Provided as an Educational Service by

Glaxo SmithKline Pharmaceuticals

The 2016 Handbook of Psychotropic Drug Interactions

C. Lindsay DeVane, PharmD
Charles B. Nemeroff, MD, PhD

Disclaimer

This pocket reference is provided as a service to medicine by the Portugese Division of SmithKline Beecham Pharmaceuticals. Sponsorship of this review does not imply the sponsor's agreement with the views expressed herein.

Although every effort has been made to ensure that drug doses and other information are presented accurately in this publication, the ultimate responsibility rests with the prescribing physician. Neither the publishers, the sponsor, nor the authors can be held responsible for errors or for any consequences arising from the use of information contained herein. Readers are strongly urged to consult any relevant primary literature. No claims or endorsements are made for any drug or compound currently under clinical investigation.

First Published in:

The 2016 Handbook of Psychotropic Drug Interactions

C. Lindsay DeVane, PharmD
Charles B. Nemeroff, MD, PhD

Dr. DeVane is professor of psychiatry and behavioral sciences at the Medical University of South Carolina in Charleston. Dr. Nemeroff is the Reunette W. Harris Professor and chairman of the Department of Psychiatry and Behavioral Sciences at Emory University School of Medicine in Atlanta, GA.

No financial, academic, or other support of this work was acknowledged by the authors.

Contents

Index of Tables and Figures

Introduction

The present 2007 Guide to Psychotropic Dosing Interactions is an update of the past edition. Since the appearance of the 2004 Guide, new psychotropic drugs have been introduced which have specific data related to their potential drug interactions. Documentation continues to appear at a steady pace in the literature of drug interactions with commonly used psychotropics. As this guide is intended to serve an educational role for the psychiatrist-in-training, as well as non-psychiatric physicians less familiar with interactions of psychoactive drugs, the bulk of the background discussion on drug metabolism and mechanisms of drug interactions remains unchanged. For the repeat reader, we have summarized important new findings on drug interactions appearing since the last update in Table 1. The interactions of three new psychoactive drugs introduced recently to the market (oxcarbazepine, modafinil, and ziprasidone) are covered in Tables 17, 22, and 32. Other additions in the tables reflect new case reports and further documentation of drug interactions.

New knowledge related to the benefits of psychiatric drug treatment results in earlier initiation of drug therapy for some psychiatric disorders, and maintenance therapy is more and more commonplace during asymptomatic periods. In fact, maintenance therapy for affective anxiety and psychotic disorders, often continuing for years or decades, is now the accepted standard of care, especially for patients with a history of recurrent episodes of illness. Long-term pharmacotherapy requires awareness and management of drug interactions.

As the population ages, more drugs are prescribed on a chronic basis for maintenance of health without treatment of overt symptoms. Increasing numbers of patients take one of the serum lipid-lowering compounds from the class of 3-hydroxy- 3-methylglutaryl co-enzyme A reductase inhibitors. These drugs can be taken for primary prevention, regardless of whether or not the patient has previously experienced a vascular event such as a myocardial infarction or stroke. With the exception of pravastatin, the drugs in this class are highly metabolized by cytochrome P450 (CYP) 3A4, a hepatic enzyme whose action can be inhibited by several antidepressants. As will be explained later, some knowledge of how the major antidepressants interact with specific liver enzymes allows the choice of an antidepressant that avoids such potential drug-drug interactions.

New drugs to treat psychiatric illness have been introduced to clinical practice in recent years. Additional antidepressants and antipsychotics are expected over the next few years. The recent introduction of ziprasidone reflects the high level of activity in drug development for treatment of psychotic conditions. Additional new drugs in this category are currently being tested in clinical trials. Each of these compounds possesses a certain potential to interact with other drugs. This is especially true since psychoactive drugs are generally highly metabolized compounds. Laboratory methodologies developed in recent years can identify the specific enzymes mediating various metabolic pathways. This information can be used to predict how a new drug will interact pharmacokinetically with a variety of other drugs already marketed. Some background knowledge of major drug-metabolizing enzymes is helpful in understanding how these predictions are made. Of course, in vitro predictions must be confirmed with in vivo studies, but supporting clinical data may not be available for months or years.

This guide summarizes psychotropic drug interactions from several viewpoints. First, examples of pharmacokinetics will be discussed to aid the reader in understanding how drugs may interact during the course of their absorption and elimination from the body. Secondly, because many interactions with psychotropic drugs occur via specific interactions with the CYP system, this hepatic enzyme system will be described and the most important enzymes involved in the metabolism or interactions of psychoactive drugs will be discussed. Some principles of drug interactions operating through competitive inhibition of hepatic enzymes will be explained, so that the reader may make informed judgments about the possibility of an interaction.

The bulk of the guide will be concerned with drug interactions that have been described with specific psychoactive drug classes. The degree of documentation varies for many interactions from theoretical conjecture, to clinical experience with patients, to well-established research outcomes. The sources of interaction data will be noted to help identify the appropriate level of confidence in the predicted consequences of combining drugs in therapy. When possible, specific management guidelines are provided to avoid or minimize some potentially negative interactions. The major psychoactive drugs, classified according to their primary therapeutic indication, are listed in Table 2. Subsequent tables will list important drug interactions for each of these classes.

Classification of Drug Interactions

Drug interactions are commonly classified as occurring by either pharmacodynamic or pharmacokinetic mechanisms. A third category, pharmaceutical interac-

tions, occurs from physical incompatibility of drugs. Examples of this last class include the precipitation of drugs following their addition to intravenous fluids of inappropriate pH, or the physical absorption of drugs to intravenous tubing. The intravenous dose of diazepam delivered can be far less than expected if it is injected into intravenous tubing distal to the point of venipuncture due to drug absorption to plasticizer in the tubing. These types of interactions are rarely of concern, because the vast majority of psychoactive drugs are prescribed for oral administration.

Pharmacodynamic Drug Interactions

A pharmacodynamic drug interaction occurs when the pharmacologic response of one drug is modified by another drug without the effects being the result of a change in drug concentration. These interactions occur at the sites of drug action. Such sites can include receptors, ion channels, cell membranes, and enzymes. We lack a thorough understanding of these drug interactions, as they are generally more difficult to detect and study than pharmacokinetic interactions. The latter are more easily documented and quantified through measurement of plasma drug concentrations. The pharmacologic effects of psychoactive drugs can be difficult to measure, especially changes in behavior or mental status. Some examples are illustrative of pharmacodynamic interactions.

Drugs that produce sedation by different mechanisms often produce additive sedation when administered together. The combination of traditional antihistamines with benzodiazepines or alcohol provides an example. Another well-known pharmacodynamic interaction is the combination of a nonselective monoamine oxidase inhibitor (MAOI) with an over-the-counter (OTC) sympatho-mimetic nasal decongestant or foods rich in tyramine. Because of differing mechanisms of action, overstimulation of the sympathetic nervous system can result in pressor effects that produce hypertension. This interaction is becoming less of a clinical concern due to the diminishing use of the MAOIs. A more relevant example for current clinical practice is provided by serotonin syndrome. This is a potentially fatal disorder, which can result from combining highly serotonergic drugs. It was first recognized in laboratory animals given MAOIs and L-tryptophan but has been documented with the newer antidepressants and other agents that have prominent serotonergic actions. It occurs in the absence of pharmacokinetic changes in drug disposition.

Some drug interactions at sites of action are specifically exploited for their therapeutic benefits. The pharmacodynamic interactions of competitive antagonists at receptor sites are the basis for development of several therapeutically useful drugs. Naloxone, propranolol, and flumazenil reverse the effects of opiates, catecholamines, and benzodiazepines at their respective receptor sites when given in close temporal proximity to their agonists. When adjunctive agents are combined with antidepressants, eg, lithium, or thyroid hormone with tricyclic antidepressants (TCAs), or pindolol with selective serotonin reuptake inhibitors (SSRIs), it is hoped that a pharmacodynamic interaction will result in an improvement in patient response.

Pharmacokinetic Drug Interactions

A pharmacokinetic interaction occurs when one drug alters the disposition of another drug, thereby resulting in a change in plasma or tissue drug concentration. The change in concentration may or may not result in clinically significant consequences. Any of the major components of drug disposition illustrated in Figure 1 can theoretically be affected.

For the psychoactive drugs, the drug dose is usually administered orally. Absorption occurs most often in the small intestine, where a favorable pH promotes transit across the GI membranes. Some portion of the absorbed dose undergoes glomerular filtration and passes out through the urine in an unchanged form. The proportion varies both among individuals and between drugs. Generally, the psychoactive drugs are excreted unchanged only to a minor degree. Exceptions are lithium and gabapentin, which are excreted unchanged. Most drugs are biotransformed to either active or inactive metabolites. Either the administered parent drug and/or active metabolites can produce pharmacologic effects at various sites of action. In turn, metabolites are to some degree excreted in the urine, or they can be further metabolized. Eventually the biotransformation process results in a metabolite that is sufficiently water-soluble to be renally excreted. Drug interactions may involve any of these various steps in the drug disposition process.

Interactions Involving Absorption

Absorption of orally administered drugs is a multistep process. Once a solid form (tablets, capsules) of a drug dosage is dissolved into solution in the GI tract, it transverses the gut lumen and wall in transit to the liver. A portion of the drug dose may never be absorbed, due to inadequate dissolution or drug interactions that promote further passage beyond the small intestine and elimination in the feces. The possible sites of drug elimination during absorption are shown in Figure 2. Drugs

such as cholestyramine can physically bind to drugs in the GI tract and produce this effect. The nonabsorbable fat substitutes may also reduce the absorption of other drugs. Cimetidine, by altering GI pH, may reduce the rate or extent of absorption of many psychoactive drugs. Similarly, anticholinergic drugs can decrease the motility of the gut and alter drug absorption.

Drugs are subject to elimination during their absorption through the gut wall by the action of carrier proteins and metabolizing enzymes. P-glycoprotein (PGP) and Cytochrome P450 (CYP) 3A4 act in concert to limit the absorption of a number of drugs. PGP is a carrier protein that exports drug molecules back into the GI tract. This creates a continual recycling of a portion of the unabsorbed drug dose and has the effect of increasing the exposure to CYP 3A4 and first-pass elimination (Figure 2). PGP transport is a saturable process, which partially explains why increasing absorption may occur with an increased dose.

The gut wall is the site of interaction of PGP or CYP 3A4 inhibitors than can increase the bioavailability of some drugs. Some natural chemicals in grapefruit juice down-regulate, or decrease protein expression of, CYP 3A4 in the gut wall, which allows greater amounts of drugs that are prominent 3A4 substrates to be absorbed. For cyclosporine, this interaction with grapefruit juice can increase drug bioavailability and result in decreased dosage requirements for immunosuppression and economic cost savings for patients.

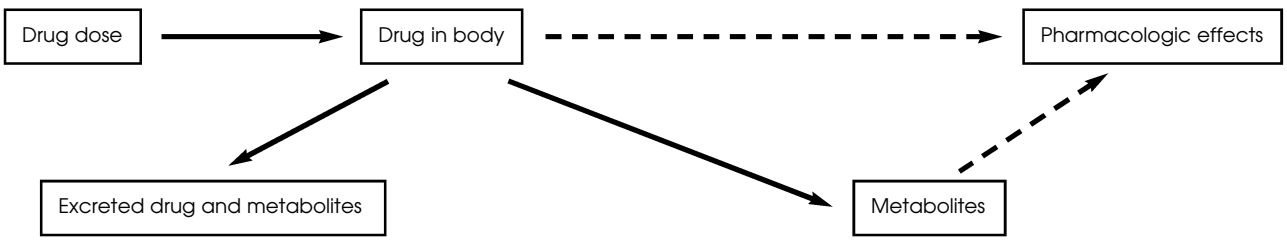
The role of PGP in drug interactions is being increasingly recognized. The cardiac glycoside digoxin is not metabolized, but renally excreted, and St. John's Wort (SJW) decreases its plasma concentration. The likely mechanism is induction of intestinal PGP to limit digoxin's oral absorption. A similar mechanism or CYP 3A4 induction may explain the lowering by SJW of indinavir, alprazolam, and cyclosporine plasma concentration. PGP also serves a protective function to limit access of drugs to the brain due to its presence in capillary endothelial cells which comprise the blood-brain barrier. Tolerance to the analgesic effects of morphine in rats was recently shown to result from induction of PGP synthesis. Induction or inhibition of PGP is a drug interaction mechanism likely to be documented in future reports altering the actions of many psychoactive drugs.

Interactions Involving Distribution and Protein Binding

Almost all drugs circulate in blood bound to some degree to specific plasma proteins, most often albumin and lipoproteins. This process presents an opportunity for drug-drug interactions to occur by one highly bound drug displacing another from its protein-binding sites. The potential consequences of this interaction can be seen in Figure 3. Normally drug bound to protein in plasma is in equilibrium with unbound drug. It is an accepted principle of pharmacology that only unbound drug is free to diffuse to sites of action, usually in tissues, and produce pharmacologic effects. When the amount of unbound drug in plasma is increased due to displacement from proteins by another drug, then more unbound drug is available to distribute to tissues where it can produce increased pharmacologic effects.

Although several drug interactions can be shown to occur through protein-binding displacement, this type of pharmacokinetic interaction may not be significant unless the binding displacement actually modifies a drug's dose-effect relationship. A classic example of this type of interaction is the displacement of warfarin from serum albumin-binding sites by phenylbutazone or salicylate analgesics. An increase in the plasma concentration of warfarin occurs accompanied by an increase in its pharmacologic effects, a prolongation of prothrombin time. However, as a result of more free (unbound) drug being in the systemic circulation not bound to plasma protein, more drug becomes available

Figure 1
Major Components of Drug Disposition



for hepatic metabolism. Eventually, the total concentration of warfarin in plasma returns to the pre- interaction level. This is a time-limited interaction in which homeostatic changes play a role in buffering the consequences of the increased free warfarin concentration.

Protein-binding interactions have been hypothesized to occur with most of the members of the SSRI class of antidepressants due to their high degree of plasma protein binding (>95% for some drugs); however, such interactions have not been shown to be a prevalent clinical problem. For example, sertraline produced a small increase in the free fraction of warfarin and a modest increase in prothrombin time in a study involving healthy male volunteers, but neither effect was considered to be clinically significant. The plasma binding of antidepressants and antipsychotics is generally greater to lipoproteins than to albumin, and, hence, warfarin-binding displacement interactions from albumin have been of more theoretical than practical significance. Nevertheless, these drugs may have a hypoprothrombinemic effect related to perturbations in platelet serotonin apart from any protein-binding interactions with anticoagulants. Alternatively, fluvoxamine may modify the enzymatic metabolism of warfarin, directly leading to enhanced pharmacologic effects.

Among the interactions of psychoactive drugs, the anticonvulsant mood stabilizers are most often involved in altering plasma protein binding. Valproate is highly bound to plasma proteins (>90%) and can displace the binding of diazepam, phenytoin, tolbutamide, and warfarin from their plasma albumin-binding sites. Valproate is also a weak inhibitor of several hepatic enzymes and may increase the pharmacologic effects of co-administered drugs. Overall, interactions involving protein binding occur with psychoactive drugs, but the examples are limited despite many psychoactive drugs' being highly plasma protein-bound.

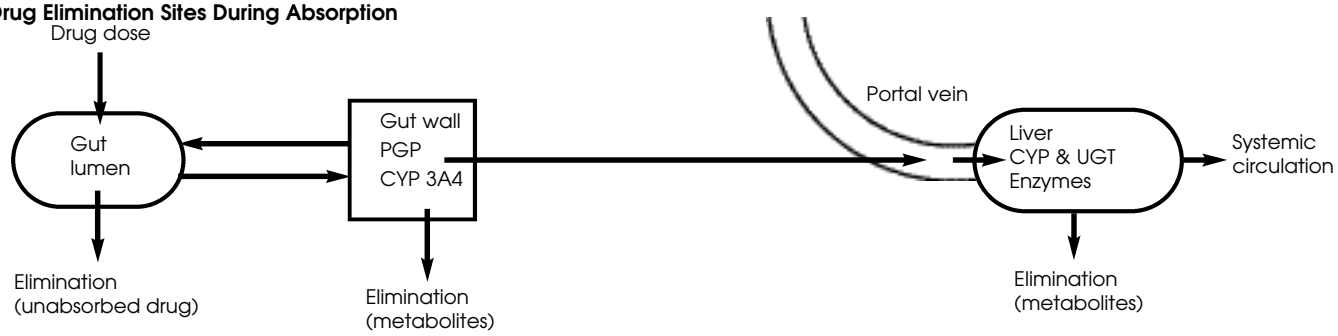
Interactions Involving Metabolism and/or Elimination

The liver is the primary site of elimination of most psychoactive drugs. It contains numerous Phase I and Phase II enzymes that oxidize or conjugate drugs, respectively. The most important of these enzymes in terms of understanding pharmaco-kinetic drug interactions is the Phase I CYP system. The majority of drug interactions of concern during the course of psychopharmacological treatment involve alterations of drug metabolism. Drug metabolism can occur in several tissues in the body, but hepatic metabolism is generally recognized as the most important, because proportionally the liver contains the highest enzyme content compared with other organs and is therefore most responsible for drug biotransformation.

Potential drug interactions involving Phase II metabolism are increasingly being recognized. The most important Phase II enzymes involved in drug metabolism are the glucuronosyltransferases. These enzymes perform conjugations by combing drug molecules with glucuronic acid, mostly in the liver. Three benzodiazepines (lorazepam, oxazepam, and temazepam) undergo Phase II reactions exclusively before being excreted into the urine. Both inducers and inhibitors of glucuronosyltransferases are known and have the potential to affect the plasma concentration and actions of important psychotropic drugs.

Drug interactions involving metabolism arise from enzyme induction or inhibition. Cigarette smoking and some specific drugs are recognized as inducers of hepatic oxidizing enzymes. The administration of these drugs can stimulate the synthesis of additional enzymes. Eventually, the increased enzyme activity

Figure 2
Drug Elimination Sites During Absorption



CYP=cytochrome P450; PGP=P-glycoprotein; UGT=uridine glucuronosyltransferases.

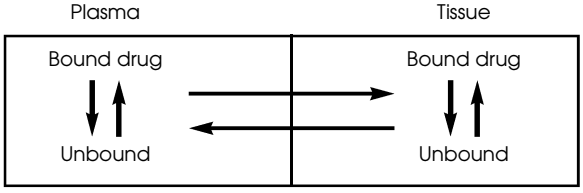
results in an enhanced clearance of drugs that are substrates for the induced enzyme. Plasma drug concentration may fall, leading to diminished pharmacologic effects. An example is the treatment of a patient with carbamazepine who is taking an oral contraceptive. Carbamazepine can induce the activity of CYP 3A4, leading to increased steroid metabolism and a loss of contraceptive effect.

An interaction involving enzyme inhibition results in impaired drug clearance and a rise in plasma drug concentration. While several types of enzyme inhibition can occur, the most common is known as competitive enzyme inhibition. This occurs when two drugs have such a strong affinity for the same enzyme that one is preferentially metabolized at the expense of the other. The concentration of the drug whose elimination has been inhibited will rise with continued dosing, due to decreased clearance. The magnitude of inhibition depends upon several factors, including the affinity of the drugs for the enzyme, the drug concentration in the plasma, the degree of partitioning into hepatocytes, and others.

Interactions involving hepatic enzyme induction or inhibition are characterized by dose and time dependence. The greater the dose of an inhibitor that is administered, within the range of clinically useful doses, the greater the extent of the inhibition that should occur. For example, fluoxetine is a competitive inhibitor of CYP 2D6 and should produce a greater inhibitory effect at a dose of 40 mg or 60 mg than at 20 mg/day. Eventually, increasing doses of an inhibitor will result in a maximum inhibition with no further effect from increasing doses.

Interactions involving competitive enzyme inhibition occur with the first dose of inhibitor, as it is the presence of the two competing drugs at the enzymatic site in the liver or GI tract that results in an interaction. In contrast, interactions occurring as a result of enzyme induction require several days to become apparent, as

Figure 3
Protein Binding: Equilibrium of Drugs



DeVane L. Principles of pharmacokinetics and pharmacodynamics. In: Schatzberg AF, Nemeroff CB, eds. *The American Psychiatric Press Textbook of Psychopharmacology*. 2nd ed. New York, NY: APA Press; 1998:155-169.

the inducing agent must stimulate the synthesis of additional metabolizing enzymes.

Drug interactions involving changes in renal elimination of drugs are infrequent with psychoactive drugs. An exception is lithium, which is totally renally cleared. Drugs and physiologic conditions that alter renal function affect lithium clearance. Foremost among the drugs that inhibit lithium clearance and increase its plasma concentration are most non-steroidal anti-inflammatory drugs (NSAIDs) and the thiazide diuretics. Drug interactions involving changes in renal elimination are unlikely to occur with the antidepressants, antipsychotics, and anxiolytics because these are highly metabolized drugs with typically less than 5% of an administered dose excreted in the urine in an unchanged form.

Prediction of Metabolic Drug Interactions

Based on an abundance of theoretical and experimental data, drug interactions as a result of competitive inhibition for the same metabolizing enzyme can be predicted. Prediction rests upon knowledge of substrate specificity for particular enzymes, the degree of affinity of a competing drug for the same enzyme, and the concentrations of the substrate and inhibitor. Mathematical equations can predict the degree of change in clearance of one drug by another under these circumstances in in vitro laboratory experiments using liver slices, intact hepatocyte preparations, or microsomes. Rarely is such complete information available for patients under clinical circumstances. In practical terms, by knowing the metabolic pathways of a drug, ie, which enzymes are involved in its metabolism, and whether a drug to be combined in therapy has inhibitory effects on that enzyme, an interaction can be predicted. The degree of interaction and whether the consequences will be clinically meaningful will depend upon multiple factors. Some of these include the specific drugs involved, drug dosage and length of therapy, and the clinical state of the patient.

While many enzymes in the liver are capable of biotransformation reactions, emphasis has focused recently on the CYP enzymes because it is estimated that collectively they participate in the metabolism of greater than 80% of all available drugs used in humans. CYP enzymes play additional roles in the metabolism of some endogenous substrates including prostaglandins and steroids. At least 30 related enzymes are divided into different families according to their amino acid homology. Some enzymes exist in a polymorphic form, meaning that a small percentage of the population possesses mutant genes that alter the activity of the

enzyme, usually by diminishing or abolishing activity. A genetic polymorphism has been well characterized with the CYP 2C19 and CYP 2D6 genes. Recently discovered but poorly categorized are polymorphisms of CYP 3A4. Table 3 lists the most important CYP enzymes, along with some of their substrates. Remarkably, for many drugs in clinical use for years, the enzymes involved in their metabolism have not been identified. This is an active research area, and information is continually being updated.

In the current approach to new drug development, candidate compounds are screened for their affinity for various P450 enzymes. A high affinity for one or more enzymes suggests a likelihood of interactions with other drugs metabolized by the same enzyme. These predictions can then be confirmed with targeted drug interaction studies in human volunteers or patients. The degree to which an interaction will occur also depends upon the concentration of the substrate and inhibitor at the enzyme site, which in turn depends upon the size of administered doses. The significance of blocking or inducing a particular cytochrome enzyme for a drug interaction will depend upon the importance of the enzyme in the overall elimination of the drug. Most drugs are eliminated through more than one pathway, and some degree of renal clearance also contributes to the elimination of many drugs. The existence of parallel pathways of elimination moderates the effects of inhibiting a single enzymatic pathway.

A qualitative approach to the prediction of drug interactions can be used by clinicians to identify the combinations of drugs that should be used cautiously or avoided, especially when preexisting information about their potential interaction is unavailable. Psychoactive drugs that inhibit or induce the enzymes listed in Table 2 would be expected to interact with the substrates of those particular enzymes. This approach provides a rough screen to predict the potential for pharmacokinetic interactions. It should be remembered that concentration changes do not necessarily translate into clinically meaningful interactions. Most drugs have acceptable therapeutic indices so that minor alterations in clearance, steady-state plasma concentration, or half-life, although statistically significant, may be clinically unimportant. Also, pharmacodynamic interactions are not predicted by this approximation and may occur in addition to or apart from pharmacokinetic interactions.

CYP Enzymes

CYP enzymes exist in a variety of body tissues, including the brain. Clearly, their presence in the GI tract, especially CYP 3A4, and in the liver is important for the elimination of administered drugs. The molecular and pharmacologic characterization of CYP enzymes and the corresponding genes that determine their synthesis is an active research area. The most prominent enzymes are discussed below, due to their importance for drug metabolism and participation in drug interactions.

CYP 1A2

The CYP 1A subfamily includes CYP 1A1 and CYP 1A2, with both genes located on human chromosome 15. CYP 1A2 is an important enzyme in the metabolism of several widely used drugs (Table 3). It comprises about 13% of the total P450 content of the human liver and is highly inducible.

Nonpsychiatric drugs metabolized by CYP 1A2 include theophylline, aminophylline, caffeine, and the antiarrhythmic propafenone. The ß-blocker propranolol is believed to have a minor component of its biotransformation mediated by CYP 1A2. The tertiary amine tricyclic antidepressants undergo demethylation to their secondary amine active metabolites by this enzyme. The traditional antipsychotic drug haloperidol and the newer atypical antipsychotics, clozapine and olanzapine, are partially metabolized by CYP 1A2. Tetrahydroacridinamine (tacrine) is hydroxylated by CYP 1A2.

CYP 1A2 is induced by cigarette smoke, charcoal-broiled foods, and some cruciferous vegetables (eg, Brussels sprouts). The effect of cigarette smoking can be prominent, and patients who stop or substantially reduce smoking can be expected over the subsequent few weeks to have a return to baseline of their CYP 1A2 activity. This situation has resulted in the appearance of seizures in a patient taking clozapine who quit smoking during therapy.

Fluvoxamine and ciprofloxacin are potent inhibitors of CYP 1A2, and interactions have been described with theophylline and clozapine. One of the most notable interactions of fluvoxamine is its ability to inhibit theophylline metabolism. Because the elevation of serum theophylline could double or more, it is recommended that when this antidepressant is prescribed for a patient receiving this bronchodilator, the patient's theophylline dose be reduced by one third of the prior dosage. Fluvoxamine is unique among the newer antidepressants in the ability to inhibit CYP 1A2. While the choice of another antidepressant in these circumstances could avoid this potential interaction, these drugs may be used safely together when dosed appropriately and cautiously. Appropriate clinical care would include moni-

toring of theophylline plasma concentration and vigilance to the appearance of side effects. Although other psychoactive drugs, including haloperidol, some tertiary amine tricyclic antidepressants, and olanzapine, are partially metabolized by CYP 1A2, their participation in competitive enzyme interactions appears to be a result of a stronger affinity for enzymes other than CYP 1A2.

CYP 2A

The genes for the expression of the CYP 2A subfamily are localized on the long arm of chromosome 19. Three genes for CYP 2A6, CYP 2A7, and CYP 2A13 have been identified and sequenced. A variant allele for CYP 2A6 has been associated with individuals who are deficient in their ability to metabolize warfarin. In in vitro studies, orphenadrine decreased the activity of CYP 2A6, but the clinical significance of this effect, if any, is unknown. CYP 2A6 comprises about 4% of the P450 content of the human liver, and its contribution to the metabolism of therapeutically used drugs is probably small.

CYP 2B

The cytochrome 2B subfamily consists of closely related P450s, 2B1, 2B2, and 2B6. CYP 2B1 has been the focus of study as it oxidizes toluene, aniline, benzene, and other solvents to reactive metabolites thought to be important in promoting carcinogenesis. It can be induced by acetone, phenobarbital, and carbamazepine. It plays a minor role in the metabolism of a few drugs used in humans, including caffeine, theophylline, coumarin, and lidocaine. In animal studies, clonazepam has been found to be a potent inhibitor of catalytic activities mediated by CYP 2B in microsomes derived from phenobarbital-pretreated rats. The monoamine oxidase inhibitors selegiline and clorgyline have been found to inactivate the activity of CYP 2B in vitro. The clinical significance of these effects is unknown.

CYP 2B6 is thought to be a minor component of P450 content in the liver, normally constituting less than 0.5% of total P450, although substantial interindividual variability has been observed. CYP 2B6 plays a role in the metabolism of the anticancer drug cyclophosphamide and is the major enzyme responsible for converting bupropion to its primary active metabolite, hydroxybupropion. Orphenadrine is a CYP 2B6 inhibitor in vitro. In a human pharmacokinetic study, carbamazepine and valproate both increased hydroxybupropion concentration, but their function as CYP 2B6 inhibitors has yet to

be established.

CYP 2C9/19

The CYP 2C subfamily consists of several closely related enzymes, 2C9, 2C10, 2C19, and others. CYP 2C comprises about 18% of the total P450 content of the human liver. A genetic polymorphism exists with CYP 2C19, with approximately 18% of Japanese and African Americans reported as poor metabolizers of CYP 2C19 substrates. Only about 3% to 5% of Caucasians inherit this deficiency. Affected individuals are identifiable by phenotyping with mephenytoin administration. Poor metabolizers have higher than normal plasma concentrations of the CYP 2C19 substrates from usual doses (Table 3). Rare polymorphisms of CYP 2C9 have been discovered.

Nonpsychiatric drugs metabolized by the CYP 2C subfamily include S-mephenytoin (2C19), phenytoin (2C19), tolbutamide (2C9), S-warfarin (2C9), ibuprofen (2C9), diclofenac (2C9), and naproxen (2C9). Other substrates of CYP 2C9 and CYP 2C19 include diazepam, clomipramine, amitriptyline, and imipramine (Table 2). Several of the NSAIDs are substrates of CYP 2C, but clinically significant metabolic interactions with negative consequences have not been described involving psychoactive drugs combined with NSAIDs.

Several antidepressants with affinity for CYP 2C (sertraline, fluoxetine, fluvoxamine) appear to have a moderate, although measurable, affinity for the CYP 2C isozymes. The nature of the dose response curves for the NSAIDs may minimize or preclude important interactions unless substantial rises in plasma drug concentration occur. In general, drug interactions are likely to be of significance when a small increase in the concentration of an inhibited drug results in substantially increased pharmacologic effects. This situation characterizes phenytoin, and significant interactions involving this anticonvulsant with fluoxetine have been reported.

CYP 2D6

This is the best characterized of the CYP enzymes. The CYP 2D6 gene locus is on chromosome 22. A genetic polymorphism exists with 7% to 10% of Caucasians inheriting an autosomal recessively transmitted defective allele. Four genotypes can be distinguished: homozygous and heterozygous efficient metabolizers, homozygous poor metabolizers, and ultrarapid metabolizers carrying a duplicated or multiduplicated CYP 2D6 gene. In African Americans, the percentage of poor metabolizers is less, generally between 1% and 4%. Poor metabolizers among Asians are rare. These ethnic differences may explain different dosage requirements of some drugs in different populations.

Poor metabolizers lack sufficient functional enzyme to metabolize the CYP 2D6 substrates listed in Table 3. They can therefore be expected to have higher plasma drug concentrations and prolonged elimination half-lives of these drugs when given in usual doses. The significance of this metabolic defect is that an exaggerated pharmacologic response is possible following standard doses of drugs that are CYP 2D6 substrates.

CYP 2D6 comprises a small percentage of the total P450 content of the liver, about 1.5%, but many useful drugs are specific substrates. Nonpsychiatric drugs metabolized by CYP 2D6 include propranolol (also 1A2 and possibly 2C19), metoprolol, timolol, mexiletine, propafenone (also 1A2 and 3A4), codeine, and dextromethorphan (also 3A4). Several of the newer antidepressants are partially metabolized by CYP 2D6. They include paroxetine, venlafaxine, and fluoxetine. The tertiary amine tricyclic antidepressants are hydroxylated by CYP 2D6.

No inducers of CYP 2D6 have been identified. While CYP 2D6 substrates have shown decreased plasma concentration under conditions of cigarette smoking and barbiturate administration, this is not a laboratory-reproducible phenomenon. Alternative explanations include effects on other enzymes that mediate parallel pathways of elimination, or increases in hepatic blood flow that increase drug clearance.

Several antidepressants, discussed below, are inhibitors of CYP 2D6, but they vary widely in their potency. For example, adding fluoxetine or paroxetine to a drug regimen including desipramine will increase the plasma TCA concentration by interference with the hydroxylation pathway. Fluvoxamine, citalopram, and sertraline in low doses are less likely to exert a similar effect.

CYP 2E

This subfamily of enzymes, with genes localized on chromosome 10, is important in the bioactivation of several carcinogens and the metabolism of organic solvents. Cytochrome 2E1 is the focus of current research for its role in alcohol metabolism. It comprises about 7% of the total P450 content of the human liver. Substrates of CYP 2E1 include chlorzoxazone, acetaminophen, halothane, enflurane, and methoxyflurane. In in vitro studies, significant inhibition of CYP 2E1 occurred with TCAs, phenothiazines, and flurazepam. Although these psychoactive drugs are not substrates for CYP 2E1, they have the potential to modulate the toxicity of nondrug xenobiotics metabolized by this isoenzyme. CYP 2E1 is induced by alcohol, which may be an important factor in its toxicity. CYP 2E1 is an active area of investigation, with limited current relevance, however, for the practice of clinical psychopharmacology.

CYP 3A4

This enzyme metabolizes the largest number of drugs used therapeutically. It constitutes approximately 30% of the P450 present in the liver and 70% of the cytochrome enzymes in the gut wall. There is little evidence for a genetic polymorphism. Everyone possesses CYP 3A4 hepatic enzyme, although there is broad variability in expressed activity among subjects. A study of the metabolism of carbamazepine suggested that CYP 3A4 activity may peak in children and show a gradual decline to adult levels of activity. This would partly account for why older children and adolescents require larger doses of some drugs than adults. The elderly, especially individuals aged 70 and above, show a reduction in overall drug metabolism related to a decrease in CYP content, although comparative rates of decline in specific CYP enzymes are not well characterized.

Nonpsychiatric drugs metabolized by CYP 3A4 include diltiazem, verapamil (also 1A2), nifedipine, alfentanil, tamoxifen, testosterone, cortisol, progesterone, ethinyl estradiol, cisapride, cyclosporine, terfenadine, astemizole, quinidine, and the protease inhibitors (Table 3). Psychoactive drugs that are metabolized by CYP 3A4 include alprazolam, diazepam (also 2C19), triazolam, carbamazepine, nefazodone, and sertraline.

Marked enzyme induction of CYP 3A4 occurs after long-term administration of rifampin and rifabutin. Other inducers include carbamazepine, dexamethasone, and phenobarbital. Significant inhibition of CYP 3A4 substrates occurs after administration of nefazodone, and fluvoxamine. The most potent inhibitors of CYP 3A4 are the azole antifungal drugs (eg, ketoconazole) and the macrolide antibiotics. A recent report of the sudden death of a child receiving pimozide who was treated with clarithromycin is a case of suspected CYP 3A4 inhibition by this antibiotic. Inhibition of terfenadine metabolism by keto- conazole, itraconazole, erythromycin, or clarithromycin poses a risk of cardiotoxicity. The noncardioactive metabolite of terfenadine, carboxyterfenadine, was recently marketed as a nonsedating antihistamine; and either this agent or loratadine is strongly preferred if a psychoactive drug must be prescribed together with an antihistamine. Among the SSRIs, paroxetine, fluoxetine, and sertraline have been specifically combined with terfenadine in vivo pharmacokinetic studies and found not to produce a significant interaction. Fluvoxamine and nefazodone,

among the newer antidepressants, are contraindicated in combination with terfenadine due to their potent CYP 3A4 isoenzyme inhibition.

Glucuronosyltransferases

The recent focus on psychotropic drug interactions has primarily emphasized the Phase I CYP system. The metabolism of drugs by Phase II reactions is accomplished by a variety of enzymes, but the emerging role of the glucuronosyltransferases as important in clinical psychopharmacology is being increasingly recognized. The uridine diphosphate-glucuronosyltransferases exist as multiple families of enzymes and have been defined with a nomenclature similar to that used to define the P450 system. The symbol UGT has been chosen to represent the superfamily of enzymes. Different UGT families are defined as having <45% amino acid sequence homology while in subfamilies there is approximately 60% homology. As many as 33 families have been defined with three families identified in humans. The most important of the enzymes for psychopharmacology are discussed below and listed with prominent substrates in Table 4.

UGT 1A1

The UGT 1A subfamily includes enzymes which can glucuronidate bilirubin, phenol derivatives, and estrogens. UGT 1A1 has been implicated in the metabolism of several opiate analgesics, including buprenorphine, nalorphine, and morphine. Phenobarbital and rifampin have been shown to induce UGT 1A1. Rifampin is also a PGP inducer.

UGT 1A3/1A4

Several tricyclic antidepressants undergo conjugation mediated by UGT 1A3 and UGT 1A4. In addition, chlorpromazine, lamotrigine, cyproheptadine, and zidovudine are substrates. Probenecid and valproate are inhibitors while several anticonvulsants/mood stabilizers are inducers. Olanzapine circulates in plasma to a large extent as a glucuronide conjugate, but the precise UGT enzymes have not been identified.

UGT 2B7

The benzodiazepines metabolized exclusively or primarily by conjugation (oxazepam, tenazepam, lorazepam) are glucuronidated by UGT 2B7 along with some opiate analgesics. A number of the NSAIDS are competitive inhibitors. Phenobarbital, rifampin, and oral contraceptives appear to act as inducers of UGT 2B7.

Specific Drug Interactions

In this section, specific drug interactions are discussed for some of the major psychoactive agents in widespread clinical use. For each drug class, tables are presented that list the medications with which the drugs in the class may interact, how the drugs may interact, and the type of data that support the relevance of the interaction. Guidelines for management are also presented.

While these tables summarize the current state of our knowledge regarding interactions of psychoactive drugs, new agents are being introduced to the market at a rapid pace, and new or suspected interactions are increasingly being described in the biomedical literature each month. Suspected drug interactions generally appear first in the form of clinical case reports. This is frequently the first indication to the physician that two drugs may interact in a previously undescribed manner. The publication of several case reports of a similar nature frequently stimulates further investigation in the form of formal pharmacokinetic studies. Often the period of time between the publication of a previously undescribed drug interaction and subsequent prospective investigation is considerable. Given the importance of case reports to the clinician who must decide whether a particular case represents a sufficiently significant finding to merit a change in prescribing behavior, questions are posed in Table 5 as guidelines for interpretation of reports of suspected drug interactions. Consideration of these issues may be helpful in determining the potential risks or benefits of combining similar drugs.

TCAs

Remarkably, TCAs are still extensively prescribed in some communities. Their generic status, allowing for relatively low cost, is a major factor in their continued prescription. Some significant interactions have been documented, which are summarized in Table 6.

The TCAs are metabolized by several P450 enzymes. CYP 1A2, 2C, and 3A4 are thought to be involved in the demethylation of the TCAs that are administered as tertiary amines (clomipramine, amitriptyline, imipramine). CYP 2D6 is involved in the hydroxylation of the secondary amine TCAs (desipramine, nortriptyline). They are further glucuronidated before being excreted in the urine. While not all TCAs have been carefully scrutinized, it can be expected that, for example, the metabolism of doxepin and trimipramine proceeds in a similar fashion.

Co-administration of the TCAs with MAOIs is contraindicated. Hyperpyretic crises or severe seizures

may occur in patients receiving such combinations. At least 2 weeks should elapse between the discontinuation of an MAOI and the initiation of a TCA.

Cimetidine is a broad CYP enzyme inhibitor and has been documented to increase the plasma concentration of several TCAs. Increased side effects, including anticholinergic-induced delirium, are a possible consequence of cimetidine and other inhibitor-induced concentration elevations. All of the SSRIs have been noted in case reports to increase TCA plasma concentrations. Their relative potency in this regard is discussed in the section below. Whenever an SSRI is prescribed to a patient already receiving a TCA, caution should be exercised and the dose of the TCA reduced if necessary.

Enzyme inducers, including cigarette smoking, carbamazepine, phenobarbital, and phenytoin, can increase the clearance of TCAs and lower their plasma concentration. Thus, in smokers, average TCA doses may be higher than in nonsmokers. Because plasma concentration measurements of the TCAs are widely available, this resource can be used to monitor the effect of adding or eliminating other drugs in a TCA-treated patient.

SSRIs

Drug interactions with the SSRIs have been the subject of intensive study. Five drugs are available for prescribing that vary considerably in their specificity and potency to inhibit various P450 enzymes. It was noted at an early point in the development of the SSRIs that inhibition of CYP enzymes, particularly CYP 2D6 in vitro, was a property of the majority of these drugs. Since their initial clinical use, numerous studies and reports have clarified some differences among these drugs. A summary of the inhibitory potential of the SSRIs and other newer antidepressants is given in Table 7. The estimated potencies are based on a consideration of in vitro evidence, case reports, and formal pharmacokinetic studies. The significance of a predicted interaction in an individual patient may vary widely. A summary of the interactions with the SSRIs is provided in Table 8.

The first SSRI marketed in the US, fluoxetine, is a potent in vitro and in vivo inhibitor of CYP 2D6. It produces an active metabolite with similar potency. The extended elimination half-life of fluoxetine and norfluoxetine means that when CYP 2D6 substrates are combined in treatment (Table 3), their metabolic elimination mediated by this enzyme can be compromised. This effect can lead to higher drug concentrations, an extended elimination half-life, and potentially increased pharmacologic effects. Interactions have been most often documented with TCAs. Fluoxetine also has some inhibitory effects on CYP 2C19, though it is not as potent an inhibitor on this enzyme as it is on CYP 2D6. Its effect on the former enzyme is sufficient to interact with diazepam and phenytoin. These drugs, therefore, should be used cautiously with fluoxetine. Fluoxetine has no recognized inhibitory potential for CYP 1A2 substrates, but its effects on CYP 3A4 are complex. A drug interaction has been noted in a pharmacokinetic study with carbamazepine, a well-documented CYP 3A4 substrate, but fluoxetine appears not to alter the metabolism of terfenadine. Fluoxetine has a potential to interact with CYP 3A4 substrates, especially as its metabolite possesses CYP 3A4 inhibition, but few reports of interactions when combined with such substrates are available.

Paroxetine is also a potent in vivo and in vitro inhibitor of CYP 2D6, and lower doses of drugs that are substrates for the isoenzyme should be used if paroxetine is combined in treatment. Paroxetine has no clinically meaningful effects on other CYP enzymes.

Sertraline is a relatively weak inhibitor of CYP 2D6, CYP 2C19, and CYP 3A4, but when used in the upper range of clinically recommended doses, it may inhibit CYP 2D6 substrates to a significant extent. This effect is inconsistent across patients but should be recognized as a possible interaction when sertraline is prescribed. The drug's effects on tolbutamide, a CYP 2C19 substrate, were documented in a pharmacokinetic study, but clinically significant case reports involving patients are lacking.

Fluvoxamine is the only SSRI that has potent inhibitory effects on the CYP 1A2 enzyme. Interactions are documented with several substrates, including clozapine, TCAs, and theophylline. This last combination requires substantial dosage decreases of the bronchodilator to avoid potential toxicity. Fluvoxamine also inhibits CYP 2C19 and CYP 3A4 to a significant extent, and dosage modifications are recommended for some substrates, such as alprazolam.

Citalopram has been shown in a pharmacokinetic study to raise plasma concentrations of desipramine, a CYP 2D6 substrate. However, its potency as an inhibitor is quite weak, and this SSRI has the least potential to interact with P450 substrates compared to the other drugs in its class. Recently a case was reported of citalopram combined with clomipramine in which the suspected mechanism of increased tricyclic plasma concentration was glucuronostraferase inhibition.

Several drugs can potentially elevate concentrations of the SSRIs. This has not been shown to be a major

concern in clinical practice because patients tolerate a broad range of SSRI plasma concentrations. However, when using cimetidine or another known inhibitor in combination with an SSRI, caution should be exercised.

Other Newer Antidepressants

SJW is one of the most commonly utilized herbal agents. Available data from clinical studies and case reports suggests that SJW is unlikely to inhibit CYP 3A4 or 2D6, but it is likely an inducer of CYP 3A4 and possibly PGP. The accumulating evidence of significant drug interactions with SJW (Table 13) should serve as an example for clinicians to be aware of the potential for herbal products to participate in important herb-drug interactions. Concomitant use of herbal agents and conventional medications should be discouraged until further information is available.

Bupropion is thought to produce its antidepressant effects primarily through enhancement of noradrenergic and perhaps dopaminergic neurotransmission without any appreciable serotonergic effects. These properties should theoretically confer a low propensity to interact pharmacodynamically with other drugs to produce a serotonin syndrome. Bupropion's proconvulsant effects in a small number of patients suggest that it should be combined cautiously with other drugs that may increase the seizure threshold, though the sustained-release form of the drug has reduced this risk. Bupropion is metabolized by multiple pathways and enzymes. Theoretically, CYP 2B1, CYP 2D6, or CYP 3A4 inhibitors could increase its clinical effects, but specific documentation is lacking. Although bupropion and its major metabolite, hydroxybupropion, are not CYP 2D6 substrates, in a healthy volunteer study one or both are potent inhibitors of this enzyme as indicated by a two- to five-fold rise in desipramine plasma concentration. The pharmacokinetic consequences of co-administration of bupropion with other CYP 2D6 substrates have not been published, but caution is advised for this potential interaction. Selected drug-drug interactions related to bupropion are summarized in Table 9.

Nefazodone possesses serotonergic activity as a 5-HT_2 antagonist and a serotonin reuptake inhibitor. The usual precautions involving combinations of drugs resulting in excessive serotonergic activity are warranted for nefazodone. The drug is a very potent CYP 3A4 inhibitor and will theoretically inhibit the metabolism of the relevant substrates listed in Table 3. Specific interactions have been documented with alprazolam and triazolam. Nefazodone increased the plasma concentration of alprazolam twofold and that of triazolam fourfold. Thus, doses of these benzodiazepines should be reduced whenever nefazodone is co-administered or when initiating anxiolytic therapy in the presence of nefazodone. One favorable report used the combination of nefazodone and alprazolam to advantage to lengthen the interdosing interval of the antipanic medication. Nefazodone's drug interactions are summarized in Table 10.

Mirtazapine has multiple effects on serotonergic neurotransmission, acting as a 5-HT_2, 5-HT_3, and presynaptic α_2-receptor antagonist. While mirtazapine is highly metabolized, it apparently possesses insufficient affinity for any of the specific CYP enzymes to be a meaningful metabolic inhibitor. Thus, specific interactions of this type have not been reported. Mirtazapine possesses significant sedative effects, so that in combination with other drugs producing sedation or psychomotor impairment, additive or synergistic effects are possible. Mirtazapine's drug interactions are summarized in Table 11.

Venlafaxine is a structurally novel antidepressant that inhibits norepinephrine and serotonin reuptake, with the latter action being the more potent of the two, and predominant at lower doses. It has a low propensity for drug-drug interactions. While its active metabolite has a measurable CYP 2D6 inhibitory effect, reports of clinically significant metabolic interactions with CYP 2D6 substrates are lacking. It does, however, have the potential to interact pharmacodynamically with potent serotonergic agents, and toxicity has been reported when combined with MAOIs. Venlafaxine's drug interactions are summarized in Table 12.

MAOIs

Interactions of the MAOIs are summarized in Table 14. Some unusual interactions have been reported, including their combination with meperidine or fentanyl to produce an apparent serotonin syndrome. The interactions of MAOIs with the TCAs have already been discussed. The extensive list of medications that these drugs have been reported to interact with has limited their popularity, despite their efficacy for major depression, atypical depression, panic disorder, and other anxiety syndromes.

The most feared interaction of the MAOIs has been the possible hypertensive crisis from combination with tyramine-rich foods or various OTC or prescription sympatho-mimetic amines. This possibility requires the counseling of patients receiving these drugs regarding the potential for diet constituents and OTC medications to interact with MAOIs.

Lithium

Lithium has a very narrow therapeutic range of serum concentration associated with therapeutic effects, above which serious toxicity can occur. Lithium is renally cleared, and drugs and physiologic conditions that influence its renal elimination pose a potential risk to increase serum lithium concentration. Among the commonly used drugs that pose such a risk are thiazide diuretics, NSAIDs, and angiotensin-converting enzyme (ACE) inhibitors. They all increase plasma lithium levels.

Concomitant use of diuretics has long been associated with the development of lithium toxicity, but the risk varies with the type of diuretic. Lithium is completely filtered and then reabsorbed along the proximal renal tubule in parallel with sodium. The thiazide diuretics act distally and produce a natriuresis that leads to an increase in the re-absorption of sodium and lithium. Diuretics that act on the proximal tubule, such as furosemide, have less effect on lithium reabsorption. The degree of these interactions is variable, but a decrease in lithium dosage is almost always necessary, especially in patients receiving a thiazide diuretic.

The osmotic diuretics enhance lithium excretion and have been used in the treatment of lithium toxicity. Potassium-sparing diuretics (triamterene, amiloride, spironolactone) have exerted variable effects on lithium clearance, sometimes increasing its clearance. Theophylline and caffeine decrease lithium concentrations to a significant degree, and dosage adjustments are likely when used together.

When the NSAIDs are used with lithium, plasma concentrations can rise to a toxic level. Because some of these drugs are now available OTC, there is controversy as to whether the lower recommended OTC doses produce as dramatic a change in lithium clearance as prescribed doses. When an NSAID must be used in combination with lithium, aspirin and sulindac are recommended because they exert the least increase, if any, on lithium concentration.

Lithium toxicity has been reported with the concomitant use of ACE inhibitors and valsartan. Case series and formal pharmacokinetic evaluations document the interaction, but the precise mechanism is uncertain. Frequent monitoring of lithium concentration is recommended when these therapies are used together. The calcium channel antagonists diltiazem and verapamil have been associated with lithium toxicity through an unknown mechanism but likely involve changes in lithium's renal clearance. These combinations require close monitoring. The continued development of anticonvulsant mood stabilizers for treatment of bipolar disorder means that some patients will

receive these drugs in combination with lithium. Topiramate transiently decreased lithium concentrations when added to a lithium regimen in healthy volunteers. A similar effect in patients has not yet been reported, but closer monitoring of lithium serum concentration appears warranted when these drugs are used together. Drug-drug interactions of lithium are summarized in Table 15 .

Other Mood Stabilizers

Carbamazepine is both a substrate of CYP 3A4 and an inducer. These characteristics account for the autoinduction and decrease in its plasma concentration observed several weeks following initiation of dosing. As a CYP 3A4 substrate, carbamazepine's clearance and plasma concentration are subject to change in the presence of inhibitors, including valproate, nefazodone, cimetidine, and others. Erythromycin can significantly increase carbamazepine concentration and produce signs of toxicity. These commonly include confusion, sedation, and ataxia. Should these appear, dosage should be decreased and plasma drug concentration should be assessed for subsequent monitoring. Valproate is often combined with carbamazepine and it may slightly impair carbamazepine clearance; carbamazepine may decrease valproate concentration. This situation requires plasma concentration monitoring of both drugs to avoid excessive concentration changes, and therefore guides dosing. Carbamazepine added to a regimen of lamotrigine decreased the latter's plasma concentration by 40%, but lamotrigine had no effect on carbamazepine concentration. The concentration of carbamazepine epoxide was increased in one study, so plasma concentration monitoring is recommended if these drugs are used concurrently. Carbamazepine and gabapentin do not affect each other's disposition.

Carbamazepine has been reported to decrease the concentration of other CYP 3A4 substrates as a result of its enzyme-inducing effects. Some dosage adjustments may be necessary. A significant interaction is the well-described effect on diminishing the concentration of oral contraceptives. These interactions are summarized in Table 16.

Oxcarbazepine is structurally related to carbamazepine and appears to be as effective as carbamazepine in the treatment of epilepsy and slightly better tolerated. Thus, it may find utility as a mood stabilizer as an alternative to carbamazepine. It appears to possess does-dependent enzyme induction, like carbamazepine, and may participate in a variety of similar drug interactions (Table 17).

Valproate's interactions (see Table 18) result from mild enzyme inhibition and the additional capacity to displace other drugs from their plasma protein-binding sites. Caution is warranted when combining valproate with aspirin, because the free fraction of valproate may increase dramatically (see Figure 3). This may not be reflected by an increased measurement of total drug concentration in plasma. In turn, valproate may increase the anticoagulant effects of aspirin.

The precise interactions between valproate and specific CYP isozymes are unclear. It inhibits glucuronosyl transferase, as evidenced by an effect on zidovudine and lorazepam, as well as producing apparent inhibitory effects on substrates of CYP 2C9 and CYP 2C19 (phenytoin and diazepam). Its interactions with other mood stabilizers are complex. An interaction with phenytoin may result from both a metabolic inhibition and an increased concentration of unbound phenytoin but without an apparent increase in total drug concentration. When lamotrigine was added to existing valproate therapy, valproate concentrations decreased by 25%. When valproate was added to lamotrigine therapy, lamotrigine concentrations increased twofold. These changes suggest that close monitoring of combined mood stabilizer therapy is necessary to optimize treatment and avoid adverse effects. Gabapentin pharmacokinetic parameters are unaffected by valproate.

Lamotrigine is metabolized predominantly by conjugation with glucuronic acid, a Phase II metabolic process by 1A4, with little or no involvement of CYP enzymes. The drug has not been reported to affect CYP enzymes. Its interactions have only been systematically studied with the common anticonvulsants. With the exception of valproate, the addition of lamotrigine to other mood stabilizers does not affect their steady-state plasma concentration. No significant effect was noted after the addition of lamotrigine to regimens of phenytoin or carbamazepine. As noted above, lamotrigine decreased valproate concentration. Phenytoin and carbamazepine decrease and valproate increases concentrations of lamotrigine. Lamotrigine is approximately 55% bound to human plasma proteins, so drug interactions secondary to binding displacement are not expected. No clinical value has yet been shown from monitoring plasma concentrations of lamotrigine. Its potential interactions with other drugs should be monitored by close clinical observation. The drug interacions of lamotrigine are summarized in Table 19.

Topiramate is an anticonvulsant with possible mood-stabilizing effects. When combined with other anticonvulsants, such as carbamazepine, phenobarbital, or primodone, topiramate has no effect on their concentrations. Nor does it have clinically relevant effects on plasma levels of classical neuroleptics, TCAs, theophylline, and Coumadin. However, concomitant use of this compound with CNS depressants can cause excessive sedation. When combined with acetazolamide or other carbonic anhydrase inhibitors, it can increase the risk of renal stones. Also, topiramate can interfere with the efficacy of contraceptive medication by decreasing levels of ethiny estradiol by one third (Table 20).

Gabapentin has been reported to have mood stabilizing effects and to be effective for social phobia. Gabapentin is not metabolized by the liver, and has no significant pharmacokinetic interactions. Its elimination is reduced in patients with impaired renal functions. Gabapentin does not interact with hepatic enzymes, causing neither inhibition nor induction of these enzymes.

Psychostimulants

The psychostimulants methyl-phenidate, dextroamphetamine, and pemoline are among the most common medications used in child and adolescent psychiatry and are often used in combination with other medications. A variety of case reports describe suspected metabolic drug interactions, but sparse data from systematic study are available. Methylphenidate appears to be involved primarily in pharmacokinetic interactions suggestive of CYP inhibition, while dextroamphetamine and pemoline are more often involved in apparent pharmacodynamic interactions. Selected interactions are summarized in Table 21.

Methylphenidate is highly metabolized but the specific enzymes involved have not been characterized. A PK study observing methylphenidate concentration with and without quinidine found no evidence for the involvement of CYP 2D6 in its metabolism. Methylphenidate plasma concentration monitoring is seldom practiced clinically. The drug's reported interactions all involve the effect of methylphenidate on the disposition of other drugs. No reports have been published that document alterations in methylphenidate concentration. Potential drug interactions should be monitored by careful patient observation of signs and symptoms suggestive of enhanced or diminished effects.

Modafinil is a recently introduced psychostimulant labeled for the treatment of narcolepsy. It may find use as a treatment for ADHD and other conditions. In vitro examination of its enzyme inductive/inhibitory effects has found little evidence for potential drug interactions (Table 22).

Anxiolytics/Hypnotics

The drugs used as anxiolytics are primarily the benzodiazepines and buspirone. The benzodiazepines zolpidem and zaleplon are used as hypnotics. Their interactions are summarized in Tables 23, 24, and 25. The benzodiazepines increase the sedative and CNS-depressive effects of other drugs. Some metabolic interactions have been documented; eg, alprazolam and diazepam concentrations increased when co-administered with CYP 3A4 inhibitor/antidepressants—nefazodone, fluoxetine, and fluvoxamine. Dosage adjustments are necessary to avoid excessive effects. These interactions usually present clinically as an exaggeration of the expected pharmacologic effects (Table 26).

Zaleplon is a hypnotic agent indicated for the short-term management of insomnia. It is metabolized by CYP 3A4 with a short half life of an hour. It has been shown to lack any pharamokinetic interaction with digoxin, ibuprofen or thioridazine; however it had an additive pharacodynamic effect with thioridazine on psychomotor testing. The short half-life of zaleplon should preclude most clinically significant interactions with CYP 3A4 inhibitors. Considerations that apply to zolpidem influence by CYP 3A4 inducers and inhibitors shoud also apply to zaleplon. In combination with alcohol or other CNS depressants, enhanced residual effects should be kept in mind.

Antipsychotic Agents

Drug interactions involving the conventional and atypical antipsychotics are summarized in Tables 25-31. These are all highly metabolized drugs producing multiple metabolites. The specific oxidizing enzymes for the metabolism of haloperidol and the atypical drugs have been reported, but fewer data are available for the older conventional drugs from which to predict drug-drug interactions. Hence, the interactions of the phenothiazines are grouped together while haloperidol and the newer drugs are considered separately.

Numerous drug interactions have been reported with the conventional antipsychotics. Antacids and anticholinergics may reduce their absorption. Formal pharmacokinetic studies have revealed mutual metabolic interactions with the TCAs, but dosage adjustments as a result are rarely considered in clinical practice. As these drugs are likely metabolized by several P450 enzymes, broad enzyme inducers such as barbiturates and inhibitors such as cimetidine predictably lead to altered plasma concentrations in the expected direction.

The metabolism of haloperidol has been studied for more than 30 years. One metabolite, reduced haloperidol, possesses 10% to 20% of the pharmacologic activity of haloperidol. The interconversion of haloperidol with its metabolite was initially hypothesized to involve CYP 2D6 based on evidence that haloperidol is apparently a CYP 2D6 inhibitor. Subsequent studies with poor and extensive CYP 2D6 metabolizers have failed to confirm evidence for CYP 2D6 involvement. There is more substantial evidence of CYP 3A4 and CYP 1A2 involvement in the metabolism of haloperidol. Rifampin, a potent CYP 3A4 inducer, decreases the concentration of haloperidol, as does carbamazepine. Nefazodone increases its concentration, as do fluoxetine and fluvoxamine, agents with CYP 3A4 inhibitory effects. Reduced haloperidol has recently been shown to be a potent CYP 2D6 inhibitor, which suggests a basis for interactions of haloperidol and CYP 2D6 substrates. Although long known to cause dose-related QTc interval prolongation, the package insert of Mellaril (thioridazine) was recently changed to reflect warnings that the CYP 2D6-mediated metabolism of thioridazine results in elevated drug plasma concentrations in patients with CYP 2D6 deficiency or in patients receiving drugs that potently inhibit CYP 2D6. Thioridazine is now contraindicated by its manufacturer with certain other drugs, including fluvoxamine, propranolol, pindolol, and any drug that inhibits CYP 2D6 (paroxetine, fluoxetine, quiaidine).

Clozapine was the first atypical antipsychotic marketed in the US. It undergoes extensive hepatic metabolism to over 10 metabolites in humans. Multiple CYP enzymes are involved in its metabolism; however, two prominent enzymes are CYP 1A2 and CYP 3A4. There is less evidence for involvement of CYP 2D6. Clozapine disposition was found to co-vary with CYP 1A2 activity, and fluvoxamine has caused robust increases in clozapine and desmethylclozapine plasma concentrations. Sertraline, paroxetine, and fluoxetine have been reported to increase plasma concentrations of clozapine. Reports are available in which co-administration of erythromycin, a relatively specific inhibitor of CYP 3A4, resulted in significant increase in clozapine concentration. Additionally, co-administration of clozapine with carbamazepine and rifampin has been shown to diminish clozapine concentration. Because the plasma concentration of clozapine has been related to its antipsychotic effect in more than six controlled studies, concomitant use with inducers or inhibitors should be accompanied by plasma concentration and clinical monitoring.

Risperidone produces a pharmacologically active metabolite, 9-hydroxy-risperidone, mediated by the actions of CYP 2D6. Its formation is highly correlated with the patient's phenotype. Combining risperidone and its metabolite in poor or extensive CYP 2D6 metab-

olizers did not affect the overall pharmacologic effects. These findings suggest that CYP 2D6 inhibitors will interact to alter the plasma concentration of risperidone but its effects may be unchanged. No routine dosage adjustments are recommended for co-administration of risperidone with CYP 2D6 inhibitors. An interaction with carbamazepine has been reported by the manufacturer, but confirmatory reports of patient complications are lacking. Risperidone's metabolism is mediated to a minor degree by CYP 3A4. Drugs that induce/inhibit CYP 3A4 may alter risperidone plasma concentrations but the clinical significance of such interactions appears to be minimal. Multiple studies and case reports document a lack of significant problems when combining risperidone with SSRIs. Overall, risperidone appears to have a relatively benign drug interaction profile.

Olanzapine undergoes extensive hepatic metabolism with at least 10 metabolites identified. Principal enzymatic pathways involve CYP 1A2 and glucuronidation. Although plasma concentration monitoring of olanzapine is not a routine clinical procedure, preliminary data suggest that plasma concentrations may predict clinical response. Theoretical drug interactions with olanzapine can be proposed, but few actual reports are available.

In vitro studies indicate that CYP 3A4 is the primary enzyme involved in the metabolism of quetiapine. A lesser role has been found for CYP 2D6. Co-administration of the CYP 3A4 inducer phenytoin resulted in a fivefold increase in the clearance of quetiapine; however, co-administration of cimetidine did not significantly affect its steady-state concentration. Unexpectedly, thioridazine, which is regarded as a CYP 2D6 inhibitor, decreased the concentration of quetiapine. Other interactions are theoretical involving CYP 3A4 inducers or inhibitors. Because the plasma concentration of quetiapine has not been reported to be correlated with clinical responses, monitoring cannot be recommended at the present time.

Ziprasidone has been introduced for oral administration as an antipsychotic. Its major routes of elimination include metabolism by a non-P450 enzyme, aldehyde oxidase, CYP 3A4 and CYP 1A2 oxidation. Ziprasidone had little in vitro inhibitory effects on the major P450 enzymes and would be expected to participate in hew pharacokinetc interactions (Table 32).

Cholinesterase Inhibitors

There are currently three cholinesterase inhibitors available for the treatment of Alzheimer disease (AD), donepezil, tacrine, and rivastrigmine. These drugs work by enhancing cholinergic function, and are based on

theories that some AD symptoms are due to a deficiency in cholinergic neurotransmission. Due to this mechanism of action, these drugs will interfere with and be counteracted by the activity of any anticholinergic medications, and this combination should therefore be avoided. Similarly, a synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents, or cholinergic agonists such as bethanechol. They are, therefore, likely to exaggerate succinylcholine-type muscle relaxation during anesthesia, and a clinically appropriate washout period is recommended. No in vivo clinical trials have investigated the effect of donepezil on the clearance of cisapride, terfenadine (CYP 3A3/4), or CYP 2D6 substrates. However, in vitro studies show a low rate of binding to these enzymes, which indicates little likelihood of interference. Ketoconazole and quinidine, inhibitors of CYP 450, 3A4, and 2D6, respectively, inhibit donepezil metabolism in vitro. Whether there is a clinical effect is unknown. Inducers of CYP 2D6 and CYP 3A4 (eg, phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of donepezil.

Co-administration of tacrine with theophylline increases theophylline plasma concentrations via competition with CYP 1A2. Theophylline concentration levels should therefore be monitored upon co-administration, and the dose of theophylline should be reduced as necessary. Formal interaction studies suggest that donepezil does not have a significant interaction with digoxin, warfarin, theophylline, and cimetidine. Rivastigmine is minimally metabolized by CYP enzymes, has low protein binding, a short plasma half-life, and a relatively short duration of action. Combination with a variety of drugs has not revealed any significant pattern of pharmacodynamic drug interactions. Rivastigmine is not thought to have CYP drug interactions. No pharmacokinetic interactions were apparent with diazepam, digoxin, fluoxetine, or warfarin. Selected drug interactions related to the cholinesterase inhibitors used in the treatment of AD are summarized in Table 33.

Anorectic/Anti-Obesity Agents

The anorectic agents should not be administered with MAOIs. It is advised to wait 14 days following the administration of an MAOI to take these drugs.

Phentermine may decrease the hypotensive effect of adrenergic neuron-blocking drugs such as guanethidine. Combination with phentermine may result in overstimulation, restlessness, dizziness, insomnia, or

tremors at some doses. Phentermine may alter insulin requirements for patients with diabetes mellitus. Related drug interactions are highlighted in Table 34.

Sibutramine, a newer anorectic agent that works as a sympathomimetic amine, is expected to have side effects similar to other anorectic agents. It has potential for causing hypertension, should not be combined with MAOIs, and may cause serotonin syndrome when combined with SSRIs.

Orlistat, a new selective inhibitor of GI lipases, reduces dietary fat absorption and could potentially interfere with the absorption of co-administered drugs. It has been shown not to affect the absorption of oral contraceptives, nifedipine, atenolol, furosemide, captopril, phenytoin, warfarin, and vitamin A. It did significantly reduce the absorption of vitamin E, which is taken by some patients for treatment of movement disorders. The effects, if any, on absorption of other drugs taken for psychotropic effects has not been reported.

Methadone

Methadone is a synthetic opiate agonist that is used in psychiatry primarily in the detoxification and maintenance treatment of opiate addiction as well as in chronic pain management programs. Despite the therapeutic use of methadone for nearly 50 years, details of its pharmacokinetics are incomplete. Consequently, regimens for methadone are often empirical, titrating dosage against clinical response. Methadone appears to be metabolized extensively by CYP 3A4 and secondarily by CYP 2D6. Methadone is a mild in vitro inhibitor of CYP 2D6, which explains its ability to increase desipramine plasma concentration. It has also blocked nifedipine oxidation, a CYP 3A4 pathway in vitro, but case reports of methadone inhibiting CYP 3A4 substrates are lacking. Fluvoxamine, more potently than fluoxetine, increased methadone plasma concentration when added to chronic therapy. Thus any CYP 3A4 inhibitors should be used with caution in patients treated with methadone. Table 35 lists selected methadone interactions.

Conclusions

Clinicians need to be alert for possible interactions in patients using multiple drugs. Many drug interactions probably cause subtle effects that are not recognized clinically. Most drug interactions are not life-threatening. Nevertheless, some interactions cause side effects that interfere with compliance, or cause decrease in drug efficacy. Whatever their consequences, drug-drug interactions represent a major public health concern. Preventable drug therapy problems increase medical costs by nearly $100 billion annually, and about 20% of that additional cost is attributed to drug-drug interactions.

Much of the emphasis on drug interactions focuses on the CYP system. The importance of other factors as determinants of plasma drug concentrations is underscored by findings involving serum protein binding and extrahepatic drug disposition. For example, serum a-1-acid glycoprotein, a serum protein to which drugs bind, fluctuates in various disorders. It is elevated in depression, arthritis, and autoimmune disorders. These elevated levels alter the disposition and actions of highly bound drugs, such as the TCAs and the SSRIs. The lungs have also been found to function as a reservoir for drugs with high affinity for the serotonin transporter. Another agent may displace an antidepressant that has accumulated in the lungs with a resultant increase in plasma concentrations and possible toxicity.

No discussion of potential psychotropic drug interactions can be all-inclusive. Current understanding of the variables that contribute to drug pharmacokinetics and pharmacogenetics is incomplete, and no interactions can be predicted or ruled out with absolute certainty. Drugs known to be potent enzyme inhibitors may fail to produce a predicted interaction, while a supposedly "clean" drug can cause a fatal interaction. New information emerges daily. Readers are encouraged to supplement this article with other sources and to be familiar with drug interactions listed in product information sheets included in the package of each drug they prescribe.

Bibliography

1. Akula SK, Rege AB, Dreisbach AW, Dejace PM, Lertora JJ. Valproic acid increases cerebrospinal fluid zidovudine levels in a patient with AIDS. *Am J Med Sci.* 1997;313: 244-246.
2. Apseloff G, Wilner KD, Gerber N, Tremaine LM. Effect of sertraline on protein binding of warfarin. *Clin Pharmacokinet.* 1997;32(suppl 1):37-42.
3. Barbhaya RH, Shukla UA, Kroboth PD, Greene DS. Co-administration of nefazodone and benzodiazepines: a pharmacokinetic interaction study with triazolam. *J Clin Psychopharmacol.* 1995;15:320-326.
4. Bergstorm RF, Goldberg MJ, Cerimele BJ, Hatcher BL. Assessment of the potential for pharmacokinetic interaction between fluoxetine and terfenadine. *Clin Pharmacol Ther.* 1997;62:643-651.
5. Bergstrom RF, Peyton AL, Lemberger L, et al. Quantification and mechanism of the fluoxetine and tricyclic antidepressant interaction. *Clin Pharmacol Ther.* 1992;51:239-248.
6. Bertz RJ, Granneman GR. Use of in vitro and in vivo data to estimate the likelihood of metabolic pharmacokinetic interactions. *Clin Pharmacokinet.* 1997;32:210-258.
7. Brosen K. Recent developments in hepatic drug oxidation: implications for clinical pharmacokinetics. *Clin Pharmacokinet.* 1990;18:220-239.
8. Cumy SH, DeVane CL, Wolfe MM. Cimetidine interactions with amitriptyline. *Eur J Clin Pharmacol.* 1985;29:429-433.
9. DeVane CL. Principles of pharmacokinetics and pharmacodynamics. In: Schatzberg AF, Nemeroff CB, eds. *Textbook of Psychophamacology.* 2nd ed. New York, NY: APA Press. 1998:155-169.
10. DeVane CL. Clinical implications of dose-dependent cytochrome P450 drug-drug interactions with antidepressants. *Hum Psychopharmacol.* 1998;13:329-336.
11. Edge SC, Markowitz JS, DeVane CL. Clozapine drug-drug interactions: a review of the literature. *Hum Psychopharmacol.* 1997;12:5-20.

12. Ereshefsky L, Riesenman C, Lam YW. Antidepressant drug interactions and the cytochrome P450 system: the role of cytochrome P450 2D6. *Clin Pharmacokinet.* 1995;29(suppl 1):10-19.
13. Finley PR, Warner MD, Peabody CA. Clinical relevance of drug interactions with lithium. *Clin Pharmacokinet.* 1995;29:172-191.
14. Flockhart DA, Richard E, Woosley RL, Pearle PL, Drici MD. A metabolic interaction between clarithromycin and pimozide may result in cardiac toxicity [abstract]. *Clin Pharmacol Ther.* 1996;59:189.
15. Greene DS, Salazar DE, Dockers RC, Kroboth P, Barbhaya RH. Coadministration of nefazodone and benzodiazepines: III. A pharmacokinetic interaction study with alprazam. *J Clin Psychopharmacol.* 1995;15:399-408.
16. Ketter TA, Callahan AM, Post R. Nefazodone relief of alprazolam interdose dysphoria: a potential therapeutic benefit of 3A3/4 inhibition [letter]. *J Clin Psychiatry.* 1996;57:307.
17. Ketter TA, Flockhart DA, Post RM, et al. The emerging role of cytochrome P450 3A in psychopharmacology. *J Clin Psychopharmacol.* 1995;15:387-398.
18. Korinthenberg R, Haug C, Hannak D. The metabolism of carbamazepine to CBZ-10,11 epoxide in children from the newborn age to adolescence. *Neuropediatrics.* 1994;25:214-216.
19. Martin DE, Zussman BD, Everitt DE, Benincosa LJ, Etheredge RC, Jorkasky DK. Paroxetine does not affect the cardiac safety and pharmacokinetics of trefenadine in healthy adult men. *J Clin Psychopharmacol.* 1997;17:451-459.
20. Maynard GL, Soni P. Thioridazine interferences with imipramine metabolism and measurement. *Ther Drug Monitor.* 1996;18:729-731.
21. McCarthy R. Seizure following smoking cessation in a clozapine responder. *Pharmacopsychiatry* 1994;27:210-211.
22. Nemeroff CB, DeVane CL, Pollock BG. Newer antidepressants and the cytochrome P450 system. *Am J Psychiatry.* 1996;153:311-320.
23. Owen JR, Nemeroff CB. New antidepressants and the cytochrome P450 system: focus on venlafaxine, nefazodone, and mirtazapine. *Depress Anxiety.* 1998;7(suppl 1):24-32.
24. Preskorn SH, Alderman J, Chung M, et al. Pharmacokinetics of desipramine co-administered with sertraline or fluoxetine. *J Clin Psychopharmacol.* 1994;14:90-98.
25. Rau SE, Bend JR, Arnold MO, Tran LT, Spence JD, Bailey DG. Grapefruit juice—terfenadine single-dose interaction: magnitude, mechanism, and relevance. *Clin Pharmacol Ther.* 1997;61:401-409.
26. Spina E, Pisani F, Perucca E. Clinically significant pharmacokinetic drug interactions with carbamazepine: an update. *Clin Pharmacokinet.* 1996;31:198-214.
27. Sporer KA. The serotonin syndrome: implicated drugs, pathophysiology and management. *Drug Safety.* 1995;13:94-104.
28. Suhara T, Sudo Y, Yoshida K, et al. Lung as reservoir for antidepressants in pharmacokinetic drug interactions. *Lancet.* 1998;351:332-335.
29. von Moltke LL, Greenblatt DJ, Cotreau-Bibbo MM, et al. Inhibition of desipramine hydroxylation in vitro by serotonin-reuptake inhibitor antidepressants, and by quinidine and ketoconazole: a model system to predict drug interactions in vivo. *J Pharmacol Exp Ther.* 1994;268:1278-1283.
30. Wilkinson GR. Plasma and tissue binding considerations in drug disposition. *Drug Metab Rev.* 1983;14:427.
31. Wong SL, Cavanaugh J, Shi H, Awni WM, Granneman GR. Effects of divalproex sodium on amitriptyline and nortriptyline pharmacokinetics. *Clin Pharmacol Ther.* 1996;60:48-53.
32. Wrighton SA, Stevens JC. The human hepatic cytochromes P450 involved in drug metabolism. *Crit Rev Toxicol.* 1992;22:1-21.
33. Chang TKH, Weber GF, Crespi CL, Waxman DJ. Differential activation of cyclophoshamide and ifosphamide by cytochromes P450 2B and 3A in human liver microsomes. *Can Res.* 1993;53;5629-5637.
34. Liston HL, Markowitz J, DeVane CL. Drug glucuronidation and its implications in clinical psychopharmacology. Submitted.
35. Miners JO, Mackenzie PI. Drug glucuronidation in humans. *Pharmacol Ther.* 1991;51:347-69.
36. Green MD, Tephley TR. Glucuronidation of amine substrates by purified and expressed UDP-glucuronosylstransferase proteins. *Drug Metab Disp.* 1998;26:860-867.
37. Greenblatt DJ, von Moltke LL, Harmatz JS, et al. Kinetic and dynamic interaction study of zolpidem with ketoconazole, itraconazole, and fluconazole. *Clin Pharmacol Ther.* 1998;64:661-671.
38. Hartman D, Guzelhan C, Zuiderwijk PB, Odink J. Lack of interaction between orlistat and oral contraceptives. *Eur J Clin Phamacol.* 1996;50:421-424.
39. Weber C, Tam YK, Schmidke-Schrezenmeier G, Jonkmann JH, van Brummelen P. Effect of the lipase inhibitor orlistat on the pharmacokinetics of four different antihypertensive drugs in healthy volunteers. *J Clin Pharmacol.* 1996;51:87-90.
40. Melia AT, Mulligan TE, Zhi J. Lack of effect of orlistat on the bioavailability of a single dose of nifedipine extended-release tablets in healthy volunteers. *J Clin Pharmacol.* 1996;36:352-355.
41. Zhi J, Melia AT, Guerciolini R, et al. The effect of orlistat on the pharmacokinetics and pharmacodynamics of warfarin in healthy volunteers. *J Clin Pharmacol.* 1996;36:659-666.
42. Melia AT, Mulligan TE, ZHi J. The effect of orlistat on the pharmacokinetics of phenytoin in healthy volunteers. *J Clin Phamacol.* 1996;36:654-658.
43. Melia AT, Koss-Twardy SG, Zhi J. The effect of orlistat, an inhibitor of dietary fat absorption, on the absorption of vitamin A and E in healthy volunteers. *J Clin Pharmacol.* 1996;647-653.
44. Haffen E, Vandel P, Bgonin B, Vandel S. Citalopram pharmacokinetic interaction with clomipramine. UDP-glucuronosyltransferase inhibition? A case report. *Therapie.* 1999:54:767-770.
45. Johne A, Brockmoller J, Bauer S, Maurer A, Langheinrich M, Roots I. Pharmacokinetic interaction of digoxin with an herbal extract from St. John's wort (hypericum perforatum) *Clin Pharmacol Ther.* 1999;66:338-345.
46. Piscitelli SC, Burstein AH, Chaitt D, Alfaro RM, Falloon J. Indinavir concentrations and St John's wort. *Lancet.* 2000;355(9203):547-548.
47. Nebel A, Schneider BJ, Baker RK, Kroll DJ. Potential metabolic interaction between St. John's wort and theophyline. *Ann Pharmacotherapy.* 1999;33:502.
48. Ruschitzka F, Meier PJ, Turina M, Luscher TF, Noll G. Acute heart transplant rejection due to St. John's wort. *Lancet.* 2000;355(9203):548-549.
49. Markowitz JS, DeVane CL, Boulton DW, Carson SW, Nahas Z, Risch SC. Effect of St. John's wort (hypericum perforatum) on cytochrome P450 2D6 and 3A4 activity in healthy volunteers. *Life Sciences.* 2000;66:133-139.

Table 1
Recent Developments Relevant to Psychotropic Drug Interactions

Recent Developments/New Data	Comment
Introduction of modafinil, oxcarbazepine, and ziprasidone	See tables 17, 22, and 32
Introduction of rivastigmine	Low potential for pharmacodynamic interactions; not thought to have any P450 drug interactions.
Boxed warning added to labeling for thioridazine	Thioridazine contraindicated with certain drugs which are CYP inhibitors
COX-2 inhibitor (celecoxib) also raises lithium concentration	Vigilance of lithium monitoring needed for most NSAIDS
Potent CYP2D6 inhibition by haloperidol's principal metabolite	Further documentation of the complexity of haloperidol's metabolic effects and need for monitoring of this drug
Olanzapine's glucuronidation pathway subject to inhibition by probenecid in volunteers	No documentation of clinical significance
Zolpidem and triazolam metabolism inhibited by ritonavir	Further documentation of the multiple interactions of protease inhibitors
Removal from the market of three drugs with significant potential cardiotoxcity in interactions accomplished (cisapride, astermizole, terfenadine)	Therapeutic alternatives available

Table 2
Major Psychotropic Drugs by Generic and Trade Names

Generic Name	*Trade Name*
ANTIDEPRESSANTS	
Fluoxetine	Prozac
Paroxetine	Paxil
Sertraline	Zoloft
Fluvoxamine	Luvox
Citalopram	Celexa
Desipramine	Norpramin and others
Imipramine	Tofranil and others
Nortriptyline	Pamelor
Doxepin	Sinequan and others
Clomipramine	Anafranil
Phenelzine	Nardil
Tranylcypromine	Parnate
Bupropion	Wellbutrin
Venlafaxine	Effexor
Nefazodone	Serzone
Mirtazapine	Remeron
Amitriptyline	Elavil
Trimipramine	Surmontil
MOOD STABILIZING AGENTS	
Carbamazepine	Tegretol
Valproate	Depakote, Depakene
Lamotrigine	Lamictal
Gabapentin	Neurontin
Topiramate	Topamax
Oxcarbazepine	Trileptal
PSYCHOSTIMULANTS	
Methylphenidate	Ritalin
Dextroamphetamine	Dexedrine and others
Pemoline	Cylert
Amphetamine salts	Adderall
Modafinil	Provigal
ANTI-ANXIETY/HYPNOTIC AGENTS	
Alprazolam	Xanax
Diazepam	Valium
Chlordiazepoxide	Librium
Buspirone	BuSpar
Lorazepam	Ativan
Triazolam	Halcion
Clonazepam	Klonopin
Zolpidem	Ambien
Zaleplon	Sonata
ANTIPSYCHOTICS	
Mesoridazine	Serentil
Thioridazine	Mellaril
Molindone	Moban
Chlorpromazine	Thorazine
Thiothixene	Navane
Haloperidol	Haldol
Clozapine	Clozaril
Olanzapine	Zyprexa
Quetiapine	Seroquel
Risperidone	Risperdal
Ziprasidone	Geodon
CHOLINESTERASE INHIBITORS	
Tacrine	Cognex
Donepezil	Aricept
Rivastigmine	Exelon
ANORECTIC/ANTI-OBESITY AGENTS	
Phentermine	Ionamin
Sibutramine	Meridia
Orlistat	Xenical
DETOXIFICATION AGENTS	
Methadone	Dolophine

Table 3
Selected Drugs with Oxidative Metabolism Associated with P450 Enzymes

CYP Enzyme	Substrates
1A2	Acetaminophen,* amitriptyline,* caffeine, clomipramine,* clozapine,* cyclobenzaprine, estradiol, fluvoxamine, haloperidol,* imipramine,* naproxen,* olanzapine,* ondansetron, phenacetin, propafenone,* propranolol,* R-warfarin, tacrine, theophylline,* verapamil,*
2C9	Dapsone, diclofenac, fluvastatin, glipizide, ibuprofen, indomethacin, irbesartan, losartan,* naproxen, piroxicam, S-warfarin, rosiglitazone, tamoxifen, tenoxicam, tolbutamine
2C19	Amitriptyline,* citalopram,* clomipramine,* cyclophosphamide, diazepam,* imipramine,* indomethacin, mephenytoin, moclobemide, omeprazole, phenytoin, propranolol,* tolbutamide
2D6	Alprenolol, amitriptyline,* amphetamine, carvedilol, chlorpheniramine, clomipramine,* codeine,* desipramine,* dextromethorphan,* encainide, fluoxetine,* haloperidol,* imipramine,* indoramin, metoprolol, nortriptyline, ondansetron,* oxycodone, paroxetine, perphenazine, propranolol,* propafenone,* risperidone, tamoxifen, thioridazine, timolol, tramadol
3A4	Alfentanil, alprazolam, amiodarone, antibiotics, atrovastatin, buspirone, carbamazepine, chlorpheniramine, clarithromycin, codeine, colchicine, cortisol, cyclophosphamide,* cyclosporine, dextromethorphan, diazepam,* diltiazem, erythromycin, estradiol, felodipine, haloperidol,* indinavir, lidocaine, lovastatin, macrolide, methadone,* metoprolol,* mexilitene,* midazolam, nefazodone, nelfinavir, nicardipine, nifedipine, nitrendipine, paclitaxel, pimozide, progesterone, propafenone,* quinidine, ritonavir, saquinavir, sertraline,* sildenafil,* simvastatin, tacrolimus, tamoxifen, testosterone, timolol,* trazodone, triazolam, verapamil,* vinblastine, zaleplon, zolpidem

*More than one P450 enzyme is known to be involved in the metabolism of these drugs.

CYP=cytochrome P450.

Table 4
Selected Drugs with Conjugative Metabolism Associated with Glucuronosyltransferase Enzymes

UGT Enzyme	Substrates
1A1	Buprenorphrine, morphine, nalorphine, naltrexone
1A3	Amitriptyline, chlorpromazine, clozapine, cyproheptadine, doxepin, imipramine, loxapine, morphine, valproate
1A4	Amitriptyline, chlorpromazine, clozapine, cyproheptadine, doxepin, imipramine, lamotrigine, olanzapine
2B7	Buprenorphine, codeine, dihydrocodeine, lorazepam, morphine, oxazepam, temazepam, valproate

UGT=glucuronosyltransferase.
DeVane CL, Nemeroff CB. *Primary Psychiatry*. Vol 7, No 10. 2000.

Table 5
Questions/Issues to Consider in Interpreting Case Reports of Suspected Drug Interactions

Drug Factors

1. Note the doses used of each drug involved in a suspected interaction. Were the doses in the usual range used therapeutically or higher than the median doses?
2. If plasma concentrations were reported, were the drugs taken long enough to be a presumed steady-state concentration and were the samples collected at an appropriate time? Were any active metabolites reported in the analytical results? Are reported concentrations in the range expected from usual doses?
3. Were multiple drugs involved beyond the ones purported to interact?
4. Could adverse events from a single drug be separated from the consequences of a drug interaction?

Patient Factors

1. Were the patients described as medically ill or unstable?
2. Could compliance with the dosage regimen be assured for inpatients or outpatients?
3. Is the age, gender, or ethnic background of the patient relevant to drug-induced effects?
4. Are other substances relevant, such as alcohol, nicotine, caffeine, drugs of abuse?

Table 6
TCA Drug Interactions

Drug	Interaction	Mechanism/ Source of Data	Management
SSRI	Increased TCA concentration; possible increased therapeutic and/or adverse effects	PD, PK, 1	Monitor TCA concentration, decrease dose as needed
MAOI	Fatal reaction possible	PD, 1	Contraindicated in combination, allow 2 weeks after MAOI before a TCA
Phenothiazines, haloperidol	Increased TCA concentration	PK, 1	Monitor plasma concentration, mutual mutual metabolic inhibition may occur
Epinephrine, sympathomimetic amines	Enhanced stimulant effects	PD, 1	Use lower doses of TCA
Cimetidine, disulfiram, methylphenidate, methadone, verapamil, quinidine	Increased TCA concentration	PK, 1, 2	Monitor TCA concentration
Carbamazepine, barbiturates	Decreased TCA concentration	PK, 1	Monitor TCA concentration, may require dosage change
Valproate	Increased valproate concentration	PK, 1	Monitor concentrations
Anticholinergics	Increased adverse events, possible toxicity	PD, 1	Lower doses as necessary

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.

PD=pharmacodynamic interaction; PK=pharmacokinetic interaction; TCA=tricyclic antidepressant; SSRI=selective serotonin reuptake inhibitor; MAOI=monoamine oxidase inhibitor.

Table 7
Newer Antidepressants and Cytochrome P450 Enzyme Inhibitory Potential

CYP ENZYME: DRUG	1A2	2C	2D6	3A4
Fluoxetine	0	++	++++ (++++)	+ (++)
Sertraline	0	+ (+)	+	+ (+)
Paroxetine	0	0	++++	0
Fluvoxamine	++++	++	0	+++
Citalopram	0	0	+	0
Nefazodone	0	0	0	++++
Venlafaxine	0	0	0 (+)	0
Bupropion	0	0	++++	0
Mirtazapine	0	0	0	0

The effect of a metabolite is shown in parentheses.

0=unknown or insignificant; +=mild and usually insignificant; ++=moderate and possibly significant; +++=moderate and usually significant; ++++=potent. CYP=cytochrome P450.

Table 8
SSRI Drug Interactions

Drug	Interaction	Mechanism/ Source of Data	Management
Alprazolam	Increased plasma concentrations of alprazolam when combined with fluoxetine, fluvoxamine, nefazodone	PK, 1	Monitor effects; may require reduced benzodiazepine dosage
Tricyclic antidepressants	Increased plasma TCA concentration possible; varies with drug and SSRI dose; not all drug combinations have been studied	PK, 1, 2, 5	Monitor TCA concentration; reduce dose if necessary
Warfarin	Increased warfarin concentration with fluvoxamine; other SSRIs may cause hypoprothrombinemic symptoms	PD, PK, 1, 2	Monitor prothrombin time; use reduced dose of fluvoxamine
MAOIs	Possible serotonin syndrome	PD, 2	Contraindicated
Clozapine	Increased clozapine concentration from fluvoxamine and other SSRIs	PK, 2	Monitor clozapine concentration
L-tryptophan	Possible serotonin syndrome	PD, 2	Contraindicated
Phenytoin	Increased phenytoin concentration; possible toxicity; documented with fluoxetine; possible with fluvoxamine, sertraline	PK, 2, 5	Monitor phenytoin concentration; adjust doses
Carbamazepine	Increased concentration of carbamazepine with fluoxetine and fluvoxamine; not consistently reported to occur	PK, 1, 2, 5	Monitor carbamazepine concentration
Tolbutamide	Possible increased hypoglycemic effects; reported with sertraline but not significant in patients	PK, 2	Monitor
Theophylline	Increased theophylline concentration with fluvoxamine concentration; adjust dose	PK, 2	Monitor theophylline downward as needed
Cimetidine	Increased SSRI concentrations	PK, 2	Monitor clinical effects
Type 1C antiarrhythmics	Increased antiarrhythmic concentration and possible effects by CYP 2D6 inhibitors (fluoxetine, paroxetine, high-dose sertraline)	PK, 5	Monitor
b-blockers	Increased concentration and enhanced effects with those metabolized by CYP 2D6 (Table 2)	PK, 5	Use lower dose of b-blocker if necessary
Codeine	Inhibited metabolism to morphine by CYP 2D6 inhibitors resulting in decreased analgesic effect	PK, 1, 2	Use different SSRI or change class of agents
St. John's wort	Serotonin syndrome due to MAOI-like activity; one case reported	PD, 2, 5	Advise patients to stop using St. John's wort before beginning SSRI

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.

PD=pharmacodynamic interaction; PK=pharmacokinetic interaction. SSRI=selective serotonin reuptake inhibitor; CYP=cytochrome P450; MAOI=monoamine oxidase inhibitor.

Table 9
Bupropion Drug Interactions

Drug	Interaction	Mechanism/ Source of Data	Management
MAOIs	Seizures, acute toxicity	Unknown, 4, 6	Contraindicated
L-Dopa	Increased adverse events	PD, 1	Use cautiously
Drugs that lower seizure threshold: theophylline, neuroleptics, abrupt benzodiazepine withdrawal	Increased seizure risk	PD, 2, 5	Use extreme caution; employ small initial doses and gradual dose increases
Orphenadrine, cimetidine, valproate	Raised drug or metabolite concentration	PK, 1, 5	Use cautiously
Carbamazepine, phenobarbital, phenytoin	Reduced drug concentration	PK, 5	Monitor effects closely
Ritonavir, Efavirenz, and Nelfinavir	Potential increased bupropiran concentration	PK, 3, 5	These antiretroviral drugs inhibit CYP 2B6
CYP 2D6 substrates	Metabolic inhibition	PK, 1, 5	Use caution and initiate with low doses

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions, 6=animal studies.

PD=pharmacodynamic interaction; PK=pharmacokinetic interaction.

Table 10
Nefazodone Drug Interactions

Drug	Interaction	Mechanism/ Source of Data	Management
Triazolam, alprazolam	Increased benzodiazepine concentration and clinical effects	PK,1	Use reduced benzodiazepine doses
MAOIs	Toxicity	PD, 2	Contraindicated
Protease inhibitors (Table 2)	Nefazodone expected to increase concentrations during HIV+ therapy from CYP 3A4 inhibition	PK, 5	Monitor surrogate markers; may require decreased dose

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.

PD=pharmacodynamic interaction; PK=pharmacokinetic interaction. MAOI=monoamine oxidase inhibitor; CYP=cytochrome P450.

Table 11
Mirtazapine Drug Interactions

Drug	Interaction	Mechanism/ Source of Data	Management
MAOIs	Toxicity	PD, 2	Contraindicated
Alcohol	Increased side effects	PD, 2	Avoid combination
Benzodiazepines	Increased side effects	PD, 2	Avoid combination

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.

PD=pharmacodynamic interaction; PK=pharmacokinetic interaction; MAOIs=monoamine oxidase inhibitors.

Table 12
Venlafaxine Drug Interactions

Drug	Interaction	Mechanism/ Source of Data	Management
MAOIs	Toxicity	PD, 2	Contraindicated
Haloperidol	Increased haloperidol concentration	PK, 2	Significance unknown, monitor and adjust doses if necessary
Cimetidine	Increased venlafaxine concentration	PK, 2	No dosage adjustment necessary
Risperidone	Increased risperidone but not metabolite concentration	PK, 2	Dosage adjustment unlikely
Diphenhydramine	Increased venlafaxine concentration	PK, 1	Monitor and adjust doses if necessary
Indinavir	Decreased protease inhibitor concentration	PK, 1	Monitor, clinical significance not established.

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.

PD=pharmacodynamic interaction; PK=pharmacokinetic interaction; MAOI=monoamine oxidase inhibitor.

Table 13
St. John's Wort Drug Interactions

Drug	Interaction	Mechanism/ Source of Data	Management
SSRI	Symptoms of mild serotonin syndrome	PD, 2	Stop both agents, monitor for symptom resolution
Digoxin	Decreased digoxin concentration	PK, 1	Increased digoxin monitoring
Indinavir (like other protease inhibitors)	Decrease indinavir concentration	PK, 1	Increased monitoring of antiviral effects
Cyclosporine	Decreased concentration and transplant rejection	PK, 2	Increased monitoring needed
Warfarin	Multiple cases of altered bleeding indices	PK, 2	Stop SJW and monitor bleeding indices
Oral contraceptives	Decreased efficacy (breakthrough bleeding)	PK, 2	Avoid use or use secondary contraceptive method
Theophylline	Decreased concentration	PK, 2	May need dosage increase
Alprazolam	Decreased concentration	PK, 1	Man need dosage increase
CYP 3A4 substrates (see Table 3)	Potentially diminished effects	PK, 5	Many need dosage increase

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds;3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.

PD=pharmacodynamic interaction; PK=pharmacokinetic interaction; TCA=tricyclic antidepressant; SSRI=selective serotonin reuptake inhibitor; MAOI=monoamine oxidase inhibitor.

Table 14
MAOI Drug Interactions

Drug	Interaction	Mechanism/ Source of Data	Management
Meperidine	Serious and potentially fatal reaction resembling serotonin syndrome	PD, 1	Combination is contraindicated
Sympathomimetic amines, phenylephrine, epinephrine, norepinephrine, or isoproterenol; tyramine-rich foods	Increased blood pressure, possible hypertensive crisis	PD, 1	Contraindicated
TCAs	Fatal reaction possible	PD, 1, 2	Contraindicated
L-tryptophan	Possible serotonin syndrome	PD, 1, 2	Contraindicated
SJW	Possible serotonin syndrome	PD, 4, 5	Avoid combination

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.

PD=pharmacodynamic interaction; PK=pharmacokinetic interaction; MAOI=monoamine oxidase inhibitor; SJW:St. John's wort.

Table 15
Lithium Drug Interactions

Drug	Interaction	Mechanism/ Source of Data	Management
Topiramate	Transient decreased lithium concentration	PK, 1	Monitor lithium
Thiazide diuretics	Increased lithium concentration concentration, reduce dose as needed	PK, 1	Avoid when possible; monitor lithium
Loop diuretics (furosemide)	Increased or decreased concentrations	PK, 1	Avoid when possible; monitor lithium concentration, alter dose as needed
Osmotic diuretics (mannitol, urea)	Decreased lithium concentrations	PK, 1	Avoid when possible; monitor lithium concentration, alter dose as needed
Acetazolamide	Decreased lithium concentrations	PK, 1	Monitor and adjust lithium doses
Potassium-sparing diuretics (amiloride, spironolactone)	Decreased lithium concentrations	PK, 1	Monitor and adjust lithium doses
Methyl xanthines (caffeine, theophylline)	Decreased lithium concentrations	PK, 1	Monitor and adjust lithium doses
Sodium bicarbonate	Decreased lithium concentrations	PK, 1	Monitor and adjust lithium doses
NSAIDS- (indomethacin, ibuprofen, diclofenac, naproxen, mefenamic acid, piroxicam, ketorolac, celecoxib)	Increased lithium concentrations	PK, 1	Use lower dose of lithium; consider using aspirin or sulindac
ACE inhibitors	Increased lithium concentrations; toxicity reported	PD, PK, 1, 2	Use lower dose of lithium; monitor
Valsartan	Increased lithium concentration	PK, 2	Monitor and adjust lithium doses
Calcium channel blockers (verapamil, diltiazem, nifedipine)	Unpredictable changes in concentration, increase or decrease	PK, 2 monitor	Awareness is needed;
Haloperidol	Neurotoxicity reported in rare cases	PD	Often used together safely

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.

PD=pharmacodynamic interaction; PK=pharmacokinetic interaction; MAOI=monoamine oxidase inhibitor.

Table 16

Carbamazepine Drug Interactions

Drug	Mechanism/Interaction	Source of Data	Management
Erythromycin	Increased carbamazepine	PK (CYP 3A4 concentration inhibition), 1	Use noninteracting antibiotic or reduce carbamazepine dose
Allopurinol	Increased carbamazepine concentration carbamazepine dose	PK, 1	Avoid combination or reduce
Cimetidine	Increased carbamazepine concentration carbamazepine dose	PK, 1	Avoid combination or reduce
Propoxyphene	Increased carbamazepine concentration carbamazepine dose	PK, 2	Avoid combination or reduce
Oral contraceptives	Decreased contraceptive effect	PK, 1	Use other contraceptive means
Valproate	Decreased valproate concentration; inconsistent increase in carbamazepine concentration	PK, 1	Monitor; adjust doses
Phenobarbital, phenytoin	Decreased carbamazepine concentration	PK, 1	Monitor; adjust doses
Warfarin	Decreased warfarin concentration	PK, 1	Monitor prothrombin time; adjust dose as needed
Haloperidol	Decreased antipsychotic concentration	PK, 1	Monitor; adjust dose
Fluoxetine, fluvoxamine	Increased carbamazepine concentration; inconsistent reports with SSRIs	PK, 1, 2, 5	Monitor concentration
Verapamil, diltiazem	Increased carbamazepine concentration; decreased effects of calcium channel blockers	PK, 2	Monitor clinical effects; adjust doses as needed
Clozapine	Decreased clozapine concentration	PD, PK, 2, 5	Monitor effects; avoid due to potential combined bone marrow toxicity
Lamotrigine	Increased carbamazepine metabolite concentration; reports are inconsistent; no effect on lamotrigine by carbamazepine	PK, 2	Monitor and decrease dose of carbamazepine if necessary
Gabapentin	No interaction by either drug on the other		—
Grapefruit	Increased carbamazepine concentration	PK, 1	Monitor and decrease dose of carbamazepine if necessary

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.

PD=pharmacodynamic interaction; PK=pharmacokinetic interaction; MAOI=monoamine oxidase inhibitor.

Table 17

Oxcarbazepine Drug Interactions

Drug	Interaction	Source of Data	Mechanism/Management
Carbamazepine	Decreased metabolism	PK, 1	Induction of oxcarbazepine active metabolite by carbazepine; may reguire dosage adjustment
Cimetidine	None	PK, 1	No adjustment needed in dosage
Oral Contraceptives	Significant decrease in contraceptive concentration	--	Additional form of contraceptive may be necessary or increased contraceptive dosage
Erythromyacin	None	PK	Poor documentation, monitor effects
Fosphenytoin	Decreased oxcarbazepine concentration, increased phenytoin concentration	PK, 1	Monitor for phenytoin toxicity; decreased phenytoin dose may be needed
Lamotrigine	Decreased lamotrigine concentration	PK, 2	Enzyme induction by oxcarbazepine monitor; may need increased lamotrigine doses or decreased lamotrigine doses if oxcarbazepine is withdrawn.
Valproic Acid	Increased free valproic drug concentration	PK, 2	Monitor and may need to decrease valproic acid doses

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case eports; 5=theoretical predictions.

PK=pharmacokinetic interaction.

Table 18
Valproate Drug Interactions

Drug	Interaction	Mechanism/ Source of Data	Management
Phenobarbital	Increased phenobarbital concentration	PK, 1	Reduce dose of phenobarbital
Mg/Al hydroxide antacids	Increased valproate concentration	PK, 1	Monitor concentration; reduce dose
Carbamazepine	Decreased valproate concentration and possible increased carbamazepine metabolite	PK, 1	Monitor concentrations; adjust doses
Aspirin, naproxen	Increased free valproate concentrations	PK, 2	Avoid use of salicylates or other drugs bound to plasma albumin
Lamotrigine	Increased lamotrigine concentration; decreased valproate concentrations reported	PK, 2	Monitor concentrations and effects
Clonazepam	Increased sedation	PD, 2	Use cautiously
Gabapentin	No effect by either drug on the other	—	No dosage adjustment required
Lorazepam	Increased lorazepam through inhibition of glucuronidation	PK, 2	Dose adjustment may be required

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.

Mechanism: PD=pharmacodynamic interaction; PK=pharmacokinetic interaction.

Table 19
Lamotrigine Drug Interactions

Drug	Interaction	Mechanism/ Source of Data	Management
Carbamazepine	Decreased lamotrigine concentration by 40% reported; no effect of lamotrigine on carbamazepine, but metabolite concentration may increase	PK, 2	Clinical monitoring; dose adjustments as warranted
Valproate	Lamotrigine concentration increased twofold; lamotrigine decreased valproate by 25%	PK, 2	May require decrease in lamotrigine dose
Phenytoin	Decreased lamotrigine concentration	PK, 2	May require increase in lamotrigine dose
Gabapentin	No pharmacokinetic interactions by either drug with the other	—	—

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.

Mechanism: PD=pharmacodynamic interaction; PK=pharmacokinetic interaction.

Table 20
Topiramate Drug Interactions

Drug	Interaction	Mechanism/ Source of Data	Management
Phenytoin	Increased phenytoin in some patients and decreased topiramate concentration	PK, 1	Monitor phenytoin concentration; adjust doses as required
Carbamazepine	Decreased topiramate	PK, 1	May require increased dose
Valproate	Slight decrease in both drug concentrations	PK, 1	Minimal dosage changes predicted
Lithium	Possible transient decrease in lithium concentration	PK, 1	Monitor lithium closely

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.

PD=pharmacodynamic interaction; PK=pharmacokinetic interaction; MAOI=monoamine oxidase inhibitor.

Table 21
Methylphenidate Drug Interactions

Drug	Interaction	Mechanism/ Source of Data	Management
Alcohol	Forms active metabolite; significance unknown	PK, 1	Avoid alcohol
TCA	Increased TCA concentration; agitated behavior	PK, 2	May require decreased TCA dose
MAOI	Toxicity; possible excessive sympatho-mimetic effects	PD, PK, 4	Avoid combination
SSRI	Symptoms of toxicity; a case of precipitated seizures	PK, 4	Avoid or use with caution
Anticonvulsants	Toxicity possible; increased concentrations	PK, 2	Monitor concentration; adjust doses
Antihypertensives	Diminished hypotensive effects	PD, 2	Monitor blood pressure; adjust doses
Pressor agents	Increased stimulation; pressor effects	PD, 2	Use with caution

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.
Mechanism: PD=pharmacodynamic interaction; PK=pharmacokinetic interaction.TCA=tricyclic antidepressant; MAOI=monoamine oxidase inhibitor; SSRI=selective serotonin reuptake inhibitor.

Table 22
Modafinil Drug Interactions

Drug	Interaction	Mechanism/ Source of Data	Management
Clomipramine	Increased TCA concentration	PK, 4	Monitor TCA levels and adjust doses as required
Cyclosporine	Decreased cyclosporine concentration	PK, 4	Monitor cyclosporine levels and adjust doses as required
Methylphenidate	None	PK, 1	No adjustment in dose required based on current documentation
Triazolam	None	PD, 1	None

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.
TCA=tricyclic antidepressant; PK=pharmacokinetic interactionPD=pharmacodynamic interaction.

Table 23
Benzodiazepine Drug Interactions

Drug	Interaction	Mechanism/ Source of Data	Management
Cimetidine	Increased diazepam concentration; not all benzodiazepines likely affected	PK, 1	Monitor for increased effects; modify anxiolytic dosage if necessary
Alcohol	Psychomotor impairment possible	PD, PK, 1	Avoid concomitant use
Nefazodone, fluoxetine, fluvoxamine	Increased concentration of diazepam, alprazolam; midazolam; other combinations not sufficiently studied	PK, 1	Reduce anxiolytic dosage
Disulfiram	Increased concentration of diazepam, alprazolam	PK, 1	Reduce anxiolytic dosage
Erythromycin; other CYP 3A4 inhibitors	Increased concentration of alprazolam, triazolam, possibly diazepam	PK, 1, 5	Reduce anxiolytic dosage
Ritonavir	Increased concentration and effects of triazolam	PK, PD, 1	Significant interaction requires dosage decrease or alternative sedative/hypnotic

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.
PD=pharmacodynamic interaction; PK=pharmacokinetic interaction; TCA=tricyclic antidepressant; MAOI=monoamine oxidase inhibitor; SSRI=selective serotonin reuptake inhibitor.

Table 24
Buspirone Drug Interactions'

Drug	Interaction	Mechanism/ Source of Data	Management
Haloperidol	Increased haloperidol concentration	PK, 1	Monitor
MAOI	Increased blood pressure	PK, 2	Avoid combination
Warfarin	Increased prothrombin time	4	Monitor
Ketoconazole	Increased buspirone concentration	PK, 1	Monitor effects; adjust doses if needed
CYP 3A4 inhibitors (nefazodone, fluvoxamine)	Possible increased concentration	PK, 5	Monitor effects; adjust doses if needed
Grapefruit juice	Increased buspirone concentration	PK, 1	Monitor effects; reduce dose if needed

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.

PD=pharmacodynamic interaction; PK=pharmacokinetic interaction; CYP=cytochrome P450; MAOI=monoamine oxidase inhibitor.

Table 25
Phenothiazine Drug Interactions

Drug	Interaction	Mechanism/ Source of Data	Management
TCAs	Mutual metabolic inhibition	PK, 1	Monitor; reduce doses
Barbiturates	Decreased antipsychotic concentrations	PK, 1	Monitor effects; adjust doses if needed
Anticholinergic medications	Therapeutic and side effects possible; decreased absorption suggested	PD, 1	Use lowest effective doses
Bromocriptine	Exacerbation of psychosis	3	Monitor clinically
Lithium	Rare neurotoxicity	4	Monitor clinically
Cimetidine	Increased plasma concentration	PK, 2	Monitor clinically
Thioridazine	Increased QTc interval when combined CYP 2D6 inhibitors and certain other drugs (propranolol, pindolol, fluvoxamine)	PK, PD, 1, 5	Contraindicated combinations due to increased risk of arrhythmia

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.

PD=pharmacodynamic interaction; PK=pharmacokinetic interaction; TCA=tricyclic antidepressant.

Table 26
Zolpidem Drug Interactions

Drug	Interaction	Mechanism/ Source of Data	Management
Chlorpromazine	Decreased psychomotor performance	PD, 1	Monitor, adjust dose if necessary
Cimetidine	No apparent effect on zolpidem	PK, 1	—
Flumazenil	Reversal of sedative effects	PK, 1	Avoid combination
Azole antifungal agents	Significant reduction in zolpidem clearance by ketoconazole, less effects by itraconazole and fluconazole	PK, 1	Reduce dose
Rifampin	Reduced concentration and effect	PK, 1	May require increased dose
Fluoxetine	Shortened onset of action	PK, 1	Nonsignificant interaction
SSRIs	Sporadic reports of possible serotonin-like syndrome	PD, 4	Monitor combined use closely
Ritonavir	Small reduction in clearance	PK, 1	Clinically unimportant, monitor for increased effects.

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.

PD=pharmacodynamic interaction; PK=pharmacokinetic interaction; SSRI=selective serotonin reuptake inhibitor.

Table 27
Haloperidol Drug Interactions

Drug	Interaction	Mechanism/ Source of Data	Management
Carbamazepine	Decreased haloperidol concentration	PK, 1	Monitor and adjust doses as required
Rifampin	Decreased haloperidol concentration	PK, 1	Monitor and adjust doses as required
TCAs	Increased TCA concentration	PK, 1	Monitor TCA concentration; adjust doses if needed
Phenobarbital	Decreased haloperidol concentration	PK, 2	Monitor and adjust doses as required
Lithium	Rare neurotoxicity	2	Monitor clinically and lithium concentration
Nefazodone, fluvoxamine, fluoxetine	Increased haloperidol concentration	PK, 2	Monitor clinically and haloperidol concentration

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.

PD=pharmacodynamic interaction; PK=pharmacokinetic interaction; TCA=tricyclic antidepressant.

Table 28
Clozapine Drug Interactions

Drug	Interaction	Mechanism/ Source of Data	Management
Benzodiazepines (lorazepam, diazepam)	Delirium, sedation,	PD, 1	Use with caution rare respiratory collapse
Lithium	Signs of neurotoxicity	PD, 4	Use with caution
Caffeine	Increased clozapine concentration	PK, 4	Monitor
Smoking	Decreased clozapine concentration	PK, 1	Monitor
Cimetidine, erythromycin	Increased clozapine concentration	PK, 1	Monitor effects/concentration
SSRIs and other SSRIs	Increased clozapine with fluvoxamine	PK, 1, 2	Monitor effects/concentration; may need dose adjustment
Valproate	Reported to increase and decrease clozapine concentration	PK, 2	Monitor effects/concentration
Phenytoin	Increased clozapine concentration	PK, 4	Monitor effects/concentration
Risperidone	Increased clozapine concentration	PK, 2	Monitor effects/concentration
Fluvoxamine	SSRI withdrawal syndrome	PK, 4	Monitor; PK interaction probable

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.

PD=pharmacodynamic interaction; PK=pharmacokinetic interaction; SSRI=selective serotonin reuptake inhibitor.

Table 29
Risperidone Drug Interactions

Drug	Interaction	Mechanism/ Source of Data	Management
Antihypertensive agents	Increased orthostasis	PD, 2	Monitor blood pressure
Levodopa, dopamine agonists	Decreased dopaminergic effects	PD, 5	Monitor clinically
CYP 2D6 inhibitors (quinidine, SSRIs)	Increased risperidone concentration; sum of parent and metabolite may remain unchanged	PK, 2, 5	Monitor effects; no dosage adjustment usually necessary
Carbamazepine	Possible increased clearance of risperidone	PK, 4	Monitor clinical effects
Valproate	Inconsistent concentration changes of both drugs	PK, 2	Monitor

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.

PD=pharmacodynamic interaction; PK=pharmacokinetic interaction; CYP=cytochrome P450; SSRI=selective serotonin reuptake inhibitor.

Table 30
Olanzapine Drug Interactions

Drug	Interaction	Mechanism/ Source of Data	Management
Smoking	Decreased olanzapine concentration	PK, 1	May require higher average doses
Omeprazole	Increased clearance of olanzapine	PK, 2	Monitor; adjust doses as needed
Ciprofloxacin	Increased concentration of olanzapine	PK, 4	Monitor; may need dose decrease
Fluvoxamine	Increased concentration of olanzapine	PK, 4	Monitor; may need dose decrease
Carbamazepine	Decreased plasma concentration	PK, 4	Monitor; may need dose increase
Alcohol, benzodiazepines	Increased orthostatic hypotension	PD, 2	Avoid combination
Caffeine	Increased olanzapine concentration	PK, 5	May require decreased dosage
Theophylline	None	PK, 1	Olanzapine lacks CYP 1A2 inhibitory effects but its metabolism by this pathway may be inhibited
Ritonavir	Olanzapine concentation decreased	PK, 1	Monitor antipsychotic effects; dosage adjustment not necessary unless clear changes in efficacy occur.

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.

PD=pharmacodynamic interaction; PK=pharmacokinetic interaction.

Table 31
Quetiapine Drug Interactions

Drug	Interaction	Mechanism/ Source of Data	Management
Thioridazine	Decreased concentration of quetiapine	PK, 2	Monitor; may require dose change
Phenytoin	Decreased concentration of quetiapine	PK, 2	Monitor; may require dose increase
Cimetidine	No effect on quetiapine concentration	PK, 2	No dosage adjustment required
CYP 3A4 inhibitors (erythromycin, ketoconazole)	Expect increased quetiapine concentration	PK, 5	May require decreased dose
CYP 3A4 inducers (rifampin, steroids, carbamazepine)	Expect reduced quetiapine concentration	PK, 5	May require increased dose

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.

PD=pharmacodynamic interaction; PK=pharmacokinetic interaction. CYP=cytochrome P450; INR=international normal ration.

Table 32
Ziprasidone Drug Interactions

Drug	Interaction	Mechanism/ Source of Data	Management
Oral contraceptiuves	None	PK, 1	No evidence of an interaction; no action required
Ketoconazole	Increased ziprasidone concentration	PK, 1	Clinical significance is doubtful
Lithium	None	PK, 1	No evidence of interaction
Carbamazepine	Modest decrease in ziprasidone concentration	PK, 1	Clinical siginificance is doubtful

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.

PK=pharmacokinetic interaction

Table 33
Selected Cholinesterase Inhibitors Drug Interactions

Drug	Interaction	Mechanism/ Type of Data	Management
Anticholinergics	Decreased effect for both drugs	PD, 2	Avoid combination if possible
Succinylcholine and similar neuromuscular blocking agents; bethanechol and other cholinergic agonists	Synergistic effect; possible cholinergic toxicity	PD, 2	See special preanesthesia and package insert for dose adjustment
Theophylline	Increased theophylline concentration with tacrine use	PK, 2	Monitor theophylline levels; avoid tacrine-theophylline combination if possible
Quinidine	Increased donepezil levels via 2D6	PK, 3	May require lower dose of donepezil
Ketoconazole	Increased donepezil levels via 3A4	PK, 3	May require lower dose of donepezil

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions. PD=pharmacodynamic interaction; PK=pharmacokinetic interaction; CYP=cytochrome P450.

Table 34
Selected Anorectic/Anti-Obesity Agents Drug Interactions

Drug	Interaction	Mechanism/ Type of Data	Management
MAOIs	Toxicity; hypertensive reaction; serotonin syndrome with sibutramine and phentramine	PD, 5	Contraindicated
SSRIs	Possible serotonin syndrome with sibutramine	PD, 2	Avoid combination if possible
Insulin	Alter insulin dosage requirements	PD, 2	Monitor clinically; check glucose levels
Antihypertensives	Decreased antihypertensive effect with phentermine use	PD, 2	Avoid combination if possible
CNS-active drugs	Additive effects (see text)	PD, 2	Monitor clinically
TCAs	Increased TCA levels causing urinary retention or dry mouth with fenfluramine use	PK, 2	Monitor clinically
Anesthetic agents (halothane)	Possible catecholamine-depleting effect which may be toxic	PD, 2	Avoid combination if possible
Ketoconazole, nasal decongestants erythromycin	Possible increase in sibutramine levels	PK, 3	Monitor clinically
Cough suppressants, tryptopham, lithium, meperidine, fentanyl, pentazocine	Possible serotonin syndrome	PK, 2	Avoid combination if possible
Vitamin E	Decreased absorption with orlistat	PK, 1	May require increased dose of 50% or more

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.PD=pharmacodynamic interaction; PK=pharmacokinetic interaction; MAOI=monoamine oxidase inhibitor; SSRI=selective serotonin reuptake inhibitor; CNS=central nervous system; TCA=tricyclic antidepressant.

Table 35
Selected Methadone Drug Interactions

Drug	Interaction	Mechanism/ Type of Data	Management
Pentazocine	Opiate withdrawal	PD, 1	Avoid
Rifampin	Decreased methadone levels	PK, 4	Use cautiously
Desipramine	Increased desipramine levels	PK, 1	Check desipramine levels; may need to decrease desipramine dose
MAOIs	Toxicity	PD, 1	Avoid
Fluvoxamine, fluoxetine	Increased methadone concentration	PK, 1	Monitor effects; dosage adjustment may be needed
Indinavir	No PK effects reported	PK, 1	No dose modification needed

Type of data: 1=in vivo studies/well established; 2=multiple case reports and/or based on related compounds; 3=in vitro studies; 4=isolated case reports; 5=theoretical predictions.

PD=pharmacodynamic interaction; PK=pharmacokinetic interaction; MAOI=monoamine oxidase inhibitor.

Notes

Notes