

# Drug and Diet Interactions: Avoiding Therapeutic Paralysis

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An explosion of information about drug and diet interactions has greatly complicated and confused the use of antidepressant drugs, yet if clearly understood, such information will actually enhance the safety and efficacy of these medications. The background against which antidepressants are discussed includes an overview of the cytochrome P450 (CYP) system (which now contains over 500 P450 genes), the concepts of enzyme specificity and selectivity, the roles of genetics and nonpharmacologic environmental factors, and examples of beneficial and detrimental drug and diet interactions. The comparative profiles of the various antidepressants are then presented with consideration given to their roles as substrates, inhibitors, and inducers of P450 enzymes such as CYP1A2, 2B6, 2C, 2D6, and 3A4. Examples of clinically important antidepressant drug/drug and drug/diet interactions are provided. (*J Clin Psychiatry* 1998;59[suppl 16]:31-39)

Imagine how dismayed your patient might be after passing an orange rubbery mass in his or her stool. A "Dear Doctor" letter recently discussed just such an experience following ingestion of carbamazepine suspension and chlorpromazine solution (Novartis Pharmaceuticals, written communication, 1998). The mixing together of these 2 liquids (and also carbamazepine suspension and liquid thioridazine) does result in precipitation of an orange rubbery mass. Whether the bioavailability of the involved medications is altered by this interaction was not tested, but the possibility is real.

The topic of drug interactions, a medical curiosity not too many years ago, is now one of great clinical importance and growing public interest. The legal profession is also becoming more attentive to the role played by drug interactions in issues of medical liability. For these and other reasons, today's psychiatrists must be attentive to the possibility of adverse interactions, not only between the drugs that he or she prescribes, but also between these medications and those prescribed by other physicians, those available over-the-counter, and those provided by well-intentioned friends and relatives. In addition, the foods we eat and the drinks we drink can also alter the

metabolism of the drugs we take. For example, a diet high in cruciferous vegetables (cabbage, broccoli, brussels sprouts, and others) or charbroiled meats can substantially reduce blood levels of drugs metabolized by cytochrome P450 1A2 (CYP1A2) because these substances are inducers of the enzyme.<sup>1,2</sup>

Grapefruit juice has achieved prominence as a potent inhibitor of several P450 enzymes (CYP1A2, 2A6, and 3A4), with its predominant effect on 3A4 in the gut wall.<sup>3</sup> The effect grapefruit juice has on drug metabolism is not trivial, as is illustrated by the following: (1) the area under the curve (AUC) of felodipine, a calcium channel blocker, was increased by 240%, and effects on blood pressure and heart rate were doubled; (2) peak concentrations of nisoldipine, another calcium channel blocker, increased 5-fold; and (3) blood cyclosporine levels increased by 300%.<sup>4</sup>

Grapefruit juice was shown to inhibit terfenadine metabolism and prolong the QT interval on the electrocardiogram of healthy volunteers,<sup>5</sup> which could increase the cardiotoxicity of terfenadine. There is actually a report of a terfenadine-associated sudden death in a 29-year-old who had consumed 2 glasses of grapefruit juice on the day of his demise.<sup>4</sup> Since the impact of grapefruit juice on the metabolism of a number of drugs is so substantial, Spence<sup>4</sup> commented quite appropriately that the public should be warned about this risk. Nonetheless, he remarked that "13 months of vigorous discussion with Canadian and U.S. regulatory authorities and the manufacturers of a number of drugs involved, as well as contact with several reporters involved in public health journalism, have failed to result in any adequate warning to the public."<sup>(p395)</sup> On the other hand, the *Australian Pharmaceutical Formulary and Handbook* has included extra warning labels stating,

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“Avoid eating grapefruit and drinking grapefruit juice while being treated with this medication,” to be attached to appropriate medication containers.<sup>6</sup>

Readers will be relieved to learn that although red wine (not white) inhibits CYP3A4 activity, it is much weaker than grapefruit juice, does so in a largely reversible fashion, and is much less likely to cause clinically meaningful drug interactions.<sup>7</sup>

Drug interactions have been divided into those that are pharmacodynamic and those that are pharmacokinetic. Pharmacodynamic interactions occur at the level of mechanism of action of drugs. For example, a delirium may result from combining several drugs with anticholinergic activity, or ataxia and incoordination may be exaggerated by combining alcohol and a benzodiazepine. Pharmacokinetic interactions, on the other hand, involve absorption, distribution, metabolism and excretion of drugs.<sup>8</sup> The “orange rubbery mass” was the result of a pharmacokinetic interaction affecting absorption. The well-known increase in serum lithium level caused by thiazide diuretics is an example of a pharmacokinetic interaction that alters excretion. The cytochrome P450 enzyme system plays a major role in pharmacokinetic interactions affecting the metabolism of drugs. This review will focus on the P450 system and the roles it plays in interactions of interest to prescribers of psychopharmacologic drugs (especially antidepressants).

Before grappling with the P450 system, readers should be aware that there is a far more vast assortment of drug-metabolizing enzymes in the body. For example, although phenobarbital is a well-known inducer of P450 enzymes, it also induces aldehyde dehydrogenase, epoxide hydrolase, NADPH-cytochrome P-450 reductase, UDPglucuronyl transferase, and several glutathione S-transferases.<sup>9</sup> The flavin-containing monooxygenases (FMOs) constitute a P450 rival in terms of being another major monooxygenase metabolic system.<sup>10</sup> The FMO enzymes, 5 in number thus far, catalyze NADPH-dependent oxidation of drugs that contain nucleophilic heteroatoms (atoms other than carbon). Included as FMO substrates to one degree or another are psychiatric drugs such as clozapine, olanzapine, phenothiazines, imipramine, and fluoxetine (which are also metabolized by P450 enzymes). Some individuals who are unfortunate enough to have a mutation of the FMO3 gene are unable to metabolize trimethylamine (a dietary choline by-product), which, in turn, causes them to smell like rotting fish. Needless to say, the fish-odor syndrome causes great psychological distress.<sup>11</sup>

### THE CYTOCHROME P450 FAMILY

The cytochrome P450 enzyme system is the major player in the metabolism of xenobiotics (foreign chemicals).<sup>12-14</sup> These heme-containing proteins are located, for the most part, in the smooth endoplasmic reticulum of

Table 1. Some of the Human P450 Enzymes

Superfamily	Family	Subfamily	Gene
CYP	1	A	2
CYP	2	C	19
CYP	3	D	6
CYP	3	A	4

cells in various organs including liver, intestine, kidney, lung, and brain. They catalyze oxidative reactions such as hydroxylation, dealkylation, deamination, *N*-oxidation, and sulfoxidation. Incidentally, the 450 in the title refers to the peak wavelength in nanometers at which light is absorbed after these heme-containing liver microsomal pigments are bound to carbon monoxide. While the number of P450 enzymes that abounds throughout the entire plant and animal kingdoms approaches (or perhaps has exceeded) 500, the number currently known to play major roles in human drug metabolism is considerably smaller.<sup>15</sup> The enzymes are classified according to degrees of similarity of their amino acid sequences with the symbol CYP referring to the entire superfamily, Arabic numbers to families, capital letters to subfamilies, and Arabic numbers to individual enzymes (or genes) (Table 1). For example, enzymes within the CYP2 family have at least 40% similarity of amino acid sequence, while enzymes within the CYP2D subfamily are at least 55% similar. Sometimes, sequences are so close that it is difficult to know whether there are meaningful differences between enzymes (CYP3A3 and CYP3A4 are 98% similar in their amino acid sequences).

Since the number of xenobiotics vastly exceeds the number of P450 enzymes, it is fortunate that these enzymes are not highly substrate specific. In other words, these enzymes are nonselective. They recognize several chemical configurations of molecules rather than individual molecules. At the same time, there is a certain degree of specificity in that a particular enzyme will preferentially metabolize a particular chemical. In the absence of such an enzyme, metabolism will not be absent, but it will be considerably less efficient.

The P450 system is characterized by its arbitrary nature in that its metabolic products are sometimes more dangerous than the parent compounds. This disturbing observation underscores the fact that these enzymes do not exist solely for the good of humankind. For example, carcinogens, mutagens, and toxins can be either inactivated or activated by these enzymes. The CYP1A subfamily actually activates over 90% of known carcinogens,<sup>12</sup> which raises the issue of whether inducers of this enzyme (e.g., charbroiled meats, crucifers, cigarette smoke) promote carcinogenesis and whether inhibitors (e.g., grapefruit juice, watercress, flavonoids, fluvoxamine) are cancer protective. The induction of CYP2E1 by alcohol (5- to 10-fold) may increase the likelihood of acetaminophen hepatotox-

icity by channeling more of the drug away from direct conjugation to conversion by 2E1 to hepatotoxic electrophilic metabolites.<sup>16</sup>

### Genetic Polymorphism

Have you noticed a peculiar odor to your urine after you eat asparagus? If so, be reassured that this experience was shared by 43% of 800 volunteers in the United Kingdom whose “asparagus urine” has been described as smelling like rotten or boiling cabbage.<sup>17</sup> This genetic difference (odor or no odor) is but one example of a genetic polymorphism—“a type of variation in which individuals with sharply distinct qualities co-exist as normal members of a population.”<sup>18(p139)</sup> Incidentally, the precursor of the odor is asparagusic acid, and the odor itself has been attributed to the production of 6 sulfur-containing alkyl compounds.<sup>19</sup> The asparagus urine polymorphism may be even more complicated; 1 study suggested that the ability to smell or not smell the odor may also be genetically determined—a polymorphic smell hypersensitivity.<sup>20</sup> To carry genetics 1 step further, a non-odor-producing woman became an odor producer as her pregnancy progressed because her baby carried the trait, even though she did not.<sup>21</sup> Finally, the finding that 100% of 103 French volunteers produced the distinctive odor after eating asparagus suggests that ethnic differences may exist with regard to this polymorphism (or that French asparagus is metabolized differently from English asparagus).<sup>22</sup>

Other genetic polymorphisms play major roles in drug metabolism. Some of the P450 enzymes exhibit this property, which means that some individuals have a functional enzyme while others do not. For example, CYP2D6 is inactive in 5%–10% of Caucasian individuals and 1%–2% of Asian individuals, whereas CYP2C19 is inactive in 18%–20% of Asian individuals and 3%–5% of Caucasian individuals. Both CYP1A2 and CYP2E1 may also exhibit some degree of genetic polymorphism.<sup>23,24</sup> Individuals lacking a functional enzyme will be very inefficient in metabolizing drugs that are substrates for that enzyme. They are referred to as poor metabolizers in contrast to their enzyme-intact brethren who are known as extensive metabolizers. There is considerable variation among extensive metabolizers, with some having partially functional enzymes (slow metabolizers) and a few having extra functional genes that make them ultrarapid metabolizers. Small wonder that even in the absence of enzyme inhibition or induction by other chemical compounds there are marked variations in the blood levels of many drugs, even among individuals receiving the same dose.

Genetic polymorphism explains, in part, why a particular drug may have reduced activity in some people and increased activity in others. For example, CYP2D6 deficient individuals will not *O*-demethylate codeine to morphine and, consequently, will get little or no analgesic effect from codeine, which, by itself, is not an effective analge-

sic.<sup>25</sup> On the other hand, a woman who experienced euphoria, dizziness, and severe epigastric pain within 30 minutes of taking a conventional dose of codeine was determined to be an ultrarapid metabolizer who was suffering from excessive conversion of codeine to morphine.<sup>26</sup> Another study that found a 45-fold difference in ability to *O*-demethylate codeine between poor metabolizers and ultrarapid metabolizers<sup>27</sup> underscores the potential for enormous variation in the clinical effects of codeine. Finally, oral opiate dependence (codeine and others) was found to be considerably less common in poor metabolizers of CYP2D6, suggesting that the impaired ability to produce active metabolites may be a “pharmacogenetic protective factor.”<sup>28</sup>

To summarize, poor metabolizers will have higher concentrations of parent drug and lower concentrations of metabolite, and they will not be susceptible to the influences of inhibitors or inducers of that particular enzyme. Extensive metabolizers, on the other hand, will have lower concentrations of parent drug and higher concentrations of metabolite, and they will be susceptible to the effects of enzyme inhibition and induction.

### Enzyme Induction and Inhibition

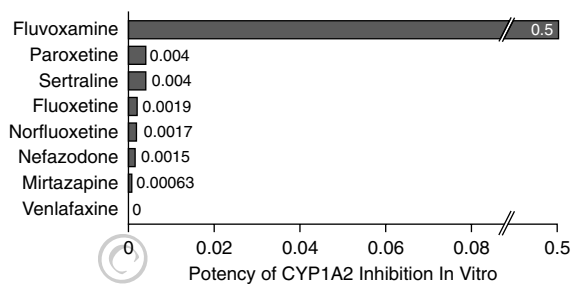
The process of induction increases the amount of an enzyme that is available, so that drugs that are substrates for the enzyme are metabolized faster. Induction is a gradual process taking place over many days, which explains why blood carbamazepine levels may decrease days to weeks after initiation of treatment despite the maintaining of a constant oral dose. Not only does carbamazepine induce its own metabolism (auto-induction), it also induces the metabolism of many other drugs. For example, enzyme induction caused by carbamazepine increases the clearance of olanzapine and haloperidol by about 50% and decreases blood levels of estrogen so that oral contraceptives may lose their effectiveness.

Potent inducers of CYP1A2 include polycyclic aromatic hydrocarbons that are found in cigarette smoke, charbroiled meats, and various environmental pollutants.<sup>29</sup> For example, the clearance of olanzapine is 40% higher in cigarette smokers, which may explain, in part, the higher-than-expected dose requirements in certain patients. The opposite would also be possible; a smoker stabilized on olanzapine treatment might experience troublesome side effects as blood levels rose following smoking cessation.

Enzyme induction is also prevalent on college campuses, as exemplified by students who can “really hold their liquor.” Perhaps these misguided youth would be less revered by their peers if it were recognized that their apparent prowess was merely a reflection of the ability of alcohol to induce the enzymes involved in its metabolism.<sup>30</sup>

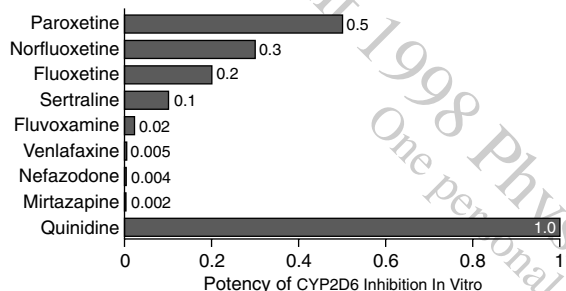
Unlike induction, enzyme inhibition occurs rapidly, resulting in increased blood levels and increased pharmacologic effects of parent compounds. For example, inhibition

Figure 1. Potency of Some Antidepressants In Vitro at Inhibiting Cytochrome P450 Enzyme (CYP) 1A2\*



\*Reprinted from reference 36, with permission. Potency data expressed as  $10^{-7} \times 1/K_i$ , in which  $K_i$  = inhibitor constant in molarity.

Figure 2. Potency of Some Antidepressants In Vitro at Inhibiting Cytochrome P450 Enzyme (CYP) 2D6\*

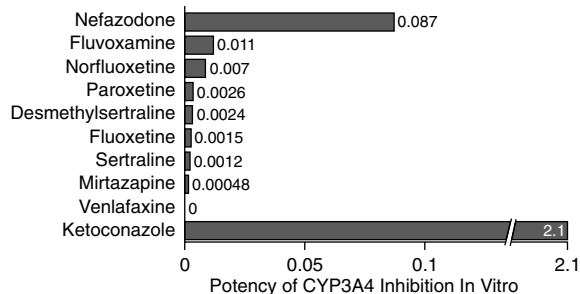


\*Reprinted from reference 36, with permission. Potency data expressed as  $10^{-7} \times 1/K_i$ , in which  $K_i$  = inhibitor constant in molarity.

of felodipine metabolism by grapefruit juice was fully developed after the first glass—no greater effect evolved after 2 weeks of daily consumption.<sup>31</sup> The terfenadine story is a tragic example of enzyme inhibition that resulted in deaths and removal of the drug from the market. Terfenadine is a pro-drug whose conversion to an active antihistamine required metabolism by CYP3A4. Potent 3A4 inhibitors such as ketoconazole not only prevented activation of the drug, but also led to the accumulation of high levels of the cardiotoxic parent compound. Lethal arrhythmias such as torsades de pointes were the consequence. Because of this, terfenadine is no longer available, but it has been replaced in the marketplace by its cardiac-safe, antihistaminic metabolite—fexofenadine.<sup>32</sup>

Just how much of an impact enzyme induction and inhibition have on the metabolism of other drugs depends considerably on the potency of the inducer or inhibitor and the nature of the substrate. A 50% increase in blood level of a drug that was in the lower range of therapeutic or a 50% decrease from the upper range of therapeutic may go unnoticed, whereas the opposite, a 50% increase from high therapeutic to toxic or a 50% decrease from therapeutic to subtherapeutic could be problematic. The hypnotic triazolam is a good example of how induction and inhibi-

Figure 3. Potency of Some Antidepressants In Vitro at Inhibiting Cytochrome P450 Enzyme (CYP) 3A4\*



\*Reprinted from reference 36, with permission. Potency data expressed as  $10^{-7} \times 1/K_i$ , in which  $K_i$  = inhibitor constant in molarity.

tion can markedly affect drug metabolism. Rifampin, an antitubercular drug, is such a potent inducer of CYP3A4 that it rendered triazolam virtually ineffective by reducing its area under the curve (AUC) to 5% of control and its maximum serum concentration to 12% of control.<sup>33</sup> On the other hand, inhibition of triazolam metabolism by ketoconazole or itraconazole increased its AUC over 20-fold and its peak concentration 3-fold.<sup>34</sup> It was estimated that the AUC of triazolam would increase almost 500 times if a patient were treated sequentially with rifampin and itraconazole.<sup>33</sup> The package insert for triazolam now states that the drug is “contraindicated with ketoconazole, itraconazole, and nefazodone, medications that significantly impair the oxidative metabolism mediated by cytochrome P450 3A (CYP3A).”<sup>35</sup>

## ANTIDEPRESSANT DRUG INTERACTIONS

All of one's working hours could be easily devoted to reading the voluminous literature that has accrued in recent years on the topic of antidepressant drug interactions. Review articles appear with regularity and are important sources of clinically valuable information.<sup>24,36-43</sup> Since authors' perspectives vary and their interpretation of the same clinical observations and research data may differ, readers are encouraged to become familiar with at least several of these reviews. Most of the literature focusing on the newer antidepressants (fluoxetine and beyond) has been directed at how much or how little they inhibit metabolism of other drugs and, at times, the boundary between marketing and science has become blurred. Considerably less attention has been devoted to how these drugs are biotransformed and the clinical implications of altering their biotransformation.

Recently, Richelson<sup>37</sup> compiled graphs comparing the in vitro inhibitory potencies of the new antidepressants on 3 of the more important P450 enzymes—CYP1A2, 2D6, and 3A4. These graphs (Figures 1, 2, and 3), reproduced here with the kind permission of the author and the publisher, can serve as reference anchors for the text that fol-

lows. However useful in vitro data might be, there are a number of factors that may modulate their applicability to the clinical setting.<sup>44</sup> These include the serum concentration of the drug, the concentration and activity of metabolites, the extent of protein binding, and the concentration of drug and active metabolites attained in the liver, intestinal wall, and other sites of biotransformation.

### Selective Serotonin Reuptake Inhibitors (SSRIs)

There are 4 SSRIs marketed in the United States for the treatment of depression—citalopram, fluoxetine, paroxetine, and sertraline. The fifth SSRI, fluvoxamine, an antidepressant elsewhere in the world, has been available in the United States for several years to treat obsessive-compulsive disorder. There are very clear differences in the P450 profiles of these 5 drugs.

**Citalopram.** This drug appears to be the “cleanest” of the 5 SSRIs with regard to P450 enzyme inhibition. Both citalopram and its major metabolite, desmethylcitalopram, cause negligible inhibition of CYP2C, 2E1, and 3A4, and inhibition of CYP1A2, 2C19, and 2D6 is so weak that it was considered unlikely that therapeutic amounts of the drug would cause clinically meaningful inhibition of drug biotransformation in humans.<sup>45</sup> Nonetheless, when healthy volunteers took 40 mg daily of citalopram for 7 days followed by a single 100-mg dose of imipramine, there was about a 50% increase in the AUC of imipramine’s metabolite desipramine.<sup>46</sup> Further in vivo work will be necessary to determine whether inhibition of CYP2D6 by citalopram will have any substantial impact on substrates of this enzyme. No change in warfarin pharmacokinetics (CYP1A2, 3A4, 2C9) was found in normal volunteers taking 40 mg daily of citalopram.<sup>47</sup>

The metabolism of citalopram to desmethylcitalopram appears to be by way of CYP3A4, with 2C19 also involved and 2D6 playing a negligible role.<sup>48,49</sup>

**Fluoxetine.** Fluoxetine and its major metabolite, norfluoxetine, are potent inhibitors of CYP2D6. Blood levels of desipramine (a CYP2D6 substrate) in normal volunteers increased about 4-fold in the presence of 20 mg daily of fluoxetine.<sup>50</sup> Fluoxetine may also have modest inhibitory effects on CYP2C and 3A4, although the clinical significance of this inhibition is unclear. There have been reports of fluoxetine-associated increases in phenytoin (2C9), diazepam (2C19), and alprazolam (3A4) levels.<sup>51</sup>

The metabolism of fluoxetine to norfluoxetine is mediated by CYP2C9, with lesser contributions from 2C19 and 3A. CYP2D6 does not appear to play a major role in fluoxetine metabolism,<sup>52</sup> although this point has not been fully resolved. One study found that fluoxetine levels were higher in poor metabolizers of CYP2D6 than in extensive metabolizers,<sup>53</sup> and another found that desipramine, a CYP2D6 inhibitor, increased fluoxetine levels in rat brain.<sup>54</sup>

**Fluvoxamine.** As is clear from Figure 1, fluvoxamine is a potent inhibitor of CYP1A2; in fact, it is the only antide-

pressant with prominent effects on this enzyme. It also has moderate inhibitory activity with regard to CYP2C and 3A4. Drugs metabolized primarily by CYP1A2 can have their levels (and effects) increased substantially by fluvoxamine. For example, blood clozapine levels can increase many-fold,<sup>55</sup> theophylline levels can become toxic,<sup>56</sup> and the elimination half-life of caffeine can increase greatly (one study found that caffeine half-life increased from 5 to 31 hours in the presence of 100 mg daily of fluvoxamine).<sup>57</sup> The package insert for fluvoxamine advises that one third the usual maintenance dose of theophylline be used when it is co-administered with fluvoxamine.<sup>58</sup> Additional package insert observations include a 98% increase in blood warfarin level with associated prolongation of prothrombin times and a 5-fold increase in minimum blood propranolol level in the presence of fluvoxamine.

All fluvoxamine drug interactions are not necessarily problematic. Fluvoxamine inhibition of clomipramine metabolism was used therapeutically to overcome treatment resistance associated with low blood clomipramine levels.<sup>59</sup> In addition, by inhibiting the conversion of clomipramine to desmethylclomipramine, fluvoxamine increases the ratio of the more serotonergic parent compound to the more noradrenergic metabolite. This may have clinical implications when considering which SSRI to use in combination with clomipramine to treat obsessive-compulsive disorder.<sup>60</sup>

The details of fluvoxamine metabolism have not been fully elucidated, but both CYP1A2 and 2D6 appear to be involved.<sup>61</sup> Cigarette smokers (CYP1A2 induction) have lower fluvoxamine levels than nonsmokers, and poor metabolizers of CYP2D6 have higher blood levels than extensive metabolizers.

**Paroxetine.** In a sense, paroxetine is a highly specialized SSRI—it potently inhibits CYP2D6, but has relatively modest effects on other P450 enzymes.<sup>62</sup> Blood desipramine levels (AUC) in normal volunteers were noted to increase by more than 400% in the presence of 20 mg daily of paroxetine.<sup>63</sup> A more graphic example of CYP2D6 inhibition by paroxetine was the demonstration that 20 mg daily increased peak plasma levels of perphenazine 13-fold and resulted in excessive sedation, impaired memory and psychomotor performance, and extrapyramidal symptoms.<sup>64</sup>

Paroxetine metabolism appears to be by way of CYP2D6, although at least 1 other enzyme also may be involved.<sup>51</sup>

**Sertraline.** Sertraline is the SSRI that has generated the most controversy about its P450 profile. Compared with fluoxetine and paroxetine, it is a considerably weaker inhibitor of CYP2D6, although “weaker than” does not mean “inert.” Blood desipramine levels increase on average of about 30% to 35% in the presence of 50 mg daily of sertraline, and even at a dose of 150 mg/day, the increase remains quite modest.<sup>51</sup> It appears that the magnitude of

sertraline-induced CYP2D6 inhibition is greater in patients whose baseline 2D6 activity is higher.<sup>65</sup>

It is important to remember that in clinical practice, one deals with individuals rather than averages. In some patients, sertraline may cause meaningful elevations in blood levels of drugs metabolized by CYP2D6. A study in elderly depressed patients found a 2% median increase in mean nortriptyline level after the addition of 50 mg daily of sertraline and a 40% median increase in those taking 100 or 150 mg/day.<sup>66</sup> At the same time, the maximum increase with 50 mg was 117%, and with 100 to 150 mg it was 239%. The package insert for sertraline quite appropriately notes: "Nevertheless, even sertraline has the potential for clinically important 2D6 inhibition."<sup>67</sup>

Aside from CYP2D6, sertraline does not seem to have clinically meaningful inhibitory effects on CYP1A2<sup>68</sup> or CYP3A4.<sup>69</sup> CYP2C inhibition by sertraline is also weak, although sertraline-related elevations of phenytoin levels without symptoms of clinical toxicity were described recently in 2 patients.<sup>70</sup>

Sertraline is metabolized to *N*-desmethylsertraline, a considerably weaker inhibitor of serotonin uptake, but an equipotent inhibitor of P450 enzymes. CYP3A4 appears to play a role in this transformation.<sup>51</sup>

### Other Antidepressants

**Bupropion.** Despite being on the market since 1989, very little is known about whether bupropion and its metabolites have inhibitory effects on the P450 system. A patient taking imipramine was noted to have higher levels of imipramine and desipramine while taking bupropion which suggested the possibility of CYP2D6 inhibition.<sup>71</sup> Unfortunately, a single case report is insufficient to allow one to reach a meaningful conclusion. Hopefully, some definitive pharmacokinetic research will be done to establish whether this drug inhibits any of the P450 enzymes.

More is known about the metabolism of bupropion, which appears to be mediated primarily by CYP2B6,<sup>72</sup> one of the less well recognized and studied P450 enzymes (CYP1A2, 2A6, 2C9, 2E1 and 3A4 play lesser roles) (Glaxo Wellcome Inc., oral communication, 1997). In addition to converting bupropion to hydroxybupropion, CYP2B6 is also involved in the biotransformation of mianserin, temazepam, diazepam, cyclophosphamide, halothane, nicotine, and styrene.<sup>73</sup> It is inhibited by orphenadrine, so that orphenadrine might be expected to increase bupropion levels. CYP2B6 is induced by phenobarbital and quite likely by carbamazepine since it appeared to markedly reduce bupropion levels and increase hydroxybupropion levels.<sup>74</sup> The fact that there was no difference in the metabolism of bupropion and its metabolites between smokers and nonsmokers suggests that CYP1A2 is not involved in any clinically meaningful way.<sup>75</sup> Despite a report finding higher hydroxybupropion levels in the presence of fluoxetine<sup>76</sup> and another study finding higher levels in

poor metabolizers of CYP2D6,<sup>77</sup> preliminary data from the manufacturer suggest that hydroxybupropion is metabolized outside the P450 system (Glaxo Wellcome Inc., oral communication, 1997).

**Venlafaxine.** The effects of venlafaxine on the P450 system are quite limited. CYP1A2 and 2C9 are not inhibited by this drug, whereas CYP2D6 is inhibited, but weakly (Figures 1, 2, and 3).<sup>78</sup> Venlafaxine and its metabolites are weak enough in vitro inhibitors of CYP3A that clinically important interactions with CYP3A substrates are quite unlikely.<sup>79</sup> Information provided in the package insert for the extended-release venlafaxine preparation notes that while the drug does not alter the kinetics of imipramine and 2-OH-imipramine, desipramine AUC and maximum concentrations ( $C_{max}$ ) increased by about 35% in the presence of venlafaxine.<sup>80</sup> In addition, 2-OH-desipramine AUC increased 2.5-fold (with 37.5 mg of venlafaxine every 12 hours) and 4.5-fold (with 75 mg every 12 hours). The clinical significance of this rather substantial increase in 2-OH-desipramine levels is unknown, although other studies have linked this compound to some of the cardiotoxic effects of desipramine. A study in healthy volunteers given 100 mg of imipramine after taking 150 mg daily of venlafaxine for 3 days found no change in imipramine levels but a 58% increase in desipramine AUC and a 28% increase in desipramine  $C_{max}$ .<sup>81</sup>

The metabolism of venlafaxine involves *O*-demethylation to its major active metabolite, *O*-desmethylvenlafaxine (ODV), via CYP2D6 and *N*-demethylation to lesser metabolites by CYP3A4.<sup>72</sup> Since venlafaxine and ODV have similar serotonin and norepinephrine uptake inhibiting potencies, inhibition of CYP2D6 should not alter the overall neurotransmitter impact of this drug.

**Nefazodone.** As shown in figures 1, 2, and 3, nefazodone is the most potent antidepressant with regard to inhibition of CYP3A4, but it has much weaker inhibitory effects on CYP1A2 and 2D6 (the same is also true for 2C19). In volunteers, 300 mg daily of nefazodone had no significant effect on blood levels of desipramine.<sup>83</sup> The failure of nefazodone to interact adversely with warfarin suggests that it does not significantly inhibit CYP2C9.<sup>84</sup> While its effects on CYP1A2, 2D6, and 2C are unlikely to be clinically meaningful, CYP3A4 inhibition is such that the use of nefazodone with terfenadine, astemizole, cisapride, and triazolam is not advised.<sup>85</sup> Furthermore, the package insert recommends that alprazolam doses be reduced by 50% if it is used with nefazodone. While alprazolam/nefazodone interactions could result in oversedation secondary to pharmacokinetic and pharmacodynamic (both are sedating) interactions, in one situation the combination was used successfully to extend the elimination half-life of alprazolam to overcome "interdose anxiety."<sup>86</sup>

Further indications that nefazodone's inhibition of CYP3A4 may be of clinical importance are case reports of carbamazepine toxicity,<sup>87</sup> myositis and rhabdomyolysis

with simvastatin,<sup>88</sup> and a 70% increase in blood cyclosporine level.<sup>89</sup> Obviously, one should be cautious about combining nefazodone with CYP3A4 substrates.

The P450 enzymes involved in the conversion of nefazodone to its 3 active metabolites have not yet been characterized. One metabolite, *m*-chlorophenylpiperazine (*m*-CPP), is biotransformed by CYP2D6. Inhibitors of this enzyme have been shown to increase plasma *m*-CPP levels.<sup>83</sup> The clinical implication of this interaction is not clear, although there has been speculation that high levels of *m*-CPP might be associated with anxiogenic effects.<sup>90</sup>

**Mirtazapine.** In vitro studies suggest that mirtazapine is not a potent inhibitor of CYP1A2 (838 times weaker than fluvoxamine), 2D6 (10 times weaker than fluoxetine), or 3A4 (1393 times weaker than ketoconazole).<sup>86</sup> The in vitro data presented by Richelson<sup>36</sup> (Figures 1, 2, and 3) support this lack of potency. Consequently, pharmacokinetic interactions do not appear to be a problem with mirtazapine, although confirmation is necessary in vivo.

Metabolism of mirtazapine involves CYP1A2 and 2D6 in formation of the 8-hydroxy metabolite and CYP3A4 in forming the *N*-desmethyl and *N*-oxide metabolites.<sup>91</sup> Mirtazapine is a racemate, and data suggest that the major enantiomer is not metabolized by CYP2D6 (the minor enantiomer is present in lower serum concentrations so CYP2D6 inhibition is unlikely to have a major impact on overall mirtazapine concentrations).<sup>92,93</sup>

**Moclobemide.** Elsewhere in the world, moclobemide, a reversible inhibitor of monoamine oxidase A, is used extensively, so its P450 profile should be of interest to many readers. An in vivo study found the drug to be a potent inhibitor of CYP2D6,<sup>94</sup> and a similar study also found inhibitory effects on CYP1A2 and 2C19.<sup>95</sup> These effects were reflected clinically by the finding that plasma trimipramine levels increased by 39% and maprotiline levels increased by 25% (N.S.) in the presence of moclobemide.<sup>95</sup> As in most studies of this type, there was a wide range in blood level change across individuals. The P450 enzymes involved in the metabolism of moclobemide have not been elucidated fully, but CYP2C19 appears to play a major role in the formation of at least 1 of the major metabolites.<sup>95</sup>

## CONCLUSION

For, in diseases of the mind, as well as in all other ailments, it is an art of no little importance to administer medicines properly: but, it is an art of much greater and more difficult acquisition to know when to suspend or altogether to omit them.

—Philippe Pinel (1745–1826), *A Treatise on Insanity*

Regardless of whether Pinel had specific knowledge of drug interactions, he recognized the need to be attentive to

how drugs are used. Clinicians today have the advantage of working with well-characterized chemical compounds (herbal medicines excluded) and a wealth of information about drug interactions. Physicians have an obligation to their patients to avail themselves of this information to allow them to provide the highest level of effective and safe care.

**Drug names:** alprazolam (Xanax), astemizole (Hismanal), bupropion (Wellbutrin), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), cisapride (Propulsid), citalopram (Celexa), clomipramine (Anafranil), clozapine (Clozaril), cyclophosphamide (Cytoxan), cyclosporine (Neoral, Sandimmune), desipramine (Norpramin and others), diazepam (Valium and others), felodipine (Plendil), fexofenadine (Allegra), fluoxetine (Prozac), fluvoxamine (Luvox), haloperidol (Haldol and others), halothane (Fluothane), imipramine (Tofranil and others), itraconazole (Sporanox), ketoconazole (Nizoral), maprotiline (Ludiomil), mirtazapine (Remeron), nefazodone (Serzone), nisoldipine (Sular), nortriptyline (Pamelor and others), olanzapine (Zyprexa), orphenadine (Norflex, Norgesic), paroxetine (Paxil), perphenazine (Trilafon), phenobarbital (Luminal and others), phenytoin (Dilantin and others), propranolol (Inderal and others), rifampin (Rifamate and others), sertraline (Zoloft), simvastatin (Zocor), temazepam (Restoril and others), terfenadine (Seldane), theophylline (Aerolate and others), thioridazine (Mellaril and others), triazolam (Halcion), trimipramine (Surmontil), venlafaxine (Effexor), warfarin (Coumadin and others).

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