Assessing the Clinical Significance of Drug Interactions in Psychiatry

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In recent years, clinicians have been bombarded with ever-increasing amounts of data regarding drug interactions. The driving force behind this surge of data has been twofold. First, polypharmacy has become increasingly common and, at times, acceptable and appropriate. However, polypharmacy can also cause clinically significant drug interactions. In addition, the US Food and Drug Administration now requires in vitro studies of potential interactions to accompany all new drug applications. These in vitro studies, which are obtained by using human microsomal liver preparations, may not be complete. Thus far, in vitro data focus on drugs metabolized through the cytochrome (CYP) P450 isoenzyme system. These data do not include information on another major monooxygenase metabolic system, the flavin-containing monooxygenase metabolic system (FMO). Certainly, these data cannot account for potential drug interactions secondary to protein binding, serum concentration-dependent interactions, and the presence of metabolites.1

In general, drug interactions can be described as either pharmacodynamic or pharmacokinetic (Figure). The clinical outcomes of these two types of interactions can differ greatly. In pharmacodynamic interactions, drug A and drug B may compete for the same site of action, with reduced activity of drug A secondary to the effect of drug B at this site. For example, the benzodiazepine antagonist flumazenil is often used to reverse the sedating effects of benzodiazepines during general anesthesia. Conversely, a pharmacodynamic interaction may cause heightened activity of drug A secondary to the effect of drug B at a site. An example of this would be heightened sedation resulting from the combination of two or more agents that block histamine receptors.

The second type of interaction is pharmacokinetic, which can occur at any phase of drug metabolism (eg, absorption, distribution, metabolism, or excretion). A second drug or even the same drug can induce or inhibit the metabolic rate of drug clearance through the liver. For example, drug A may either induce or inhibit the hepatic metabolism of drug B, resulting in a shorter or longer elimination half-life, respectively. Enzyme induction causes either greater amounts of CYP P450 enzymes to be produced or increases hepatic blood flow. The elderly appear to have a decreased risk for enzyme induction. Likewise, patients with cirrhosis or hepatitis may also have a lower incidence of enzyme induction.2 Conversely, enzyme inhibition causes decreased hepatic metabolism secondary to competitive binding at the enzyme's binding site.3 Further, drugs that are a racemic mixture may inhibit isoenzymes to varying degrees. For example, the s-enantiomer of fluoxetine is a much more potent inhibitor of CYP 2D6 than its r-enantiomer.4

This article will review potential pharmacodynamic and pharmacokinetic drug interactions in the chronically mentally ill.
Mechanisms of drug interactions such as changes in protein binding, zero-order pharmacokinetics, and the metabolism of drugs by way of the hepatic microsomal enzyme system known as the CYP P450 system will be discussed. The FMO system will be discussed briefly. Factors such as age and genetics that affect drug metabolism will also be presented. The section discussing the CYP P450 system will be presented separately.

PHARMACOKINETIC INFLUENCES

Only a small number of psychotropic drugs are not hepatically metabolized, and these agents thus depend on renal clearance for elimination from the body. The most common drugs used in psychiatry that depend on renal clearance are lithium and, more recently, gabapentin. Renal clearance is particularly important in lithium use because this agent has a narrow therapeutic index. Therefore, drugs that alter renal blood flow or lithium excretion within the kidney itself are likely to cause changes in lithium serum concentrations. Many nonsteroidal anti-inflammatory agents (eg, indomethacin, ibuprofen, naproxen) increase lithium serum concentrations secondary to prostaglandin E inhibition. Alternative analgesic agents for patients receiving lithium include aspirin and acetaminophen. Diuretics that act on the distal tubule in the kidney increase sodium clearance, which activates a compensatory increase of both sodium and lithium reabsorption in the proximal tubule and elevates lithium serum concentrations. Methylxanthines (eg, theophylline and caffeine), verapamil, aminophylline, and osmotic diuretics all increase the glomerular filtration rate, increasing lithium clearance and decreasing lithium serum concentrations. In general, clinicians should intensify the clinical as well as serum concentration monitoring when adding or stopping a drug that is known to affect the pharmacokinetics of lithium.

As a natural part of aging, the elderly experience changes in their ability to metabolize drugs. For example, increasing adipose tissue and loss of muscle mass result in an increased volume of distribution. Renal function also decreases with age. These changes pharmacokinetics frequently necessitate medication adjustments to minimize toxicity.

Hepatic dysfunction may affect drug effects. For instance, onset of action of a pro-drug may be delayed secondary to a decrease in its metabolism from the inactive parent compound to the active metabolite. Alternatively, delayed changes in drug or metabolite metabolism may increase the incidence of side effects.

Alterations in protein binding may lead to increased toxicity, especially with drugs that have a narrow therapeutic index (eg, warfarin, theophylline, phenytoin) and hepatic clearance restricted by plasma protein binding. The selective serotonin reuptake inhibitors (SSRIs), nefazodone, and mirtazapine are all highly bound to protein and may cause protein-binding displacement of other loosely bound drugs. When protein-binding displacement occurs, the free fraction of drug available to exert its pharmacologic action increases, which may lead to toxicity. Unlike other antidepressants, venlafaxine is not highly protein bound, making protein-binding displacement interactions unlikely. For low-extraction drugs, the free drug is hepatically eliminated and eventually plasma drug concentrations return to the preinteraction level. With high-extraction drugs, increased free drug may increase pharmacologic effects. The plasma concentrations of these drugs increase and stay elevated.

Valproic acid is a mood stabilizer that at times may exhibit puzzling pharmacokinetic parameters for the clinician. Valproic acid is extensively bound to plasma proteins. Further, the protein-binding ability of valproate is concentration dependent and varies widely among patients. Up to a certain point, an increase in the valproate total daily dose causes an increase in serum concentrations. Once protein-binding saturation occurs, the drug is displaced from the protein, causing an increase in free (active) drug. Free drug concentrations may be
**TABLE**

**Examples of Substrates and Inhibitors of CYP Isoenzymes Pathways**

<table>
<thead>
<tr>
<th>CYP 1A2</th>
<th>CYP 2D6</th>
<th>CYP 2C9</th>
<th>CYP 2C9</th>
<th>CYP 3A4/5,7</th>
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<tbody>
<tr>
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<td>Desipramine</td>
<td>Diazepam</td>
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<td>Venlafaxine</td>
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**Enzyme Inhibitors**

<table>
<thead>
<tr>
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<td>Sertraline</td>
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*Italics—mild to moderate inhibitors; bold—potent inhibitors.*

Increased without a corresponding increase in total drug serum concentration. Because of the increase in free drug concentration, patients may experience an increase in side effects such as tremor.

**Cytochrome P450 Isoenzyme System**

The cytochrome P450 isoenzyme system (CYP) is a collective term that refers to multiple gastrointestinal and hepatic isoenzymes that are responsible for the phase I oxidative metabolism of drugs. These isoenzymes are categorized into families and subfamilies. Isoenzymes are classified by their amino acid sequences and isoforms. 1,2,7 In recent years, there have been tremendous gains in clinicians' knowledge and identification of various CYP isoenzymes. To date, more than 30 isoenzymes have been identified. The best-characterized isoenzymes include CYP 2D6, CYP 3A4, CYP 1A2, CYP 2C9, and CYP 2C19. In general, CYP 3A3 and CYP 3A4 are referred to collectively as CYP 3A3/4 because they possess almost identical enzymatic activity and amino acid structure. Clinicians must understand the CYP 2D6 and CYP 3A4 systems because they are responsible for metabolizing...
the vast majority of psychotropic agents. Drugs that are metabolized by a given pathway are referred to as a substrate (Table). Unfortunately, many drugs may be substrates for more than one isoenzyme. Active metabolites may be metabolized by different isoenzymes than the parent compound. For example, imipramine is a substrate for CYP 3A4/5, CYP 1A2, and CYP 2C19, whereas desipramine, an active metabolite of imipramine, is a substrate for CYP 2D6. In addition, many of these substrates may induce or inhibit isoenzymes for which they are substrates. Clinicians must understand isoenzyme specific substrates and to what degree a particular drug modulates isoenzymes. Isoenzyme modulation can vary from minimal to potent. Potency may also depend on a given agent's serum concentrations. For example, with drugs that possess nonlinear pharmacokinetics (eg, fluoxetine, paroxetine), the potential for a drug interaction may escalate with higher doses. Both these phenomena must be taken into account to determine the risk of clinically significant drug interactions.

Finally, genetic differences can influence hepatic metabolizing capacity. Several specific isoenzymes can be influenced by polymorphism. CYP 2D6 expression is controlled by an autosomal recessive gene. Approximately 5% to 10% of whites, 8% of African Americans, and 2% to 10% of Asians lack this gene, resulting in an absence of this enzyme or production of a dysfunctional enzyme. CYP 2C19 exhibits polymorphism as well. For these isoenzymes, two phenotypes have been identified: poor and rapid metabolizers. Patients who are poor metabolizers will manifest enhanced bioavailability, increased plasma concentrations, and prolonged elimination half-lives compared with those who are extensive metabolizers. Because of these altered pharmacokinetic parameters, poor metabolizers are at risk for drug accumulation with subsequent increases in dose-dependent side effects. On the other hand, extensive metabolizers will exhibit lower serum concentrations of the parent drug and higher concentrations of metabolites. There is some thought that CYP 1A2 is also polymorphic secondary to a trimodal pattern of caffeine metabolism. However, this has not been genetically confirmed.

Isoenzyme CYP 1A2

Although a relatively small number of drugs have been identified as substrates for CYP 1A2, several clinically significant drug interactions have been identified. One of the best-documented CYP 1A2 interactions involves theophylline and fluvoxamine (a potent inhibitor). Reports in the literature support theophylline toxicity secondary to fluvoxamine administration. Coadministration of theophylline and fluvoxamine requires that the total daily dose of theophylline be reduced by 33%. One less well-studied but potentially clinically relevant interaction involves CYP 1A2 inhibitors and caffeine. Theoretically, a potent CYP 1A2 inhibitor, such as fluvoxamine, could produce significant changes in the pharmacokinetic parameters of caffeine. The clinical presentation of this potential drug interaction (eg, increased stimulatory effects) may be somewhat misleading. Clinicians may incorrectly attribute the observed stimulatory effects as a common side effect of fluvoxamine when in fact it may be secondary to increased serum concentrations of caffeine. Another clinically relevant and potentially dangerous interaction involves fluvoxamine inhibition of clozapine metabolism. Ample data support a marked increase in serum concentrations of clozapine and its active metabolites, N-desmethylclozapine and clozapine N-oxide, when it is given with fluvoxamine. This interaction not only increases the incidence of side effects, but more important, places patients at greater risk of seizure due to abrupt and significant elevations in serum concentrations of clozapine.

Isoenzyme CYP 2B6

The newest identified isoenzyme that may be of relevance to psychiatry is CYP 2B6. Bupropion is converted to its major metabolite by way of this isoenzyme. In addition, the heterocyclic antidepressant, mianserin, is in part metabolized by this particular isoenzyme. Genetic polymorphism has not been confirmed but is likely, since this enzyme was undetectable in liver microsomal samples taken from 15% of whites and 70% of Japanese.

Isoenzyme CYP 2D6

CYP 2D6 has been the most rigorously studied of all the CYP isoenzymes. Many psychotropic agents are substrates for this pathway. In addition, a number of psychotropic agents are either inducers or inhibitors of the CYP 2D6 isoenzyme. The amount of in vitro data, as well as the number of clinical case reports involving the CYP 2D6, can be traced back to the marketing of the first SSRI, fluoxetine. At this time, many patients were switched from tricyclic antidepressants (TCAs) to fluoxetine. During this titration phase, the first reports of significantly elevated desipramine levels began to appear in the literature. In vitro pharmacokinetic studies support the in vitro data, which demonstrate that both fluoxetine and paroxetine are potent inhibitors of the CYP 2D6. Sertraline, fluvoxamine, and citalopram possess mild inhibitory effects on this isoenzyme system, while nefazodone and venlafaxine appear to have a negligible effect on it. Other clinically significant interactions include the use of several beta-blockers (eg, metoprolol, propranolol) with potent CYP 2D6 inhibitors, causing bradycardia. It is not known whether a number of other CYP 2D6 substrates are involved in clinically significant drug interactions, but clinicians should keep this possibility in mind and
monitor patients closely for the development of clinically significant sequelae.

However, it should be noted that while Vandel, et al confirmed the existence of an interaction between fluoxetine and tricyclic antidepressants, fluoxetine was not in all cases associated with a marked increase in TCA plasma level. This pharmacokinetic change did not induce any significant in some patients, even when the plasma level increased significantly. Thus, although a potential drug-drug interaction has been reported, and indeed has been associated with an increase in plasma level in some patients, it may not have a clinically significant effect on a particular individual. Clinically, practitioners should be aware of changes in patient status, any time a new medication is added to an existing medication regimen.

**Isoenzyme CYP 2C19**

There are only a small number of known substrates for the CYP 2C 19 isoenzyme. Further, limited data are available that assess the inhibitory effects of most antidepressants on CYP 2C19. The exception appears to be fluvoxamine, which has a strong inhibitory effect on this isoenzyme. For example, a study by Perucca and colleagues showed that fluvoxamine 100 to 150 mg/day significantly altered the pharmacokinetics of diazepam. Through this isoenzyme pathway, diazepam undergoes demethylation to the active metabolite, desmethyl Diazepam. When fluvoxamine was given with a single 10-mg dose of diazepam, the half-life of diazepam increased from 51 to 118 hours. Analyzing case reports of drug interactions involving CYP 2C19 substrates is difficult, since many of these substrates are metabolized by various isoenzyme pathways. Fluoxetine has been reported to have moderate inhibitory effects on this isoenzyme pathway. Other antidepressants (eg, paroxetine, nefazodone, sertraline, and venlafaxine) do not appear to have any clinically significant effects on CYP 2C19.

**Isoenzyme CYP 2C9**

A second member of the CYP 2C family is CYP 2C9. Much research has been done in the past few years to characterize its amino acid sequence and metabolic activities. To date, there are only a few known substrates for this isoenzyme pathway. The most clinically significant interactions involving CYP 2C9 have occurred with phenytoin and s-warfarin. Fluoxetine and fluvoxamine have potent inhibitory actions on this isoenzyme. Certainly, ample evidence supports these interactions. The serum concentration of warfarin increases by nearly 100% when fluvoxamine is added, increasing prothrombin time. Likewise, a recent review of all case reports involving fluoxetine and phenytoin reported a mean increase in serum phenytoin concentrations of 161%. One additional factor that makes phenytoin drug interactions so clinically significant is that these interactions undergo zero-order kinetics. Therefore, adding a CYP 2C9 inhibitor will cause exponential increases in serum phenytoin concentrations. This may result in an accidental phenytoin overdose in previously stable patients. Clearly, patients taking phenytoin or warfarin should not be given fluoxetine or fluvoxamine.

**Isoenzyme CYP3A4**

One of the most important isoenzyme pathways is the CYP 3A4. This particular subfamily is responsible for one quarter of the total CYP P450 system in the average adult. A wide variety of psychotropic agents (eg, TCAs, benzodiazepines, and carbamazepine) are known substrates for the CYP 3A isoenzyme. A number of other types of medications (eg, nonsteroidal antiinflammatories, calcium channel blockers, steroids, and immunosuppressant agents) are substrates as well. To complicate the picture further, there are a number of known CYP 3A3/4 inhibitors and inducers.

Several clinically significant interactions involving potent CYP 3A inhibitors (eg, ketoconazole, erythromycin, and itraconazole) with terfenadine, astemizole, and cisapride have led to potentially fatal consequences. Terfenadine is a prodrug with potential cardiotoxic effects. When terfenadine metabolism to its active metabolite, terfenadine carboxylate, is inhibited, the resultant significant elevations in serum terfenadine levels have been shown to block potassium channels in the heart. The resulting sequelae may include disturbances in cardiac conduction (eg, prolonged QT intervals) and possible ventricular arrhythmias (eg, ventricular fibrillation and torsades de pointes). As a result, terfenadine is now off the market and has been replaced by its active metabolite (fexofenadine), which has no cardiotoxic properties. Several antidepressants (eg, nefazodone, sertraline, fluvoxamine, and fluoxetine) have known inhibitory effects on CYP 3A. Although they are less potent inhibitors of CYP 3A than are ketoconazole, itraconazole, and erythromycin, they may produce clinically relevant drug-drug interactions. They should not be given to patients taking astemizole or cisapride. When other known CYP 3A substrates have been given with nefazodone, sertraline, fluvoxamine, and fluoxetine, clinically significant increases in substrate serum concentrations have occurred. For instance, the use of nefazodone with alprazolam and triazolam has resulted in significant increases in serum concentrations of both benzodiazepines. Thus, the total daily dose of alprazolam and triazolam should be reduced by 50% and 75%, respectively, when administered with nefazodone to minimize additive central nervous system (CNS) depression. Because lorazepam and oxazepam are metabolized by way of conjugation rather than oxidation, there is a reduced risk of benzodiazepine accumulation, and these agents would be better choices. Other potential interactions
with relevance to the psychiatric patient include increased bradycardia when calcium channel blockers and fluoxetine or fluvoxamine are combined, and elevated serum concentrations of carbamazepine and its epoxide metabolite due to the inhibitory properties of fluoxetine.\textsuperscript{7,22}

Carbamazepine, rifampin, phenobarbital, and phenytoin are known CYP 3A inducers. In fact, carbamazepine induces its own metabolism (autoinduction). Adding other enzyme inducers may further induce the metabolism of carbamazepine.\textsuperscript{23} Adding an enzyme inducer to carbamazepine will decrease its serum concentration and potentially increase the ratio of carbamazepine epoxide: carbamazepine. The result is twofold: decreased symptom control secondary to lower carbamazepine serum levels and potential exacerbation of side effects and toxicity associated with increased epoxide serum levels.

Because of its inducing properties, carbamazepine has been involved in a number of clinically relevant interactions. Carbamazepine induction of the metabolism of oral contraceptives is well documented.\textsuperscript{24} Thus, to avoid an unwanted pregnancy, women receiving carbamazepine should practice another method of birth control. Carbamazepine has been associated with an accelerated hepatic metabolism of several newer anticonvulsant agents (eg, lamotrigine and tiagabine). In healthy volunteers, giving carbamazepine with lamotrigine decreased the half-life of lamotrigine from approximately 24 hours to 14 hours.\textsuperscript{25}

Clinically significant interactions have occurred with rifampin when it is used with benzodiazepines such as midazolam and triazolam. This interaction may result in a loss of hypnotic or anxiolytic properties. Likewise, rifampin increases the metabolism of opioids, which may result in opioid withdrawal.\textsuperscript{26} Several calcium channel blockers have been used or are currently being investigated as potential mood stabilizers. Data have demonstrated a 3-fold increase in verapamil clearance when rifampin is added.\textsuperscript{2} When calcium channel blockers are used with potent CYP 3A enzyme inducers, the net effect may be loss of efficacy in mania or cardiovascular disease.

Enzyme-inducing agents have also been shown to lower serum concentrations of other psychotropic agents such as antidepressants, antipsychotics, and benzodiazepines. In patients receiving enzyme inducers' subtherapeutic serum concentrations of other psychotropic agents may lead to therapeutic failure. These patients may require higher doses of a particular substrate to achieve the desired effect.

Flavin-Containing Mono-oxygenases

In addition to the CYP metabolic system, the FMO are also responsible for drug metabolism. While this system is not an inducible system like the CYP, it appears that the metabolic capacity of FMO may be inhibited. Currently, there are only five known FMO families (FMO 1-5). This system may work in conjunction with the CYP in the metabolism of certain substrates. For example, olanzapine is metabolized by CYP 1A2, CYP 2D6, and FMO 3.\textsuperscript{2} Certain, alterations in the metabolism of one system may influence the metabolism of the other system, leading to the potential clinically relevant drug interactions.

PHARMACODYNAMIC INTERACTIONS

An example of a pharmacodynamic interaction encountered in these patients is serotonin syndrome, which may be characterized by mental status changes (confusion, agitation), myoclonus, hyperreflexia, autonomic fluctuations, diaphoresis, fever, seizure, and coma. Diagnosis of serotonin syndrome may at times be confusing. Many of its symptoms mimic side effects associated with SSRI monotherapy. Because of this clouded clinical picture, Sternbach published diagnostic criteria for serotonin syndrome that may help clarify the diagnosis.\textsuperscript{27} Serotonin syndrome, which is thought to be the result of excessive serotonin neurotransmission, may be precipitated by the concomitant use of serotonergic drugs at high doses, by combinations of serotonergic drugs at therapeutic doses, or during the transition from one antidepressant to another.\textsuperscript{28} The most severe cases of serotonin syndrome have traditionally been associated with the concomitant use of an SSRI and a monoamine oxidase inhibitor (MAOI). This combination blocks serotonin reuptake into the presynaptic nerve terminal and inhibits serotonin degradation by monoamine oxidase. Thus, any drug that has a net effect of increased serotonin neurotransmission could potentially trigger serotonin syndrome. Combinations that have been associated with serotonin syndrome include MAOI and SSRI, MAOI and TCA, SSRI and lithium, SSRI and L-tryptophan, and SSRI and carbamazepine. Further, meperidine, pentazocine, and dextromethorphan exhibit significant serotonin reuptake inhibition and have been associated with serotonin syndrome.\textsuperscript{29} Symptoms of serotonin syndrome may begin within hours after a dose is increased or serotonergic agents are added. Generally, treatment involves discontinuing all serotonergic agents and providing supportive care.

When multiple medications are used, patients are always at risk of developing additive and synergistic side effects. For example, patients may experience additive anticholinergic effects when diphenhydramine is added to a medication regimen that contains other agents with anticholinergic properties. These additive anticholinergic effects (eg, dry mouth, blurred vision, urinary retention, delirium) may be especially problematic in the elderly.\textsuperscript{30,31} Additive and synergistic CNS depression would be an expected yet undesirable side effect in patients who drank alcohol while taking psychotropic agents. Conversely, the enhanced CNS sedative effects of two or more medications can be bene

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ficial in an agitated or severely psychotic patient. Drugs with alpha-adrenergic blocking properties should be used cautiously in combinations to minimize orthostatic hypotension. A particularly problematic combination is low-potency antipsychotic agents and tertiary TCAs.

Lithium has been associated with neurotoxicity when used with antipsychotic agents, carbamazepine, methylprednisolone, and verapamil. It appears that the elderly are at increased risk of neurotoxicity associated with lithium. Since initial reports of lithium-antipsychotic neurotoxicity in the 1970s, there has been much debate over its incidence. Possible explanations for this interaction include use of higher doses of high-potency antipsychotic agents, use of elevated lithium serum concentrations, incorrectly diagnosed symptoms, and additive or synergistic effects resulting in toxicity.15

Because use of these combinations is now common, clinicians should prescribe the lowest effective dose of both the antipsychotic agent and lithium to minimize the risk of toxicity and enhance tolerability.

CONCLUSION

A number of potential pharmacodynamic and pharmacokinetic drug interactions may be clinically relevant to the psychotic patient, but an ever-expanding armamentarium of psychotropic agents makes it impossible for clinicians to memorize all possible drug interactions. For the most part, basic knowledge of potential CYP 450 inhibitors and inducers is necessary to analyze various drug combinations for potential pharmacokinetic interactions. Identification of significant interactions before certain combinations are prescribed will minimize side effects and maximize therapeutic outcomes for many patients. Unfortunately, in most cases, it is not possible to predict all drug interactions, nor to predict if a specific interaction will be clinically significant in a given patient. Clinicians can only use caution when adding new medications to an existing medication regimen, and continue to build on the current database of reported drug-drug interactions. Clinicians should also develop an understanding of a drug’s receptor-binding affinities to help predict potential pharmacodynamic interactions and prevent unnecessary drug misadventures.

REFERENCES