Pharmacokinetics, Metabolism, and Drug-Drug Interactions of Atypical Antipsychotics in Special Populations

Zafar A. Sharif, M.D.

An awareness of the cytochrome P450 (CYP) system of primarily hepatic enzymes is crucial to managing the potential for drug-drug interactions involving the atypical antipsychotics. A coadministered drug may inhibit an enzyme that metabolizes the prescribed antipsychotic, or, conversely, a coadministered drug may induce the action of that enzyme. The result of inhibition is a higher plasma level of antipsychotic, which can cause adverse effects, while the result of induction is a lower plasma level of antipsychotic, which can compromise therapeutic efficacy. In addition, younger people tend to metabolize drugs faster than older people, men faster than women, and, for some antipsychotics (clozapine and olanzapine), those who smoke cigarettes faster than those who do not. Comorbid medical conditions and gene polymorphism may also affect drug metabolism. At times, altered CYP enzyme activity may require increasing or decreasing the dose of antipsychotic. Dose reductions in vulnerable populations (such as the elderly) are especially necessary when 2 or more factors affecting plasma clearance are present.

(Primary Care Companion J Clin Psychiatry 2003;5[suppl 6]:22–25)

Pharmacokinetics refers to the processes by which a drug is absorbed into systemic circulation, distributed through tissue, metabolized, and excreted and describes the relationship of these processes to the drug's therapeutic and adverse effects (Table 1). The distinct pharmacokinetics of a drug defines its potential for drug-drug interactions, which can affect dosing, particularly in special populations. The cytochrome P450 (CYP) system of enzymes is of primary importance to the pharmacokinetics of psychotropic drugs. These enzymes are concentrated in the liver but are also present in the tissues of other organs such as the kidneys and lungs.

The activity of CYP enzymes can be affected by the substrates they work to modify. Substrate A may inhibit or induce the enzymes that metabolize substrate B, rendering substrate B more or less effective. That is, one drug may competitively inhibit the enzymes that metabolize a second drug by engaging those same CYP subtypes, thereby raising the plasma level of the second drug. Conversely, a drug may induce the action of an enzyme, making it more efficient at metabolizing a second drug and thereby reducing the second drug's bioavailability (i.e., the fraction of the dose that reaches systemic circulation). In order to avoid dose-related side effects resulting from inhibition and breakthrough symptoms resulting from induction, a clinician must be aware of potential interactions via the CYP enzyme system. Some, but not all, of these interactions may require adjusted dosing. CYP enzyme subtypes of particular importance to the metabolism of atypical antipsychotics are 1A2, 2D6, and 3A4.

DRUG-DRUG INTERACTIONS VIA THE CYTOCHROME P450 SYSTEM AND THEIR EFFECT ON DOSING

Determining the appropriate dosage of an atypical antipsychotic requires the integration of several factors, including potential drug-drug interactions via the cytochrome P450 enzyme system.[1] Additionally, a clinician must take into account certain factors inherent to the patient. For example, younger people tend to metabolize drugs faster than older people and men faster than women. Those who smoke cigarettes metabolize clozapine and olanzapine faster than those who do not. Comorbid medical conditions that decrease hepatic function, such as cirrhosis or congestive heart failure, are likely to decrease the rate of drug metabolism. Further, cytochrome P450 enzymes are polymorphic: there exist ethnic differences in hepatic enzymes that influence the pharmacokinetics of drugs. For example, approximately 5% to 10% of Caucasians are poor metabolizers via the CYP enzyme 2D6, while approximately 20% of Japanese and Chinese are

From the Creedmoor Psychiatric Center, Queens Village, N.Y.

This article was derived from the planning roundtable "Using Atypical Antipsychotics in Primary Care," which was held June 2–4, 2002, in Washington, D.C., and supported by an unrestricted educational grant from Janssen Pharmaceutica, L.P.

Corresponding author and reprints: Zafar A Sharif, M.D., Creedmoor Psychiatric Center, 80-45 Winchester Blvd., Queens Village, NY 11427 (e-mail: zas1@columbia.edu).

Table 1. Definitions of Pharmacokinetic Terminology[a]

Pharmacokinetics	The quantitative study and characterization of the time course of drug absorption, distribution, metabolism, and excretion; it is concerned with the relationships of these processes to intensity and time course of therapeutic and adverse effects
Drug absorption	The rate at which the medication enters systemic circulation; for intravenous administration, there is no discernible absorption phase; for depot neuroleptics, the slow absorption rate controls the time for the drug to reach steady state
Bioavailability	The fraction of the dose that reaches systemic circulation
Distribution	The rate at which a drug moves from the central compartment into peripheral compartments, eg, tissue
Elimination	The rate of metabolism for a medication, frequently expressed as the "half-life"; for antipsychotics, this is principally hepatic, although extrahepatic metabolism in the lung and kidneys does occur
Steady state	The equilibrium state reached when the amount of drug administered every day is exactly counterbalanced by the amount of drug eliminated

[a]Adapted with permission from Ereshefsky.[1]

poor metabolizers via the CYP enzyme 2C19.[2] Poor metabolism will increase the bioavailability of some drugs, increasing their likelihood of side effects.

Dosing is also affected by variations in steady state plasma half-life. The term *half-life* refers to the rate of drug elimination from the plasma, but not necessarily from the brain, where the drug may linger longer. *Steady state* is the condition of equilibrium reached when the amount of drug administered each day equals the amount of drug eliminated. Any condition that increases a drug's half-life (e.g., drug interactions, age of patient) will potentially increase time to steady state by slowing down dose titration.[1] Like other drugs, the atyptical antipsychotics vary in these and other pharmacokinetic properties.

Clozapine

Clozapine, the first atypical antipsychotic on the market, is now frequently reserved for the treatment of patients with refractory schizophrenia and suicidality. Clozapine has a half-life of about 12 hours, meaning that dosing occurs twice a day. As with most drugs, it takes about 5 half-life durations for the drug to reach steady state in plasma. Thus, clozapine reaches steady state in 1 to 2 days. Clozapine has been shown to have wide interpatient variability and several drug-drug interactions.

Clozapine is metabolized by the CYP enzymes 1A2, 2D6, and 3A4 (Table 2). When inhibitors of CYP1A2 such as the selective serotonin reuptake inhibitor (SSRI) fluvoxamine are coadministered with clozapine, the plasma level of clozapine can rise. As a result, it may be necessary

Table 2. Inhibitors and Inducers of Antipsychotic-Metabolizing Cytochrome P450 Enzymes

Cytochrome P450 (CYP) Enzyme Subtype	Inhibitor	Inducer
CYP1A2 Involved in metabolism of clozapine, olanzapine	Fluvoxamine Grapefruit juice in large quantities	Cigarette smoking
CYP2D6 Involved in metabolism of clozapine, olanzapine, risperidone	SSRIs (especially fluoxetine, paroxetine, high-dose sertraline)	
CYP3A4 Involved in metabolism of clozapine, quetiapine, ziprasidone	Erythromycin and other macrolide antibiotics Ketoconazole and other antifungal drugs Protease inhibitors	Barbiturates Carbamazepine Phenytoin Rifampin Glucocorticoids

Abbreviation: SSRI = selective serotonin reuptake inhibitor.

to reduce the dose of antipsychotic in order to avoid seizure, sedation, or other side effects. Grapefruit juice, consumed in large amounts, is also an inhibitor of CYP1A2. Drugs that inhibit enzymes CYP2D6 (fluoxetine, paroxetine, high-dose sertraline) or CYP3A4 (protease inhibitors, erythromycin and other macrolide antibiotics, and some antifungal drugs like ketoconazole) can also raise plasma levels of clozapine by hindering its metabolism. When these drugs are used alongside clozapine, a reduction in the dose of clozapine may be required.

Still other substrates induce the action of enzymes responsible for metabolizing clozapine, resulting in lower plasma levels of clozapine. A major inducer of CYP1A2 is cigarette smoking; thus, a heavy smoker may need a higher dose of clozapine to maintain the same plasma drug level as a nonsmoker. This is a common interaction, as approximately 78% of patients with schizophrenia smoke.[3] If a patient starts or stops smoking during treatment, his or her plasma level of clozapine could change. Inducers of CYP3A4 include barbiturates, the anticonvulsants phenytoin and carbamazepine, the antibiotic rifampin, and the anti-inflammatory glucocorticoids. (Of note is the fact that carbamazepine is contraindicated with clozapine due to a risk of bone marrow suppression unrelated to the cytochrome P450 system.) Use of any of these drugs concurrent with clozapine treatment is cause for a clinician to consider an increase in the dose of clozapine.

Olanzapine

Olanzapine is metabolized through multiple metabolic pathways: CYP1A2, CYP2D6, and glucuronidation. Fluvoxamine, fluoxetine, paroxetine, high-dose sertraline, large amounts of grapefruit juice, and cigarette smoking may theoretically alter the level of olanzapine in blood plasma. However, such changes in the level of olanzapine

via inhibition or induction of the CYP system are unlikely to be of practical clinical significance. On the whole, olanzapine has relatively low potential for drug-drug interactions.

A dose adjustment is usually necessary only when several factors affecting the metabolism of olanzapine coexist. For example, a patient who is young, male, and a smoker may require an olanzapine dose of 20 mg/day or more to achieve therapeutic effect, while a patient who is elderly, female, and a nonsmoker may need only 5 mg/day of olanzapine. Olanzapine has a 30-hour half-life, which means it can be administered once a day but takes almost a week to reach steady state.

Risperidone

In metabolizing risperidone, CYP2D6 converts a proportion of the parent compound (risperidone) to its equipotent active metabolite (9-hydroxy risperidone). In the large majority of the population, the plasma ratio of 9-hydroxy risperidone is several times greater than that of the parent compound risperidone. However, in poor metabolizers this proportion is reversed. Because the 2 moieties have equivalent efficacy, therapeutic effect is essentially the same for normal and slow metabolizers.

The SSRIs (especially paroxetine, fluoxetine, and high-dose sertraline) are potent inhibitors of CYP2D6. They essentially change a normal metabolizer to a slow metabolizer. Again, this reversal has little clinical significance since the parent compound and its active metabolite are equipotent. An adjustment of risperidone dose due to drug-drug interactions via CYP enzymes is usually unnecessary. However, a reduced dose may be appropriate for the occasional patient with troublesome side effects. The mean half-life of risperidone plus its active metabolite is about 20 hours, so risperidone can be dosed once daily and takes almost a week to reach steady state.

Quetiapine and Ziprasidone

Both quetiapine and ziprasidone are metabolized almost exclusively via the CYP enzyme 3A4. Macrolide antibiotics, protease inhibitors, and some antifungal agents could raise the plasma level of either antipsychotic and produce a risk of sedation or orthostatic hypotension unless the dose of antipsychotic is reduced. (Generally, orthostatic hypotension will not occur once steady state is reached, except among some elderly patients.) Quetiapine and ziprasidone may demonstrate reduced effectiveness if administered with CYP3A4 enzyme inducers, such as barbiturates, glucocorticoids, rifampin, phenytoin, and carbamazepine. In these situations, a clinician should consider increasing the dose of antipsychotic.

Ziprasidone seems to be the only atypical antipsychotic whose absorption is greatly improved by the presence of food. If a patient stops taking ziprasidone with food, steady state may be compromised. Ziprasidone reaches steady state in 1 to 2 days, with a half-life of about 7 hours, requiring twice daily dosing. Quetiapine, too, reaches steady state in 1 to 2 days and is dosed twice daily, but has a mean half-life of about 6 hours.

DOSING IN SPECIAL POPULATIONS

Treatment with antipsychotics has frequently been associated with weight gain—possibly resulting in part from sedation and possibly contributing to health problems like diabetes. Among the atypical antipsychotics, clozapine[4] and olanzapine[5] cause the most weight gain, and there is an additive effect when these drugs are coadministered with mood stabilizers or antihistamines. Atypical antipsychotics also have the potential to cause orthostatic hypotension. This risk is exacerbated by a fast rate of titration to steady state. It is also higher among patients who have cardiovascular disease, who are concomitantly taking antihypertensives, or who are elderly.

Dose reductions in special populations are especially necessary when 2 or more factors affecting plasma clearance are present. Elderly patients who have dementia are frequently treated with atypical antipsychotics to control symptoms of agitation, aggression, and/or psychosis. For this population, the appropriate dose of antipsychotic will be lower than for nondemented elderly patients. For example, Katz et al.[6] reported that 1 mg/day of risperidone is effective in treating the psychotic symptoms and behavioral disturbances associated with dementia without significant risk of motor side effects. In such vulnerable populations, risperidone dosing can be initiated at twice a day, then switched to a single bedtime dose. When olanzapine is used to treat elderly patients with dementia, an appropriate starting dose might be 2.5 mg/day with a target dose of 5 to 10 mg/day.[7] However, it is my opinion that drugs with anticholinergic activity, such as clozapine and olanzapine, may attenuate the therapeutic effects of acetylcholinesterase inhibitors used to treat the cognitive symptoms of dementia. It is commonly known that antipsychotics may also counter the therapeutic effects of dopamine agonists used in the treatment of Parkinson's disease. Though the target dose is not yet well defined, I think that quetiapine may be successfully used to treat behavioral symptoms of dementia; no controlled data for using ziprasidone in this population are currently available.

For treating nondemented elderly patients with schizophrenia, the appropriate dose of atypical antipsychotic is somewhat higher: 2 to 3 mg/day of risperidone, 10 to 15 mg/day of olanzapine.[8,9] Again, gradual titration is important to avoid orthostatic hypotension and sedation. Clozapine, olanzapine, and quetiapine are sedating antipsychotics. An additive effect occurs when other sedating drugs, such as alcohol or antihistamines, are used.

For treating patients with bipolar disorder, the appropriate dose ranges for most atypical antipsychotics have not

been definitively determined. The exception to this is olanzapine, which is approved by the U. S. Food and Drug Administration (FDA) for the short-term treatment of acute manic and mixed episodes. The appropriate dose range of olanzapine is 10 to 15 mg/day.[10] The probable dose range for risperidone is 2 to 4 mg/day.[11] No clear data are available for quetiapine or ziprasidone dosing in bipolar disorder.

CONCLUSION

The pharmacokinetics of a drug defines its potential for drug-drug interactions. Such interactions can affect dosing, particularly in special populations. An awareness of the cytochrome P450 system of primarily hepatic enzymes is crucial to managing the potential for drug-drug interactions among the atypical antipsychotics.

The activity of CYP enzymes can be affected by the substrates they work to modify. A second drug may competitively inhibit an enzyme that metabolizes the prescribed antipsychotic or may induce the action of that enzyme. The result of inhibition is a higher plasma level of antipsychotic, which can cause adverse effects, while the result of induction is a lower plasma level of antipsychotic, which can compromise therapeutic efficacy. Inhibitors of the CYP enzyme 1A2, which plays a role in the metabolism of clozapine and olanzapine, include fluvoxamine and grapefruit juice (in large quantities); an inducer of this enzyme is cigarette smoking. The SSRIs (especially fluoxetine, paroxetine, and high-dose sertraline) are inhibitors of CYP2D6, which metabolizes clozapine, olanzapine, and risperidone. CYP3A4 is responsible for the metabolism of quetiapine and ziprasidone and plays a role in the metabolism of olanzapine. Inhibitors of CYP3A4 include erythromycin and other macrolide antibiotics, ketoconazole and some other antifungal drugs, and protease inhibitors. Inducers of CYP3A4 include barbiturates, phenytoin, carbamazepine, rifampin, and glucocorticoids. In some circumstances, increasing or decreasing the dose of antipsychotic should be considered.

However, not all drug-drug interactions via the CYP enzyme system are of clinical significance. In addition, a clinician must take into account factors pertaining to the patient. Younger people tend to metabolize drugs faster than older people, men faster than women, and (for clozapine and olanzapine) those who smoke cigarettes faster than those who do not. Comorbid medical conditions and gene polymorphism may also affect drug metabolism. Dose reductions in special populations are especially necessary when 2 or more factors affecting plasma clearance are present.

Drug names: carbamazepine (Carbatrol, Tegretol, and others), clozapine (Clozaril and others), erythromycin (E-Mycin, Ery-Tab, and others), fluoxetine (Prozac and others), ketoconazole (Nizoral, Ketozole, and others), olanzapine (Zyprexa), paroxetine (Paxil), phenytoin (Dilantin, Phenytek, and others), quetiapine (Seroquel), rifampin (Rifater, Rifamate, and others), risperidone (Risperdal), sertraline (Zoloft), ziprasidone (Geodon).

Disclosure of off-label usage: Dr. Sharif has determined that, to the best of his knowledge, olanzapine and quetiapine are not approved by the U.S. Food and Drug Administration for the treatment of dementia-related psychosis; and risperidone is not approved for the treatment of dementia-related psychosis and bipolar disorder.

REFERENCES

1. Ereshefsky L. Pharmacokinetics and drug interactions: update for new antipsychotics. J Clin Psychiatry 1996;57(suppl 11):12–25
2. Stahl SM. Psychopharmacology of Antipsychotics. London, England: Martin Dunitz Ltd; 1999
3. de Leon J, Becona E, Gurpegui M, et al. The association between high nicotine dependence and severe mental illness may be consistent across countries. J Clin Psychiatry 2002;63:812–816
4. Barnes TRE, McPhillips MA. Critical analysis and comparison of the side-effect and safety profiles of the new antipsychotics. Br J Psychiatry 1999;174(suppl 38):34–43
5. Bhana N, Foster RH, Olney R, et al. Olanzapine: an updated review of its use in the management of schizophrenia. Drugs 2001;61:111–161
6. Katz IR, Jeste DV, Mintzer JE, et al. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia. J Clin Psychiatry 1999;60:107–115
7. Street JS, Clark WS, Gannon KS, et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer's disease in nursing care facilities. Arch Gen Psychiatry 2000;57:968–976
8. Jeste DV, Madhusoodanan S, Barak F, et al. Risperidone versus olanzapine in elderly patients with schizophrenia. In: New Research Abstracts of the 154th Annual Meeting of the American Psychiatric Association; May 10, 2001; New Orleans, La. Abstract NR754
9. Madhusoodanan S, Brecher M, Brenner R, et al. Risperidone in the treatment of elderly patients with psychotic disorders. Am J Geriatr Psychiatry 1999;7:132–138
10. Physician's Desk Reference, 57th Ed. Montvale, NJ: Thomson PDR; 2003
11. Sachs GS, Grossman F, Ghaemi SN, et al. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of safety and efficacy. Am J Psychiatry 2002;159:1146–1154