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A review of pharmacokinetic and pharmacodynamic interactions with antipsychotics

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Abstract

Introduction: Antipsychotics are widely used and often in combination with other drugs, thereby frequently subjected to drug-drug interactions. This review will provide a summary of potential pharmacokinetic (PK) and pharmacodynamic (PD) drug interactions associated with antipsychotic drugs.

Methods: A literature search was conducted for clinically significant drug interactions with antipsychotics.

Results: Most common PK drug interactions take place via the cytochrome P450 (CYP) system. PK profiles of first generation antipsychotics are inadequately studied; nevertheless most common drug interactions involve changes to their metabolic processes. Interactions with second generation antipsychotics are somewhat well-established, documented, and give some guidance for therapeutic treatment interventions. PD interactions occurring at the receptor level result in additive, synergistic, or antagonistic effects.

Discussion: This review summarizes a collection of relevant literature of significant PK and PD interactions occurring with antipsychotics. The involvement of multiple CYP enzymes makes it more difficult to predict the extent of the interaction and clinicians should take into consideration the timeline when evaluating potential interactions.

Keywords: pharmacokinetic, pharmacodynamic, antipsychotic, drug interactions

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Introduction

Antipsychotics are widely used in patients who suffer from schizophrenia, bipolar disorder, and other psychiatric illnesses, often long term as these conditions are chronic, treatment resistant, or lifelong. As a disease worsens, antipsychotics are often used in combination with other psychotropic medications.[1] Thus, the likelihood of drug interactions increases and may result in complex and unpredictable outcomes. Clinicians should have a good understanding of these drug interactions to maximize the therapeutic benefit and minimize side effects. The aim of this article is to review significant pharmacokinetic (PK) and pharmacodynamic (PD) interactions with antipsychotics.

Pharmacokinetic Interactions of Antipsychotics

The potential combination or removal of other drugs may affect the way an antipsychotic or its metabolites are handled in the body, resulting in changes to the antipsychotic or its active by-products by altering its absorption, distribution, metabolism, or excretion.[1] From a clinical perspective, these PK interactions help explain or predict bioavailability, onset, duration of activity, and interactions between drugs that alter their metabolism and excretion.[2] It is beyond the scope of this article to review every PK interaction reported. Thus, the focus will be limited to drug-drug interactions with oral antipsychotics that may have a substantial influence in the clinical setting.

TABLE 1: First-generation antipsychotic metabolism and the potential for drug interactions[5-11]

Antipsychotic	Metabolism	Pharmacokinetic Interaction With FGA
Chlorpromazine Oral: tablet	Extensive *CYP2D6* (major)– and *CYP1A2* (minor)–mediated metabolism to several active and inactive metabolites.	*CYP1A2* inhibitors (eg, ciprofloxacin, fluvoxamine) and *CYP2D6* inhibitors (eg, paroxetine, fluoxetine) can reduce chlorpromazine clearance. Patients may experience chlorpromazine dose-dependent adverse drug reactions.
Fluphenazine Oral: elixir, solution, tablet	Extensive *CYP2D6* metabolism.	Fluphenazine, a substrate and an inhibitor of *CYP2D6*, may inhibit its own metabolism. The plasma concentrations and the effects of fluphenazine may therefore be increased and prolonged by drugs that are either substrates or inhibitors of *CYP2D6*.
Haloperidol Oral: tablet, solution	Primarily hepatic clearance is by glucuronidation, followed by *CYP3A4*-mediated reduction. Some metabolites are potentially active.	Haloperidol is a substrate and an inhibitor of *CYP3A4* and *CYP2D6*. Reduced haloperidol is also a substrate of *CYP3A4* and an inhibitor of *CYP2D6*. Interactions with most drugs lead to only small changes in plasma haloperidol concentrations, suggesting that the interactions have little clinical significance. However, it is expected that co-administration of carbamazepine, phenytoin, phenobarbital, rifampin, or quinidine may alter PK of haloperidol resulting in clinical changes.
Perphenazine Oral: tablet	*CYP2D6*-mediated hydroxylation to active and inactive metabolites.	Drugs that inhibit *CYP2D6* (eg, TCAs, fluoxetine, sertraline, paroxetine) may acutely increase plasma concentrations of perphenazine. Dose reductions and close monitoring may be necessary.
Pimozide Oral: tablet	Extensive dealkylation primarily by *CYP3A4* and to a lesser extent by *CYP 1A2*, *2D6* to 2 other metabolites.	Manufacturer contraindicates the concomitant administration with *CYP3A4* inhibitors: macrolide antibiotics (eg, clarithromycin, erythromycin, azithromycin), azole antifungals (eg, itraconazole, ketoconazole), protease inhibitors (eg, ritonavir, saquinavir, indinavir, nelfinavir), and nefazodone. Concomitant use with citalopram, escitalopram, paroxetine, sertraline, and other strong *CYP2D6* inhibitors is also contraindicated. *CYP3A4* and *2D6* enzyme inhibition may impede pimozide metabolism, leading to QT prolongation. Grapefruit juice may inhibit the metabolism of pimozide via *CYP3A4* and cause QT prolongation.
Thioridazine Oral: tablet	Hydroxylation dependent on the level of *CYP2D6* isozyme activity. Active metabolite mesoridazine (no longer available in the United States).	The effect of fluvoxamine (25 mg twice daily for 1 week) on thioridazine steady-state concentration was evaluated in 10 male inpatients with schizophrenia. Concentrations of thioridazine and its 2 active metabolites, mesoridazine and sulforidazine, increased 3-fold. Co-administration should be avoided. Concurrent administration of propranolol (100-800 mg daily) has been reported to produce increases in plasma levels of thioridazine (approximately 50%-400%) and its metabolites (approximately 80%-300%). Co-administration should be avoided. Concurrent administration of pindolol and thioridazine have resulted in moderate, dose-related increases in the serum levels of thioridazine and 2 of its metabolites, as well as higher than expected serum pindolol levels. Co-administration should be avoided.

TABLE 1: First-generation antipsychotic metabolism and the potential for drug interactions[5-11] (continued)

Antipsychotic	Metabolism	Pharmacokinetic Interaction With FGA
Trifluoperazine Oral: tablet	Extensive hepatic metabolism by *CYP1A2*.	Trifluoperazine levels may be increased by *CYP1A2* strong inhibitors. Smoking (*CYP1A2* inducer) may decrease levels of trifluoperazine.

CYP = cytochrome P450; FGA = first-generation antipsychotic; IV = intravenous; PK = pharmacokinetics; QT = QT interval on the electrocardiogram; TCA = tricyclic antidepressant.

Pharmacokinetic Interactions With First-Generation Antipsychotics

Pharmacokinetic profiles of first-generation antipsychotics (FGAs) are not well described in the literature. Many of their potential metabolites remain undiscovered or their physiological activity inadequately studied. Nonetheless, general statements can be made when comparing the conventional antipsychotics as a group. All FGAs are well absorbed, with peak concentrations obtained 1 to 4 hours after oral administration. They attain clinical efficacy of improving illness symptoms of schizophrenia as rapidly as 15 minutes.[3] Most FGAs are highly protein bound (85%-90%), and although changes in protein binding can have an influence on individual PK parameters, those changes caused by drug-drug interactions will usually not influence the clinical exposure of a patient, and no routine adjustments in dosing regimen are necessary.[3,4]

Oral formulations undergo extensive liver metabolic transformations including glucuronidation, oxidation, reduction, and methylation. Most FGAs are metabolized by the cytochrome P450 (CYP) system, and most common PK drug-drug interactions involve effects on metabolism via the CYP system as listed in Table 1. Because of the many active metabolites and biological variability, there exist differences of the clinical response among FGAs and significant difficulty in predicting those interactions most likely to cause harm if not detected. The elimination half-lives of FGAs vary from 18 to 40 hours, and steady-state levels of oral drugs are reached in approximately 3 to 8 days. Numerous factors such as genetically determined metabolic rates, age, and co-administration of other hepatically metabolized drugs affect the half-life to such a degree that plasma levels may vary among individuals by 10- to 20-fold. The major routes of excretion are through urine and feces by way of bile, with minor pathways of excretion via sweat, saliva, tears, and breast milk.[2,3]

Pharmacokinetic Interactions With Second-Generation Antipsychotics

Most PK interactions with second-generation antipsychotics (SGAs) arise at the stage of drug metabolism and usually involve changes to drug-metabolizing enzymes when other psychotropic agents or medications in the treatment of concomitant medical illness are added.[12] A summary of PK drug interactions related to metabolism is presented in Table 2. In addition to drug-drug interactions related to the metabolism of SGA discussed in Table 2, it is important to take into consideration PK interactions consisting of changes in the absorption, distribution, or elimination of the antipsychotic that may result after the addition of another chemical agent.

In theory, studies of PK interactions conducted during the drug-development stage in a controlled environment in animal models, and thereafter in healthy volunteers using population PK modeling, are unambiguous; however, in reality, it is prudent to keep in mind that the interactions may be multifactorial. For example, formulation and drug-molecule differences, food-dependent absorption, lipophilicity resulting in high volume of distributions, and competition for protein binding leading to subsequent displacement interactions interfere with PK. In addition, the state of the hepatic portal system and a patient's genetic variability, which in turn may affect the drug's hepatic and renal clearance, play important roles, resulting in clinically significant drug interactions.[1]

Pharmacodynamic Interactions

Pharmacodynamic drug-drug interactions occur when drugs being added to the antipsychotic compete at the receptor level, interfering with the therapeutic efficacy or perhaps contributing to an adverse effect. For example, when levodopa, a drug used for Parkinsonism with agonistic action at dopamine D_2 receptor is added, the antipsychotic through its dopamine antagonism can oppose the effects of levodopa. The result may culminate in worsening motor function, a relapse of psychosis or a combination thereof.[2] Table 3 lists several examples of PD interactions resulting in antagonistic, additive, or synergistic effects most often leading to adverse effects but, at times, rarely and deliberately augmented to obtain a favorable effect.

Discussion

Nondrug patient factors (such as age, sex, concomitant diseases, genetic polymorphisms, caffeine and drug intake

TABLE 2: Second-generation antipsychotic metabolism and the potential for drug interactions[1,3,5,12-14]

Antipsychotic	Metabolism	Pharmacokinetic Interaction With Second-Generation Antipsychotic
Aripiprazole Oral: IR tablet, disintegrating tablet, solution	*CYP2D6*, *3A4* catalyze dehydrogenation to active dehydroaripiprazole. Does not undergo glucuronidation.	*CYP3A4* inducers lower aripiprazole levels by about 60%, while *CYP3A4* inhibitors increase levels by about 45%.
		Ketoconazole and quinidine decrease aripiprazole metabolism, so aripiprazole dose should be decreased by half during co-administration. Although itraconazole is a potent *CYP3A4* inhibitor, there was no clinically significant difference in one small study (n = 24).
		Carbamazepine reduces aripiprazole and metabolite levels by 70%, so aripiprazole doses may need to be doubled when added to carbamazepine and halved when carbamazepine is discontinued.
Asenapine Oral: sublingual tablet (wide variability in PK observed in clinical studies)	Direct glucuronidation by *UGT1A4* and oxidative metabolism by *CYP1A2*.	Fluvoxamine increases plasma concentration of asenapine by 29%. Should be co-administered with caution, while observing for adverse effects such as drowsiness, dizziness, and increased appetite.
		Asenapine (*CYP2D6* inhibitor) increases paroxetine levels 2-fold.
Clozapine Oral: tablet, orally disintegrating tablet	Extensive first-pass in the liver and gut; predominantly metabolized by *CYP1A2*, *2D6*. Also, contributed by *CYP3A4* to active norclozapine.	Caffeine and clozapine are both metabolized by *CYP1A2*, and caffeine at 400 to 1000 mg may competitively inhibit clozapine metabolism with significant increase (26%) in clozapine levels.
		Fluoxetine, possibly by *CYP2D6* inhibition increases clozapine and norclozapine levels. It is suggested that measuring clozapine levels may be useful.
		Fluvoxamine inhibition of *CYP1A2* leads to a significant increase in clozapine levels.
		Paroxetine significantly increases plasma clozapine and norclozapine levels and may expose to clozapine toxicity.
		Sertraline may produce significant increases in plasma clozapine levels—the risk of clozapine toxicity should be considered.
		Phenytoin may reduce serum concentrations of clozapine via *CYP1A2* induction.
		Cimetidine may increase clozapine levels by 50%. Ranitidine is a safer alternative.
		Digoxin and warfarin are highly protein-bound drugs. Dose should be monitored and adjusted as necessary.
Iloperidone Oral: tablet	Extensive hepatic metabolism via carbonyl reduction, hydroxylation (*CYP2D6*), and O-demethylation (*CYP3A4*); forms active metabolites.	Iloperidone dose should be decreased by 50% with strong *CYP2D6* inhibitors (eg, paroxetine, fluoxetine, quinidine), and when *CYP2D6* inhibitor is discontinued return to previous dose.
		Iloperidone dose should be decreased by 50% with strong *CYP3A4* inhibitors (eg, ketoconazole, clarithromycin) and when *CYP3A4* inhibitor is discontinued return to previous dose.
		Iloperidone dose should be decreased by 50% in poor metabolizers of *CYP2D6*.

TABLE 2: Second-generation antipsychotic metabolism and the potential for drug interactions[1,3,5,12-14] (continued)

Antipsychotic	Metabolism	Pharmacokinetic Interaction With Second-Generation Antipsychotic
Lurasidone Oral: tablet	Primarily via *CYP3A4* to 2 active metabolites (main: exo-hydroxy metabolite).	Contraindicated with strong *CYP3A4* inhibitors (eg, ketoconazole, clarithromycin, ritonavir, voriconazole) as they elevate lurasidone levels, and inducers (eg, rifampin, carbamazepine, phenytoin, St John's wart) as they decrease lurasidone levels. Lurasidone dose should be reduced to half the original dose if prescribed concomitantly with a moderate *CYP3A4* inhibitor (eg, diltiazem, atazanavir, erythromycin, fluconazole, verapamil). Manufacturer recommends avoiding grapefruit and grapefruit juice.
Olanzapine Oral: tablet, disintegrating tablet	Highly metabolized via direct glucuronidation by *UGT1A4* and *CYP1A2*, 2D6-mediated oxidation to inactive metabolites; 40% removed via first-pass metabolism.	Fluvoxamine (100 mg/d) inhibits olanzapine metabolism raising olanzapine peak levels by 49%, AUC by 70%, half-life by 40%, and steady-state levels by 12%-112%. Smoking increases olanzapine clearance by 40%. Olanzapine clearance decreased by 30% in females. PK do not differ significantly between extensive and poor *CYP2D6* metabolizers.
Paliperidone Oral: osmotic controlled release tablet	Hepatic metabolism via *CYP2D6* and *CYP3A4* (limited role in elimination); minor metabolism (<10%) via dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission.	Carbamazepine, a strong inducer of both *CYP3A4* and P-gp, decreased the AUC by 37%. In vitro studies have shown that paliperidone is a P-gp substrate. Paroxetine, a potent *CYP2D6* inhibitor, increased paliperidone on average 16%, but the clinical relevance is unknown. Divalproex sodium ER formulation increased C_{max} and AUC by 50%; manufacturer recommends a dose reduction of paliperidone after clinical assessment.
Quetiapine Oral: tablet, extended release tablet	Primarily hepatic metabolism via *CYP3A4* to active N-desalkyl quetiapine and 2 inactive metabolites. Metabolism reduced by ~30% with advancing age.	Carbamazepine, phenytoin, rifampin, and St John's wort will increase quetiapine clearance. Up to a 5-fold increase of the original quetiapine dose is advised by the manufacturer if used in combination long term (>7-14 days); also advised is to reduce quetiapine dose accordingly upon discontinuation of strong *CYP3A4* inducers. *CYP3A4* inhibitors such as ritonavir, erythromycin, ketoconazole, and nefazodone may increase quetiapine levels. The manufacturer advises a reduction in the quetiapine dose to one sixth if used concomitantly.
Risperidone Oral: tablet, disintegrating tablet, solution	Extensive metabolism via *CYP3A4* and *CYP2D6* to 9-hydroxyrisperidone (active); N-dealkylation as a minor pathway.	Risperidone dose should be increased and titrated up to double the patient's usual dose when adding to carbamazepine and other inducers. The initial dose of risperidone should be reduced (max = 8 mg per day) with *CYP2D6* inhibitors such as fluoxetine and paroxetine.
Ziprasidone Oral: capsule	Extensive hepatic metabolism via aldehyde oxidase to active S-methyl-dihydroziprasidone; less than one third of total metabolism via *CYP3A4* and *CYP1A2* (minor).	CYP-enzyme inducers and inhibitors have little potential for clinically important PK interactions with ziprasidone. Literature reports no clinically significant inhibitors of aldehyde oxidase, suggesting less drug-drug interactions.

AUC = area under the curve; C_{max} = peak serum drug concentration; CYP = cytochrome P450; ER = extended release; IR = immediate release; P-gp = P-glycoprotein transporter; PK = pharmacokinetics; SGA = second-generation antipsychotic; UGT = uridine 5-diphosphate-glucuronyltransferases.

TABLE 3: Pharmacodynamic interactions with antipsychotics[1,13,15-18]

Possible PD Interaction	High-Risk Antipsychotic(s)	Combined Drug or Class[a]
Anticholinergic and related side effects: blurred vision, constipation, dry mouth, urinary retention, confusion	Chlorpromazine Clozapine Pimozide Trifluoperazine	Anticholinergic drugs (eg, hyoscine, atropine) Tricyclic antidepressants
Blood dyscrasias: neutropenia/ agranulocytosis	Clozapine	Antibiotics reported to cause leukopenia/ neutropenia: clindamycin, sulphonamides, ciprofloxacin, erythromycin, metronidazole Carbamazepine Carbimazole Chloramphenicol Cytotoxics Lithium (increases neutrophil count but does not protect against agranulocytosis) Long-acting depot antipsychotics Penicillamine Phenylbutazone
Metabolic changes and weight gain	Chlorpromazine Clozapine Olanzapine Perphenazine Phenothiazines	Antipsychotics Lithium Metformin or topiramate added to an antipsychotic may result in weight loss Mirtazapine Tricyclic antidepressants Valproic acid
Sedation	Chlorpromazine Clozapine Olanzapine Quetiapine	Alcohol Antihistamines Benzodiazepines Mirtazapine Opioids Sedative hypnotics Trazodone Tricyclic antidepressants: higher incidence with amitriptyline
Sedation and cardiorespiratory depression	Short-acting intramuscular olanzapine	Intramuscular lorazepam
Seizures	Chlorpromazine Clozapine Most phenothiazines	Bupropion Sudden alcohol and benzodiazepine withdrawal Trazodone Tricyclic antidepressants
Orthostatic hypotension and related falls	Asenapine Clozapine Iloperidone Olanzapine Risperidone	Alcohol Antihypertensives Tricyclic antidepressants
QT prolongation	Haloperidol Pimozide Thioridazine Ziprasidone Recent dose increase or high doses of antipsychotic (including overdose) Intravenous antipsychotic(s)	Amantadine Antiarrhythmics: quinidine, disopyramide, procainamide, sotalol, amiodarone, dofetilide Antibiotics: erythromycin, clarithromycin, trimethoprim-sulfamethoxazole, pentamidine, levofloxacin, moxifloxacin Antifungals: fluconazole, ketoconazole Antimalarials: chloroquine, mefloquine, quinine Citalopram Cyclosporine Diphenhydramine Escitalopram Hydroxyzine Methadone Tamoxifen Tricyclic antidepressants

PD = pharmacodynamics; QT = QT interval on the electrocardiogram.

[a]More updated and current lists can be accessed via www.torsades.org or www.qtdrugs.org.

habits, and use of herbal medications) as well as drug-related factors (such as formulation, dose, and route of administration) contributing to antipsychotic drug interactions are beyond the scope of this review; nevertheless, these factors should be taken into consideration when assessing PK- and PD-drug interactions comprehensively. Some studies find proposed PK principles lacking a significant impact on the plasma levels of the antipsychotic, suggesting that theoretical drug interactions may not always occur as anticipated. In addition, researchers suggest that multiple CYP enzyme involvement in an antipsychotic metabolism will make it more difficult to predict the extent of the drug interaction because at low doses one type of CYP metabolism may predominate, while at higher doses another CYP enzyme interaction may possibly be prominent.[1]

During this review, it is also noted that newer antipsychotics introduced in recent years have more-specific, standardized PK information and recommendations in their product labeling compared with those agents marketed decades ago. However, there is little information on monitoring of plasma concentration levels to gauge the response of a drug interaction. The blood-brain distribution of the antipsychotic drugs or their potentially active metabolites may or may not contribute to varying plasma concentrations among individuals, suggesting that plasma levels may not be a useful measure in evaluating PK and PD interactions. Moreover, the time course of the drug interactions are rarely mentioned in literature, but clinicians should take into consideration the timeline (eg, half-life, time for steady state) when evaluating potential PK and PD interactions especially in patients on multiple and long-term drug treatment. Lastly, avoidance of unnecessary polypharmacy, knowledge of drug-interaction profiles, experience, and good clinical judgement are essential in preventing significant and potentially adverse PK- and PD-drug interactions in patients receiving antipsychotics.

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