

Olanzapine<sup>45</sup>

Caution should be taken when olanzapine is taken in combination with other centrally acting drugs and alcohol. Olanzapine may enhance the effects of certain antihypertensive agents. Olanzapine may antagonize the effects of levodopa and dopamine agonists. Agents that induce CYP1A2 or glucuronyl transferase enzymes (e.g. omeprazole and rifampin) may cause an increase in olanzapine clearance and, consequently, decrease the maximum concentration. CYP1A2 inhibitors may reduce olanzapine clearance and, consequently, increase the maximum concentration. Carbamazepine increases the clearance of olanzapine. Fluoxetine and fluvoxamine decrease the clearance of olanzapine.

Quetiapine<sup>44</sup>

Caution should be taken when quetiapine is taken in combination with other centrally acting drugs and alcohol. Quetiapine may enhance the effects of certain antihypertensive agents. Quetiapine may antagonize the effects of levodopa and dopamine agonists. CYP3A inhibitors could potentially reduce quetiapine clearance and, consequently, increase the maximum concentration. Co-administration of quetiapine and phenytoin or thioridazine increases the mean oral clearance of quetiapine and, consequently, reduces the maximum concentration.

*(continued on next page)*

CYP, cytochrome P-450.

<sup>a</sup>Prescribing information is currently unavailable for paliperidone extended-release, asenapine, and bifeprunox.Conley RR, Kelly DL. *Psychopharmacology Bulletin*. Vol. 40. No. 1. 2007.

## DRUG-DRUG INTERACTIONS AND ANTIPSYCHOTICS

TABLE 2 (continued)

## CLINICALLY RELEVANT DRUG-DRUG INTERACTIONS AS REPORTED IN SECOND-GENERATION ANTIPSYCHOTIC PRESCRIBING INFORMATION

SECOND-GENERATION  
ANTIPSYCHOTICPACKAGE INSERT INFORMATION<sup>a</sup>

	Coadministration of quetiapine and divalproex, ketoconazole, or cimetidine decreases the mean oral clearance of quetiapine and, consequently, increases the maximum concentration The mean oral clearance of lorazepam is reduced in the presence of quetiapine
Ziprasidone <sup>42</sup>	CYP3A4 inducers may increase ziprasidone clearance and, consequently, decrease the maximum concentration CYP3A4 inhibitors may decrease ziprasidone clearance and, consequently, increase the maximum concentration Carbamazepine increases ziprasidone clearance Ketoconazole decreases ziprasidone clearance Should not be used in combination with other drugs that prolong the QTc
Aripiprazole <sup>41</sup>	Alcohol should be avoided when receiving aripiprazole CYP3A4 inducers may increase aripiprazole clearance and, consequently, decrease the maximum concentration CYP3A4 and CY2D6 inhibitors may decrease aripiprazole clearance and, consequently, increase the maximum concentration Ketoconazole and quinidine decrease aripiprazole clearance and, consequently, increases the maximum concentration Carbamazepine increases aripiprazole clearance and, consequently, decreases the maximum concentration
Clozapine <sup>92</sup>	Clozapine should not be used with other agents having a well-known potential to suppress bone marrow function due to the risk of agranulocytosis with clozapine use Collapse/respiratory arrest/cardiac arrest risk when administered with benzodiazepines or other psychotropic drugs Clozapine may potentiate the hypotensive effects of hypotensive drugs and the anticholinergic effects of atropine-type drugs Caution should be taken in patients receiving concomitant treatment with drugs that are inhibitors or inducers of CYP1A2, 2D6, and 3A4 Phenytoin, nicotine, and rifampin may decrease clozapine levels resulting in a decreased effectiveness Cimetidine, caffeine, citalopram, ciprofloxacin, and erythromycin may increase clozapine levels potentially resulting in adverse events Fluvoxamine, paroxetine, and sertraline may result in modest elevations of clozapine and metabolite concentrations when clozapine is taken concomitantly with these agents Concomitant use of clozapine with other drugs metabolized by CYP2D6, such as antidepressants, phenothiazines, carbamazepine, and Type 1C antiarrhythmics, or drugs that inhibit the isozyme, such as quinidine, should be used cautiously

help with predicting potentially serious DDIs. Table 2 summarizes the potential drug-drug interactions for all second-generation antipsychotic agents that are detailed in respective prescribing information.

Olanzapine is primarily metabolized by CYP1A2 and because of a wide therapeutic margin, dose adjustments may not be necessary when it is coadministered with inducers/inhibitors of this enzyme. However, if factors leading to reduced or enhanced CYP1A2 activity are compounded (polypharmacy, age, and gender), clinically significant interactions may occur, leading to dangerous or ineffective olanzapine plasma levels.<sup>16,67</sup> Additionally, with the increased prevalence of smoking in patients with schizophrenia, olanzapine doses may need to be increased to accommodate enhanced CYP1A2 activity.<sup>12</sup> Furthermore, should the patient cease smoking, CYP1A2 activity will be reduced, leading to increased olanzapine plasma levels that will need to be regulated.

Risperidone is metabolized predominantly by CYP2D6; however, as the active concentration is the combined mean plasma level of both risperidone and 9-hydroxyrisperidone together (active moiety), CYP2D6 polymorphisms do not appear to affect the drugs' overall clinical efficacy, only the ratio of the compounds.<sup>53</sup> The ratio between risperidone and 9-hydroxyrisperidone is characterized by CYP2D6 activity and, as such, understanding of this enzyme in specific situations can help individualize treatment, so that potentially dangerous side effects can be avoided.<sup>49</sup>

Quetiapine is predominantly metabolized by CYP3A4 and, as such, will be affected by potent inducers or inhibitors of this enzyme, whereas ziprasidone is primarily metabolized by cytosolic aldehyde oxidase, with CYP3A4 providing an alternative, minor pathway. As such, DDIs between ziprasidone and other CYP-metabolized drugs are unlikely to cause clinically relevant outcomes. However, care should be taken when co-prescribing potent CYP3A4 inducers/inhibitors with ziprasidone.

Aripiprazole is a relatively new antipsychotic agent and, as such, there is limited clinical information available regarding any relevant DDIs. However, as the drug is primarily metabolized by CYP2D6 and CYP3A4, potent inhibitors/inducers of these enzymes are likely to influence aripiprazole metabolism.

Clozapine, like olanzapine is primarily metabolized by CYP1A2, but can also be metabolized by CYP3A4 to a certain extent. However, clozapine has much narrower therapeutic margin than olanzapine, making drug-drug interactions more critical with this agent when patients are receiving concomitant medications.

Paliperidone ER is also a new psychotropic under development for the treatment of schizophrenia. Since the limited data available regarding its metabolism suggest that ~60% of paliperidone ER is excreted

unmetabolized, metabolic interactions are unlikely to influence the clinical application of paliperidone ER therapy. Metabolic data for the in-development compounds asenapine and bifeprunox are not yet available.

### *Drug-Drug Interactions in the “Real-World” Setting*

The clinical relevance of a DDI is dependent on the therapeutic margin of a drug. While it is prudent to monitor changes in the plasma level of any second-generation antipsychotic resulting from DDIs, as long as the concentration remains within the range at which the drug is effective and any adverse events are outweighed by this efficacy, then the interaction is unlikely to be clinically relevant. However, should the plasma level of a second-generation antipsychotic increase beyond the therapeutic range due to enzyme inhibition, then measures should be taken to either reduce the dose or switch one of the medications causing the interaction. Increased levels of second-generation antipsychotics can cause especially unpleasant adverse events such as parkinsonism,<sup>40</sup> extrapyramidal symptoms,<sup>62</sup> anticholinergic side effects,<sup>68</sup> and prolonged QT interval.<sup>69,80</sup> Conversely, should the plasma level of a second-generation antipsychotic decrease due to enzyme induction, then the dose may need to be increased or the therapy switched in order to ensure efficacy and prevent relapse.

In certain cases, the prescribing clinician may be unaware of certain factors that could potentially lead to DDIs. While it has been noted that many patients with schizophrenia have comorbid medical conditions or substance abuse, clinicians may not be aware of this in specific cases and, therefore, be unable to account for it in prescribing a suitable therapy. Additionally, the patient themselves may be unaware of certain conditions, such as hepatitis C, that can intrinsically affect drug metabolism and clearance. Furthermore, for patients initially started on second-generation antipsychotics (for example, first-episode patients), DDIs may be particularly relevant as they may increase the time required to reach steady state plasma levels at which the drug is most effective.<sup>16</sup>

Clinical trials are an informative method of initially assessing the relevance of certain DDIs, but “real-world” settings vary considerably compared with tightly controlled clinical trials. In addition to those situations previously mentioned, patients may be receiving more than two concomitant medications, may be abusing substances while receiving medication or receiving over-the-counter or herbal medications that interact with antipsychotic agents. Any of these aspects is unlikely to be taken into account in a clinical trial, which will generally assess only the impact of two treatments in a selected population. Additionally, some patients (gender, age, hepatic/renal impairment, polymorphisms) may

be intrinsically more susceptible to the effects of DDIs due to a naturally lower CYP activity or clearance rate.

Considering the multitude of variables that can contribute to the attained plasma levels of second-generation antipsychotics, it is necessary to consider all aspects of a patient and their condition(s) prior to initiating and during therapy. This not only applies to the addition of concomitant medications and comorbid illness but also the occurrence of comorbid substance abuse. This will optimize the potential for identifying DDIs, which may affect patient prognosis. When DDIs reach clinical significance, patients may experience adverse events, either mild or potentially serious, or previously effective treatments may become ineffective, heightening the potential for relapse, deterioration of symptoms, and loss of function. In cases where DDIs may potentially be an issue, clinicians should carefully monitor the second generation antipsychotic plasma level to ensure that it remains within the therapeutic margin. However, this is not always practically or financially feasible, nor is the potential for DDIs always known, as in the case of unknown substance abuse and, therefore, cannot be monitored for. As such, drugs that minimize the potential for interactions are preferable to ones with a higher risk as they will be accessible to a wider spectrum of patients and offer greater assurance of sustained effective treatment with a lower risk of unanticipated DDI-related adverse events.

It should be highlighted that, although this review has focused on drug interactions with second-generation antipsychotics in schizophrenia, this class of agents is increasingly being used in other therapeutic areas. Some second-generation antipsychotics are now also indicated for bipolar disorder, however most are likely effectively used alone or in conjunction with a mood stabilizer.<sup>93</sup> As in schizophrenia, many bipolar patients also have comorbid disorders, including substance abuse.<sup>94,95</sup> Atypical agents are also used for the treatment of unipolar depression,<sup>96</sup> childhood disorders,<sup>97</sup> dementia,<sup>98</sup> and anxiety symptoms,<sup>99</sup> and often in combination with other therapies for augmentation or for comorbidities. Thus, there are many conditions for which second-generation antipsychotics are implicated and with an increased risk of DDIs because of the use of concurrent medications.

It should also be remembered that patients with psychiatric disorders often have comorbid medical illness. For instance, bipolar patients have shown a greater mortality from cardiovascular and respiratory diseases, and a higher prevalence of diabetes than that of the general population.<sup>100</sup> It is estimated that nearly 50% of patients with schizophrenia have a comorbid general medical disorder,<sup>101</sup> including anxiety disorders, depression, cardiovascular disease, diabetes, and infection with human HIV and hepatitis C. Thus, regardless of treatment with

antipsychotic agents, these patient populations are at an increased risk of DDIs requiring polypharmacy for these medical disorders.<sup>2-4</sup> While the significance of DDI interactions has not been of major clinical concern previously, vigilance should now be increased with respect to the general risk of DDIs in the treatment of these different populations.

## CONCLUSION

With increasing use of polypharmacy and when considering treatment in special populations, DDIs are an important consideration. Some of the currently available second generation antipsychotics have extensive potential for DDIs, which can cause serious adverse events or reduce the efficacy of treatment. The lower the potential a drug has for DDIs, the safer that treatment becomes in the “real world” setting, where multiple variables, which are often unaccounted for in clinical trials, may influence the systemic concentration of a drug. ❀

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