

Drug Interactions—Friend or Foe?

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An explosion of knowledge about interactions of drugs with other drugs and with foods threatens to inundate clinicians. This review provides a better understanding of the cytochrome P450 system with a focus on those enzymes most involved in drug metabolism. Emphasis is placed on antidepressant medications, how they are metabolized by the P450 system, and how they alter the metabolism of other drugs. The role of antidepressants in precipitating the serotonin syndrome is also discussed.

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Charcoal-broiled beef—an appetizing, yet instructive way to begin a discussion of drug interactions. When normal volunteers who were taking phenacetin, an analgesic, ate a charcoal-broiled beef diet for 4 days, the average peak concentration of the drug decreased by 78%.¹ All that was necessary to potently induce the hepatic microsomal enzyme (CYP1A2) involved in phenacetin metabolism was to eat an 8-ounce beef burger for lunch and a 6-ounce beefsteak for dinner that had been broiled over an open charcoal flame (the control diet included the same meat cooked over a charcoal flame but separated from it by a layer of aluminum foil).¹

While drug interactions have been attracting the attention of psychiatric clinicians for only a few years, they have been occurring throughout the history of pharmacotherapy. Even before the advent of pharmaceuticals, a complex system of enzymes had been evolving in all living organisms for hundreds of millions of years to play a role in what the physician/author Michael Crichton described as an evolutionary arms race.² Through the processes of spontaneous mutation and natural selection, plants evolved a variety of toxic chemicals that discouraged animal predators. Through the process of enzyme induction, the levels of these substances could be increased substantially when plants were under attack (being eaten). Enzymatic evolution also took place in animals, allowing them to deactivate plant toxins that they had previously found noxious. A specific example involves black swallowtail butterfly larvae and xanthotoxin, a poisonous chemical produced by carrots, parsley, and other plants. While most insects avoid xanthotoxin-producing plants, these larvae have acquired

the ability to produce large amounts of cytochrome P450 6B1 (another example of enzyme induction), which oxidatively metabolizes xanthotoxin and renders it harmless.³ P450 6B1 is but one member of the complex system of cytochrome P450 enzymes that exists today.

In recent years, knowledge of the cytochrome P450 superfamily of heme-containing monooxygenase enzymes has grown enormously. As of October 1995, 481 P450 genes had been identified among all living organisms, compared with only 221 in 1992.⁴ With rare exceptions, each gene is thought to be responsible for the production of a single protein enzyme. The P450 superfamily has been divided into families, and families into subfamilies, based on degrees of similarity in amino acid sequencing. CYP, standing for cytochrome P450, is the root symbol for the superfamily, while families are designated by Arabic numbers, subfamilies by capital letters, and individual genes (or enzymes) by Arabic numbers. Hence, the xanthotoxin-inactivating enzyme is known as CYP6B1 (family 6, subfamily B, gene 1). Thus far, fewer than 50 P450 genes have been identified in humans, and far fewer than 50 are known to play important roles in drug metabolism.⁴ This is unlikely to be the case for very long.

The P450 system was named many years ago when it was observed that enzyme-inducing drugs such as phenobarbital caused large amounts of a red pigment to accumulate in liver microsomes. When bound to carbon monoxide, this heme-containing pigment absorbed light at a peak wavelength of 450 nm. The combination of cyto- (hollow vesical), chrome (color), pigment (P), and wavelength (450) resulted in the term *cytochrome P450*, which is abbreviated CYP.

The P450 system is involved in phase I metabolism of foreign chemicals, otherwise known as xenobiotics (drugs are one type of xenobiotic). P450 enzymes are involved in oxidative reactions that include hydroxylation, demethylation, dealkylation, and ring oxidation in which an oxygen atom is inserted into a drug to prepare it for phase II, or conjugation reactions. These enzymes may function in

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ways that are beneficial or detrimental to the organism. Reactions that deactivate toxins, carcinogens, and mutagens can be lifesaving, while reactions that convert otherwise innocuous substances into dangerous ones can be just the opposite. For example, the production of hepatotoxic electrophilic metabolites from acetaminophen by CYP2E1 may account for the liver toxicity associated with overdoses of this drug.⁴³

Enzyme Specificity

Despite the ever expanding number of known P450 enzymes, there are overwhelmingly more xenobiotics to challenge them. Therefore, there are limitations to the concept of enzyme specificity, which, at its extreme, posits that each xenobiotic has an enzyme uniquely devoted to its metabolism. In fact, several enzymes may be involved in the metabolism of a particular drug, and a single enzyme may preferentially metabolize many drugs. For example, CYP1A2, CYP2C8, and CYP3A4 are all involved in the demethylation of imipramine to desipramine, while CYP2D6 converts desipramine to its hydroxy metabolite.^{11,63}

Chirality

Matters are further complicated by the fact that many synthetic drugs are characterized by chirality. Because of their asymmetric structure, they exist in two forms (known as stereoisomers, racemates, or enantiomers) that are mirror images of the same chemical structure (referred to by prefixes such as dextro- and levo-, [+], [-], [d] and [l], or [R] and [S]). Examples of marketed drugs that are racemic mixtures or racemates include bupropion,⁵ fluoxetine,⁶ warfarin,⁷ and propranolol.

The stereoisomers of racemic drugs may have quite different actions in the body. For example, dextropropoxyphene is an analgesic marketed as Darvon, while levopropoxyphene was an antitussive once marketed as Novrad (Darvon spelled backward).⁸

In addition, racemates may be metabolized differentially by the P450 system and have different enzyme-inhibiting potencies. For example, the R-form of warfarin is metabolized by CYP1A2 and CYP3A4, while the more potent S-form is converted to 7-hydroxywarfarin by CYP2C9.⁷ Consequently, drugs that inhibit 2C9 are more likely to have a clinically meaningful impact on warfarin metabolism.⁷ Fluoxetine is a racemic mixture, as is its major metabolite, norfluoxetine. The S-enantiomers of these two compounds are 5 to 6 times more potent inhibitors of CYP2D6 than are the R-forms.⁶

PEOPLE ARE DIFFERENT

Genetic Factors

Genetic factors play a role in the composition of individual P450 systems. The most extreme example of this

variability is genetic polymorphism, which means basically that, within a normal population, some people have a functional enzyme, while others do not. Not all P450 enzymes exhibit this characteristic; those that do include CYP2C19, CYP2D6, and CYP2E1. People who have a functional enzyme are known as extensive metabolizers, or EMs, while those with the genetically nonfunctional variant are referred to as poor metabolizers, or PMs. Ethnic differences exist with regard to the percentage of a population who are EMs or PMs. For example, CYP2C19 is functionally inactive in 3%–5% of Caucasians and 18%–20% of Asians, while CYP2D6 is inactive in 5%–10% of Caucasians but only 1%–2% of Asians.¹¹ It has been suggested that this genetic diversity adds survival value to the population as a whole (for example, in one scenario, those who could inactivate a lethal global toxin [the EMs] would survive, while in another, the PMs might triumph because they could not convert a safe substance to its deadly metabolite). This theory fails to explain, however, why all P450 enzymes are not genetically polymorphic.

From the perspective of drug metabolism, having or lacking a particular enzyme results in wide variations of blood drug levels across individuals. Incidentally, there is more to the genetics of these enzymes than merely all or nothing—some people have more than the usual complement of functional genes and more than the usual amounts of certain enzymes (these people are referred to as ultra-rapid metabolizers), while others have partially functional enzymes and are slower metabolizers than normal. These factors account, in part, for the extremely wide range in blood levels of drugs such as tricyclic antidepressants across individuals receiving the same dose.

Genetic polymorphism explains why some individuals fail to get an adequate analgesic response from codeine. By itself, codeine is an ineffective analgesic—it must be metabolized to morphine to be activated. Since this process of O-demethylation is facilitated by CYP2D6, the 5%–10% of the Caucasian population lacking this enzyme will not respond well to codeine.¹¹ The full analgesic effect of tramadol also depends on CYP2D6 to facilitate formation of the M1 metabolite—PMs had less of an increase in experimental pain perception thresholds than did EMs.⁹

The efficient metabolism of class Ic antiarrhythmic drugs also depends on CYP2D6. It was suggested that the high cardiac death rate associated with encainide and flecainide (6.4% vs. 2.1% with placebo) in the Cardiac Arrhythmia Suppression Trial (CAST) was due to PMs attaining arrhythmogenically high blood levels of these drugs.¹⁰ One can only speculate whether genotyping of study subjects might have averted the outcome.

Environmental Factors

How efficiently drugs and other xenobiotics are metabolized depends greatly on environmental factors. De-

pending on the type of interaction, metabolism can be induced (speeded up) or inhibited (slowed down) by substances we put into our bodies. For example, if your breakfast drink of choice is grapefruit juice, you are inhibiting CYP1A2 and CYP3A4 in clinically meaningful ways (increasing blood levels of drugs such as caffeine, cyclosporine, midazolam, triazolam, terfenadine, ethinyl estradiol, and a number of calcium channel blockers).¹¹ Incidentally, the latest candidate for the active ingredient in grapefruit juice responsible for its inhibitory effects on CYP3A4 is a furanocoumarin compound known as 6',7'-dihydroxybergamottin.¹² A diet high in cruciferous vegetables (broccoli, cabbage, brussels sprouts) has been shown to reduce blood phenacetin levels by as much as 67% through induction of CYP1A2 by indole-3-carbinol, a chemical common to these vegetables.¹¹ The relatively young science of nutraceuticals has revealed enough to suggest that some rather striking changes in blood levels of drugs may be caused by factors other than drug interactions or poor compliance.

Drug metabolism may be influenced by in utero or neonatal contact with medications. Neonatal exposure of rats to phenobarbital not only produced the expected transient induction of P450 enzymes that resolved quickly when the drug was withdrawn, but it also caused a permanent alteration in induction mechanisms. This imprinting by early response resulted in overproduction of CYP2B1 and CYP2B2 when adult rats were rechallenged with phenobarbital.¹³ The authors of the study speculate that neonatal exposure to enzyme inducers could result in higher rates of metabolism of substrates for these enzymes later in life (and the possibility of decreased drug efficacy). In addition, they suggest that the formation of hepatotoxic, mutagenic, and carcinogenic metabolites from drugs and other chemicals may be increased by the same process. The implications are not trivial—the authors point out that “between 1950 and the late 1970s, it has been estimated that 23 million children were born in the United States to mothers prescribed barbiturates during pregnancy.”^{13(p998)}

Flavin-Containing Monooxygenases

Before embarking on an overview of the P450 system and drug interactions, readers should be aware of another major monooxygenase metabolic system. The new atypical antipsychotic drug olanzapine is metabolized not only by CYP1A2 and CYP2D6, but also by a flavin-containing monooxygenase known as FMO3.¹⁴ The FMO family, which has only five members thus far (FMO1–5), differs from most CYP enzymes in that it is not inducible by xenobiotics. Nonetheless, these two systems may be involved in the metabolism of the same drugs, and they interact in important ways. For example, indole-3-carbinol, the naturally occurring chemical in cruciferous vegetables, shows promise as a cancer-preventing agent. In rats, it potently

induces CYP enzymes such as 1A1 and 1A2, but potently inhibits FMO1. Such shifts in CYP/FMO balance may have important implications with regard to the metabolism of pharmaceuticals.¹⁵

DRUG-DRUG INTERACTIONS AND THE P450 SYSTEM

Fortunately for clinicians, a finite number of P450 enzymes appear to be involved in most of phase I drug metabolism. These include CYP1A2, the CYP2C subfamily, CYP2D6, CYP2E1, and CYP3A4. This cozy grouping is more likely a reflection of our current state of knowledge than a true representation of the universe of drug metabolism. For example, CYP2B6 presented itself recently as the enzyme primarily responsible for the conversion of bupropion to its hydroxy metabolite (see below).

CYP1A2

This potentially nasty enzyme is involved in activating a number of carcinogenic and mutagenic substances.^{16,17} It is induced by cigarette smoke, which may account, in part, for the increased incidence of various cancers in smokers. Other CYP1A2 inducers include charbroiled foods, cruciferous vegetables, omeprazole, and caffeine.^{16,17} Drugs metabolized, at least in part, by CYP1A2 include caffeine, ondansetron, tamoxifen, theophylline, phenacetin, clozapine, olanzapine, tertiary tricyclics such as imipramine and clomipramine, tacrine, and warfarin.^{16,17} Induction of this enzyme in cigarette smokers may account for their seemingly ceaseless consumption of coffee, whereas, in contrast, cessation of smoking has been associated with a 250% increase in serum caffeine level.^{16,48} Tacrine hepatotoxicity may be related to its conversion by CYP1A2 to cytotoxic electrophilic metabolites (a correlation has been found between CYP1A2 levels and the formation of these toxic products).¹⁸ Finally, CYP1A2 is a liver-specific enzyme that may exhibit genetic polymorphism in humans.

CYP2B6

CYP2B6 is the new kid on the psychopharmacology block. On the basis of in vitro human liver microsome studies, it is the enzyme primarily responsible for converting bupropion to its major metabolite, hydroxybupropion (package insert for Wellbutrin SR, 10/96). It is also involved in the metabolism of mianserin, a tetracyclic antidepressant.¹⁹ CYP2B6 appears to be one of the lesser drug-metabolizing P450s. In a study using immunoblotting analysis of 50 human liver samples, the enzyme was detectable in only 12 (24%), and the highest concentrations represented less than 2% of the total P450 concentration.²⁰ Similar conclusions were reached by Shimada et al.,²¹ who found that CYP2B6 represented less than 1% of total P450 concentration and was undetectable in 70% of liver microsome samples from Japanese and in 15% from Caucasians.

Whether these observations are indicative of genetic polymorphism is not yet known.

Styrene, a substance used in the manufacture of plastics and polyester resins, is oxidized in the body to electrophilic genotoxic intermediate metabolites such as styrene 7,8-oxide. In cultured cells, CYP2B6 was the most effective enzyme in catalyzing the formation of styrene glycol (CYP1A2, CYP2C8, and CYP2E1 were also involved).²² CYP2B6 also plays a role in the metabolism of cyclophosphamide, an anticancer drug,²³ the oxidation of gaseous haloethanes,²⁴ the N-demethylation of S-mephenytoin,²⁵ and the demethylation of diazepam and temazepam.²⁶ A study of 12 human P450 enzymes found that CYP2B6 had the highest rate of nicotine metabolism, converting it to one of its major metabolites, an electrophilic iminium ion.²⁷ A more recent study using lower substrate concentrations found that CYP2A6 was the major enzyme involved in nicotine metabolizing, with CYP2B6 and CYP2D6 playing lesser but still substantial roles.²⁸

CYP2B6 is induced by phenobarbital, and there is indirect evidence suggesting induction by carbamazepine.²⁹ Orphenadrine, a drug used to treat acute painful muscular conditions, is a potent but not selective inhibitor of CYP2B6.^{30,31}

CYP2C

Members of the CYP2C subfamily that have been of particular interest with regard to drug metabolism are CYP2C9 (sometimes referred to as 2C9/10) and CYP2C19 (sometimes referred to as CYP2C18/19).³² Substrates for CYP2C9 include tolbutamide, warfarin, a number of nonsteroidal antiinflammatory drugs, phenytoin, and tetrahydrocannabinol (THC).³² A rare polymorphism has been described for CYP2C9. It is inhibited by sulfaphenazole.

As discussed earlier, CYP2C19 polymorphism is quite common, especially in Asians. Substrates for this enzyme include S-mephenytoin, omeprazole, diazepam, propranolol, several tricyclic antidepressants, citalopram, and moclobemide.^{33,34} CYP2C19 is inhibited by omeprazole, tranilcypramine, fluvoxamine, and, to a lesser extent, fluoxetine.^{33,34} Rifampin is an inducer of both CYP2C19 and CYP2C9.^{33,34}

CYP2D6

In contrast to CYP2B6, CYP2D6 is well known among psychiatrists, in large part because of the heavy scientific and marketing focus placed on it by manufacturers of serotonin selective reuptake inhibitors (SSRIs). But even prior to the "my drug is a less potent inhibitor of CYP2D6 than yours" campaign, the enzyme had achieved prominence as a classic example of genetic polymorphism (see above).³⁵ The PM phenotype is an autosomal recessive trait caused by several different mutations of the CYP2D6 gene (located on chromosome 22), which render the en-

zyme inactive. For example, when timolol eye drops were administered intranasally, CYP2D6 PMs had significantly greater reductions in exercise heart rate and higher blood timolol levels than did EMs.³⁶ Heterozygote carriers of these mutant alleles metabolize CYP2D6 substrates more slowly than normal. Others who carry duplications of functional CYP2D6 genes are very rapid metabolizers of CYP2D6 substrates and require higher than usual doses of these drugs to achieve therapeutic blood levels.³⁷

The list of drugs metabolized, at least in part, by CYP2D6 is extensive^{35,38,39} and includes antiarrhythmic drugs (encainide, flecainide, propafenone); tricyclic antidepressants; certain β -blockers; venlafaxine; codeine; dextromethorphan; and some antipsychotic drugs, including risperidone, thioridazine, and perphenazine.

Inhibitors of CYP2D6 include quinidine, some of the SSRIs (see below), the antimalarials primaquine and chloroquine, propafenone, yohimbine, methadone, moclobemide, tricyclic antidepressants, and certain neuroleptics.³⁹ The weight loss drug fenfluramine also appears to be a CYP2D6 inhibitor as evidenced by its causing a 110% average increase of blood desipramine levels in 12 subjects.⁴⁰

CYP2D6 is not a liver-specific enzyme; extrahepatic locations include the brain. The presence or absence of CYP2D6 has been associated with differential susceptibility to Parkinson's disease, certain cancers, and Alzheimer's disease and may exert effects on personality traits and food preferences.¹¹

CYP2E1

Genetic polymorphism has been identified for the CYP2E1 gene, which is located on chromosome 10.⁴¹ This enzyme is involved in the metabolism of low molecular weight compounds such as ethanol, benzene, halothane, theophylline, acetaminophen, chlorzoxazone, and carbon tetrachloride.^{41,48} It is an activator of certain carcinogens, including N-nitrosamines. The myelotoxicity of benzene requires its conversion by CYP2E1 to reactive metabolites.⁴² Thus, toxicity was enhanced when CYP2E1 was induced by ethanol and was minimized in a strain of mice lacking functional CYP2E1.

The ability of ethanol to induce CYP2E1 is striking—a 5- to 10-fold increase has been found in human liver biopsies after alcohol consumption.⁴³ This accounts, in part, for alcohol tolerance in alcoholics, but it may also be related to the high risk of acetaminophen hepatotoxicity in alcoholics (the most common form of acute liver failure in the United States). When induced, CYP2E1 plays a more important role in acetaminophen metabolism, converting it to potentially hepatotoxic metabolites. These metabolites are detoxified, in part, by glutathione, but both alcohol and acetaminophen reduce glutathione levels, thus further increasing susceptibility to hepatotoxicity.⁴³

Disulfiram is a potent inhibitor of CYP2E1, so it may exert protective effects against certain hepatotoxins. One

possibility might be to use disulfiram to inhibit the oxidative metabolism of the anaesthetic halothane to prevent formation of trifluoroacetyl chloride, which is thought responsible for the uncommon, but often fatal halothane hepatitis.⁴⁴

CYP3A4

Enzymes within the CYP3A subfamily are the most abundant P450s in human liver and the predominant form in intestinal mucosa.⁴⁵ CYP3A4 (or 3A3/4 as it is sometimes called because of the almost identical structures of 3A3 and 3A4), the major CYP3A enzyme in liver and gut, has also been identified in brain where it is thought to be involved in neurosteroid and, possibly, psychotropic drug metabolism. While genetic polymorphism has not been identified with CYP3A4, there are substantial differences in its expression among individuals (by a factor of 30 times in the liver and 11 times in the gut).⁴⁶

CYP3A4 is both inducible and inhibitable. Inducers include dexamethasone, prednisone, phenobarbital, phenytoin, and rifampin. The well-known auto-induction of carbamazepine metabolism is mediated through CYP3A4.^{46,47} Substrates for this enzyme are numerous, and extensive lists are provided in many reviews.^{17,46–48} Among the drugs metabolized, at least in part, by CYP3A4 are cyclosporine, many calcium channel blockers, warfarin, many benzodiazepines (especially the triazolol types), macrolide antibiotics such as erythromycin and clarithromycin, zolpidem, tertiary amine tricyclic antidepressants, sertraline, cisapride, tamoxifen, HIV-1 protease inhibitors such as indinavir, zidovudine, and saquinavir,⁴⁹ and antihistamines such as terfenadine and astemizole.

The list of inhibitors of CYP3A4 is also extensive and includes antifungals such as itraconazole and ketoconazole, the macrolide antibiotics, antidepressants such as nefazodone and fluvoxamine, cimetidine, and some of the calcium channel blockers.^{46,47}

The potential for both dangerous and beneficial drug interactions through induction or inhibition of CYP3A4 is great. Inhibition has resulted in cardiotoxic blood levels of the nonsedating antihistamine, terfenadine. Deaths associated with this interaction have led the FDA to ask that terfenadine be withdrawn from the market. The major metabolite of terfenadine, which is both effective as an antihistamine and cardiac-safe, is currently being marketed as fexofenadine. Inhibition of CYP3A4 has also been associated with marked increases in blood levels of cisapride and potential cardiotoxicity.¹⁰⁷

Inhibitors of CYP3A4 greatly impaired the metabolism of triazolobenzodiazepines such as alprazolam, midazolam, and triazolam. In one study, the half-life of triazolam was extended from 4 to 17.7 hours in the presence of ketoconazole.⁵⁰ Because of concerns about toxicity, recent package insert revisions now state that the use of alprazolam and triazolam is contraindicated with ketoconazole

and itraconazole (and triazolam also with nefazodone).

Concern about potentially dangerous interactions (those that cause arrhythmias or excessive sedation) has led to package insert wording that the protease inhibitor indinavir (an inhibitor of CYP3A4) not be combined with terfenadine, astemizole, cisapride, triazolam, or midazolam.

The value of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors in treating hypercholesterolemia is well established. Skeletal muscle toxicity, an uncommon side effect of lovastatin and simvastatin, may be increased by drugs that inhibit their metabolism via CYP3A4. The maximum concentration of lovastatin was increased by more than 20 times in the presence of the CYP3A4 inhibitor itraconazole.⁵¹

Finally, enzyme induction has the potential for serious consequences. Antifungal drugs such as itraconazole and ketoconazole are used long-term to control systemic fungal infections. Serum concentrations of itraconazole and its metabolite, hydroxyitraconazole, were decreased by more than 10 times by phenytoin,⁵² enough to render patients susceptible to devastating exacerbations of the mycoses. A similar result might be expected with enzyme induction by carbamazepine, phenobarbital, or rifampin.

In the presence of carbamazepine, blood haloperidol levels decrease by about 50%, and a recent communication reported that thiothixene blood levels were often undetectable when that drug was used with carbamazepine.⁵³ Induction of CYP3A4 by rifampin has markedly decreased blood levels of midazolam and triazolam.⁵⁴ Such possibilities should be considered if a patient complains that a drug has little or no effect despite receiving what is generally considered a therapeutic dose.

A case report in which nefazodone was used to prolong the half-life of alprazolam and overcome “interdose anxiety” related to the latter suggests that drug interactions can be utilized constructively.⁵⁵ Another example of a beneficial drug interaction was the use of ketoconazole in heart transplant patients to inhibit metabolism of the immunosuppressant cyclosporine and reduce average per patient drug costs by \$5200 at the end of 1 year (the drug combination was also associated with fewer infections and transplant rejections).⁵⁶

ANTIDEPRESSANTS AND DRUG INTERACTIONS

Where there is much desire to learn, there of necessity will be much arguing, much writing, many opinions; for opinion in good men is but knowledge in the making.

—John Milton, *Areopagitica*, 1644

In recent years, the psychiatric profession has been inundated by educational materials, claims, pleas, and innuendos about the comparative benefits and risks of various antidepressants when used in combination with each other and with other drugs. Many thorough review articles,

especially with regard to SSRIs, are available for scrutiny.^{38,39,57-65}

Some areas of disagreement exist among reviewers based on differing perspectives of the same research and clinical data. These have been addressed at the lectern and in exchanges of Letters to the Editor.⁶⁶⁻⁶⁹ Readers are encouraged to digest a broad cross section of these reviews so they can leave the literary dining table with a sense of dietary balance.

Serotonin Selective Reuptake Inhibitors

Four SSRIs are available currently in the United States (fluoxetine, fluvoxamine, paroxetine, and sertraline), and a fifth is waiting in the wings (citalopram). They differ with regard to their routes of metabolism and how they influence the P450 system. Considerably less is known about how the SSRIs are metabolized than one might think.^{63,64} Blood fluvoxamine levels are reduced by cigarette smoking (cigarette smoke is an inducer of CYP1A2), thus suggesting a role for that enzyme in its metabolism.⁷⁰ Brain fluoxetine levels in rats were stereoselectively increased by desipramine, an inhibitor of CYP2D6, thereby implicating CYP2D6 in its metabolism.⁷¹

As Brøsen appropriately cautions, P450 inhibitory differences among SSRIs, while real, must be viewed in the context of confounding factors.³⁸ For example, the extent of drug-induced inhibition depends, in part, on the amount of enzyme available to be inhibited. Even though fluoxetine and paroxetine are potent inhibitors of CYP2D6, they would have no effect on the 5%–10% of the Caucasian population who are genetically deficient in this enzyme. Likewise, sertraline, a weaker CYP2D6 inhibitor than fluoxetine or paroxetine, appears to have a greater inhibitory effect in individuals who have higher baseline CYP2D6 activity than in those with lower baseline activity.⁷² The package insert for sertraline does acknowledge that while it “has a less prominent inhibitory effect on 2D6 than some others in the class. . . . even sertraline has the potential for clinically important 2D6 inhibition.”¹⁰⁷

Also, the inhibitory potency of equimolar amounts of the various SSRIs *in vitro* may not carry over directly into the clinical arena because of marked differences in blood level, protein binding, and blood/liver partition at therapeutic doses of these drugs. The fact that some SSRIs exhibit nonlinear kinetics implies that larger than expected increases in blood level will occur as doses of these drugs are titrated upward. Also to be considered in the clinical setting is the degree to which metabolites contribute to enzyme inhibition. What follows must be considered with these cautions in mind.

Citalopram. Citalopram is a racemic drug whose enantiomers stereoselectively inhibit serotonin reuptake (the S-form is more potent). Both CYP2C19 and CYP2D6 appear to be involved in its metabolism,⁵⁸ although a recent

report using human liver microsomes to study the N-demethylation of citalopram found CYP3A4 to be the major enzyme involved, with CYP2C19 playing a minor role and CYP2D6 having no detectable activity.⁷³ With regard to enzyme inhibition, citalopram is a minor player among the SSRIs. It is a weak inhibitor of CYP2D6 (weaker than sertraline, stronger than fluvoxamine) and has little or no effect on CYP1A2 or CYP2C19.⁷⁴

Fluoxetine. Fluoxetine and its major metabolite, norfluoxetine, are both racemates. While CYP2D6 plays some role in fluoxetine metabolism, all of the pathways have not been determined. Harvey and Preskorn note that “Identification of the enzymes involved in the metabolism of FLX [fluoxetine] has proven to be quite difficult.”^{64(p347)}

There is little doubt that therapeutic doses of fluoxetine potentially inhibit CYP2D6. Preskorn et al.⁷⁵ found that blood desipramine levels increased about 400% in the presence of 20 mg daily of fluoxetine. There are also data to suggest a moderate inhibitory effect of fluoxetine and its metabolite on CYP2C19 and CYP3A4.⁵⁸ The clinical implications of a moderate degree of inhibition are less clear than is the more potent impact on CYP2D6. For example, fluoxetine, by inhibiting CYP3A4, increased blood alprazolam levels by about 30%,⁷⁶ and case report data suggest that fluoxetine reduces hepatic clearance of phenytoin.⁷⁷

Fluvoxamine. Fluvoxamine, an achiral drug, is extensively metabolized, but the specific P450 enzymes involved have not yet been identified. As mentioned earlier, indirect evidence from cigarette smokers has implicated CYP1A2. A recent study suggests that both CYP1A2 and CYP2D6 are involved.⁷⁸

Fluvoxamine is the only SSRI that inhibits CYP1A2, and it does so very potently.⁷⁹ For example, 100 mg daily of fluvoxamine increased the half-life of caffeine from 5 to 31 hours.⁸⁰ In case reports, blood clozapine levels were reported to increase 5- to 10-fold in the presence of fluvoxamine.⁸¹ Finally, because fluvoxamine decreased the clearance of theophylline by a factor of 3, there is a package insert recommendation that theophylline dose be reduced to 1/3 of usual if it is co-administered with fluvoxamine.¹⁰⁷

Fluvoxamine also inhibits CYP2C19 and CYP3A4 to moderate degrees, which may be enough to produce clinically meaningful increases in blood levels of benzodiazepines such as diazepam, alprazolam, and triazolam. On the other hand, the degree of CYP3A4 inhibition does not appear sufficient to justify the package insert contraindication to the co-administration of fluvoxamine with terfenadine, astemizole, or cisapride. Using a scaling model to apply *in vitro* data to clinical situations, von Moltke et al.⁸² predicted that even at a dose of 300 mg per day, fluvoxamine would be highly unlikely to produce a clinically significant inhibition of terfenadine metabolism.

Other drugs whose metabolism is inhibited by fluvoxamine include warfarin (a 98% increase in blood level) and propranolol (a 500% increase in blood level).¹⁰⁷

Paroxetine. Although paroxetine is a chiral drug, only the trans isomer is used clinically. CYP2D6 plays a major role in its metabolism, although other enzymes may also be involved.

The ability of paroxetine to inhibit the P450 enzyme system appears restricted to its potent inhibitory effect on CYP2D6.⁶⁴ In normal volunteers, blood levels of desipramine were increased by over 400% when co-administered with 20 mg daily of paroxetine.⁸³

Sertraline. While there is some suggestion that the N-demethylation of sertraline involves CYP3A4, details of its routes of metabolism remain to be determined. There were no differences found in the pharmacokinetics of sertraline and desmethylsertraline between CYP2D6 PMs and EMs, suggesting no major role for that enzyme.⁸⁴

Sertraline does have inhibitory effects on CYP2D6 that are less potent than those of fluoxetine and paroxetine, but more potent than those of citalopram and fluvoxamine. The clinical implications of this inhibition have been the matter of extensive debate. “Lumpers” tend to describe fluoxetine, paroxetine, and sertraline as potent inhibitors of CYP2D6 and focus more on similarities than differences,⁶² while “splitters,” somewhat more convincingly in my opinion, set sertraline apart from the other two as being less potent in this regard.⁸⁵ Nonetheless, sertraline can elevate blood levels of drugs metabolized by CYP2D6.

Sertraline does not appear to have major inhibitory effects on CYP1A2, 2C9, or 3A4. In their review, Harvey and Preskorn report no effect on CYP1A2, slight inhibition of CYP2C9/10, minor effects on CYP2C19, and “modest, but complex” effects on CYP3A3/4.⁶⁴ A study by Ring et al. concluded that sertraline and desmethylsertraline “would be predicted to inhibit metabolic clearance of a coadministered CYP3A metabolized drug by less than 4%.”^{86(p1131)} Recently, two patients were described in whom sertraline appeared to increase blood levels of phenytoin, thus suggesting an inhibitory effect on CYP2C19.⁸⁷

Other Antidepressants

Venlafaxine. Venlafaxine, a serotonin/norepinephrine reuptake inhibitor, is marketed as a racemic mixture. It is oxidized to its major active metabolite, O-desmethylvenlafaxine (ODV) by CYP2D6. A lesser metabolic pathway is N-demethylation to N-desmethylvenlafaxine by CYP3A4.⁸⁸ Venlafaxine and ODV have similar neurotransmitter reuptake inhibitory potencies; therefore, the inhibition of CYP2D6 should not be particularly problematic since the total concentration of venlafaxine plus ODV would remain roughly the same.

Venlafaxine does not have pronounced inhibitory effects on the P450 system. It does not inhibit human microsomal CYP1A2, 2C9, or 3A4,⁸⁹ and it is a relatively weak inhibitor of CYP2D6 (in human liver microsomes, paroxetine, fluoxetine, sertraline, and fluvoxamine were at least 171, 80, 10, and 7 times more potent, respectively).⁸⁸ Ov-

erall, venlafaxine does not appear to be problematic with regard to P450 interactions. At the same time, safety within the P450 system does not confirm immunity from any possibility of adverse drug interactions. Combining venlafaxine with a monoamine oxidase inhibitor (MAOI) is contraindicated because of the risk of a serotonin syndrome (see below). Recently, one such event was reported in a patient taking tranylcypromine who received but a single dose of venlafaxine.⁹⁰

Nefazodone. Nefazodone, a phenylpiperazine antidepressant with a half-life of 2–4 hours, has three active metabolites—hydroxynefazodone, meta-chlorophenylpiperazine (*m*-CPP), and a triazoledione. The specific P450 enzymes involved in the formation of these metabolites have not been determined, although CYP2D6 appears to catalyze the metabolism of *m*-CPP (plasma levels of *m*-CPP were considerably higher in CYP2D6 PMs than in EMs),^{91,92} and desipramine increased the maximum concentration of *m*-CPP by about 40%.⁹³

With regard to P450 enzyme inhibition, nefazodone specializes in CYP3A4; its effects on CYP1A2, 2C19, and 2D6 are not of clinical consequence. On the other hand, inhibition of CYP3A4 by nefazodone is important clinically. Co-administration with terfenadine, astemizole, or cisapride is contraindicated because of concern about cardiac arrhythmias (just how real these concerns are remains to be determined).^{91,107} Serum levels of alprazolam and triazolam are increased substantially in the presence of nefazodone, and oversedation is quite likely unless compensatory dose reduction of benzodiazepine occurs. On the other hand, nefazodone does not alter the pharmacokinetics of lorazepam, because the latter does not require oxidative metabolism.⁹⁴ Nonetheless, since both drugs are sedating, their use together may still require some dose reduction to avoid excessive sedation.

Bupropion. Bupropion is metabolized extensively to four pharmacologically active metabolites—the erythro- and threo-amino alcohols, the erythro-amino diol, and a morpholinol metabolite that is better known as hydroxybupropion. Blood hydroxybupropion levels are at least 10 times higher than those of the parent compound, suggesting that it has a major pharmacologic role to play.

In vitro studies indicate that CYP2B6 is responsible for converting bupropion to hydroxybupropion, with the better known P450 enzymes having no more than minor roles (package insert for Zyban [bupropion hydrochloride], 5/97 and personal communication from Glaxo Wellcome, 1997). In an open, single-dose study of the sustained-release (SR) form of bupropion, no significant differences in pharmacokinetics were noted between smokers and nonsmokers, suggesting that CYP1A2 (induced in smokers) is not involved in bupropion metabolism (package insert for Zyban [bupropion hydrochloride], 5/97). On the other hand, the major role of CYP2B6 in nicotine metabolism and bupropion's effectiveness as a smoking cessation

agent suggest some interesting but as yet unexplored possibilities of interactions at these levels. The observation that carbamazepine decreased blood bupropion levels and increased hydroxybupropion concentration suggests that the drug is an inducer of CYP2B6.²⁹ Valproate, on the other hand, did not alter bupropion concentrations, but did increase hydroxybupropion levels, suggesting inhibition of the metabolism of the latter.⁵⁵

The routes of hydroxybupropion metabolism have not been determined, and despite a clinical report suggesting that CYP2D6 may be involved,⁹⁵ preliminary data from the manufacturer (personal communication from Glaxo Wellcome, 1997) suggest that the P450 system is not involved in a meaningful way. Preskorn did describe a patient who had considerably higher blood bupropion metabolite levels in the presence of fluoxetine than when the same dose of bupropion was given alone,⁹⁶ and another case report suggested that bupropion increased the blood levels of imipramine and its metabolite desipramine.⁹⁷ Since bupropion/SSRI combinations are being used to overcome both treatment-resistant depression and SSRI-induced sexual dysfunction, a more definitive answer to the question of pharmacokinetic interactions is awaited eagerly.

Mirtazapine. Mirtazapine is a racemate with the (+) enantiomer responsible for its α_2 and 5-HT₂ receptor-blocking effects and the (-) enantiomer for the 5-HT₃ receptor blockade. It is metabolized extensively by CYP1A2 and CYP2D6 to an 8-hydroxy metabolite and by CYP3A4 to N-desmethyl and N-oxide metabolites.⁹⁸ An in vitro study in CYP2D6 EMs and PMs, however, suggested that the role of CYP2D6 in the metabolism of mirtazapine is minor.⁹⁹

Mirtazapine is a competitive inhibitor of CYP1A2, 2D6, and 3A4, but it is a relatively weak inhibitor and, consequently, not likely to cause clinically significant interactions with P450 substrates. Once again, it should be mentioned that the absence of pharmacokinetic interactions does not mean the absence of any interactions. For example, mirtazapine has an additive effect on the impairment of motor skills caused by diazepam or alcohol.¹⁰⁷

SEROTONIN SYNDROME

Too much serotonin may have toxic consequences in predisposed individuals. While the serotonin syndrome has been known for almost 40 years, it has attained greater prominence recently because of the widespread use of potent serotonin reuptake inhibitor antidepressants.¹⁰⁰⁻¹⁰³

A serotonin overload syndrome in animals consisting of hyperactivity, stereotypy, seizures, and fever can be prevented by pretreatment with p-chlorophenylalanine, an inhibitor of serotonin synthesis, or with methysergide, a serotonin antagonist. In humans, the syndrome includes myoclonus, hyperreflexia, tremor, delirium, fever, shiver-

ing, sweating, and diarrhea. While it is often reversible with discontinuation of the offending agent(s), deaths have occurred. Treatment is symptomatic and supportive, although benefit has been reported anecdotally with propranolol, methysergide, cyproheptadine, and even mirtazapine.¹⁰⁴

Preventing the serotonin syndrome can be best done by recalling the admonition that "too much serotonin can be hazardous to your health." The big offender appears to be combinations of MAOIs with potent serotonergic drugs such as tryptophan, SSRIs, venlafaxine, and tricyclics. Selegiline is an MAOI, and even though it is a selective type B inhibitor at conventional doses, serotonin syndrome has been described when it has been used with tricyclics, SSRIs, or meperidine. Another area of concern is the combination of serotonin-affecting weight loss agents such as fenfluramine or dexfenfluramine with MAOIs or other serotonergic agents such as SSRIs. While SSRIs and dexfenfluramine have been used together safely,¹⁰⁵ adverse reports are also beginning to appear.¹⁰⁶ The package insert for dexfenfluramine contains a contraindication to use with MAOIs and a precaution stating that it "should not be administered with other serotonergic agents."

As is the case with most uncommon, but potentially severe adverse reactions, combining two drugs safely once does not necessarily mean that it will always be safe to combine the same two drugs. If one prescribes potent serotonergic agents, either alone or together, one must remain attentive to the possibility of a serotonin syndrome.

CONCLUSION

*A little learning is a dangerous thing;
Drink deep, or taste not the Pierian spring.*

—Alexander Pope, *Essay on Criticism*, 1711

With the ever-expanding knowledge base on drug interactions, clinicians will be obligated to take deep draughts from this pharmacologic spring if they are to continue to provide safe and efficacious care for their patients. Drug interactions themselves are mindless; they have no inherent evil intent, yet there is the potential for great harm unless they are recognized and properly managed. Furthermore, drug interactions can be used constructively to improve treatment effectiveness, reduce side effects, and provide pharmacoeconomic benefits.

Drug names: alprazolam (Xanax), astemizole (Hismanal), bupropion (Wellbutrin, Zyban), carbamazepine (Tegretol and others), chloroquine (Aralen), chlorzoxazone (Parafon Forte, Remular-5), cimetidine (Tagamet), cisapride (Propulsid), clarithromycin (Biaxin), clomipramine (Anafranil), clozapine (Clozaril), cyclophosphamide (Cytoxan), cyclosporine (Neoral, Sandimmune), cyproheptadine (Periactin), desipramine (Norpramin), dexamethasone (Decadron and others), dexfenfluramine (Redux), diazepam (Valium and others), disulfiram (Antabuse), erythromycin (Emgel and others), ethinyl estradiol (Brevicon and others), fenfluramine (Pondimin), flecainide (Tambacor), fluoxetine (Prozac),

fluvoxamine (Luvox), haloperidol (Haldol and others), halothane (Fluothane), imipramine (Tofranil and others), indinavir (Crixivan), itraconazole (Sporanox), ketoconazole (Nizoral), lovastatin (Mevacor), meperidine (Demerol and others), methadone (Dolophine and others), methysergide (Sansert), midazolam (Versed), mirtazapine (Remeron), nefazodone (Serzone), olanzapine (Zyprexa), omeprazole (Prilosec), ondansetron (Zofran), orphenadrine (Norflex and others), paroxetine (Paxil), perphenazine (Trilafon and others), phenobarbital (Luminal and others), phenytoin (Dilantin and others), prednisone (Delta-Dome and others), propafenone (Rythmol), propoxyphene (Darvon), propranolol (Inderal), rifampin (Rifadin and others), risperidone (Risperdal), ritonavir (Norvir), saquinavir (Invirase), selegiline (Eldepryl), sertraline (Zoloft), simvastatin (Zocor), tacrine (Cognex), tamoxifen (Nolvadex), temazepam (Restoril and others), terfenadine (Seldane), theophylline (Quibron and others), thioridazine (Mellaril and others), thiothixene (Navane), tramadol (Ultram), tranlycypromine (Parnate), triazolam (Halcion), venlafaxine (Effexor), warfarin (Coumadin and others), yohimbine (Yocon and others), zolpidem (Ambien).

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