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REVIEW OF THE PHARMACOKINETICS, PHARMACOGENETICS, AND DRUG INTERACTION POTENTIAL OF ANTIDEPRESSANTS: FOCUS ON VENLAFAXINE

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Improving outcomes for patients with depression involves selecting the best possible drug therapy. Considerations relevant to drug product selection include: 1) pharmacokinetic issues such as half-life and time to steady-state, and protein binding; 2) pharmacodynamic drug-drug interactions; and 3) drug metabolism-related drug interactions. A comparison of selected antidepressants with an emphasis on venlafaxine's similarities and differences is presented. Based on these parameters, selecting an antidepressant medication, such as venlafaxine, that has a low potential for drug interactions at the Cytochrome P450 (CYP) enzyme system, and is easy to monitor and dose, facilitate successful treatment of patients. Venlafaxine has been evaluated in clinical studies that demonstrate low to negligible drug interaction potential at CYP2D6, CYP1A2, CYP2C19, and CYP3A4. Its short half-life and time to steady-state, when coupled with the extended release characteristics of the preferred dosage formulation allow for once daily dosing and rapid attainment of therapeutic effects. The CYP3A4 system is involved in both first-pass metabolism and systemic clearance of medications. Drug interactions at this isoenzyme have proven to be of high clinical relevance ranging from cardiovascular toxicity and death with commonly used drugs such as cisapride, to subtherapeutic levels of cyclosporine or protease inhibitors leading to transplant rejection or HIV relapse. Reasons for the under detection and reporting of drug interaction mediated adverse events include healthcare system structure, the poor return to follow up of non-adherent patients, the need for greater education and training of clinicians to recognize drug-related adverse events, and the reluctance of patients to spontaneously communicate about the unpleasant effects of their medication. Depression and Anxiety, Volume 12, Supplement 1:30–44, 2000.
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INTRODUCTION

THE RELEVANCE OF PHARMACOKINETICS AND DRUG INTERACTIONS

A drug interaction is an event in which the usual effectiveness or safety of a drug is altered by a concomitant substance. The drug that is altered is commonly referred to as the object drug, whereas the substance that causes the alteration is usually called the precipitant. The precipitant substance can be a second drug or drugs, an herbal product, such as St John's Wort, a food substance such as coumarin compounds in grapefruit, or an environmental toxin such as cigarette smoke. Drug interactions can cause significant morbidity and rarely mortality; they can add significantly to the cost of therapy by increasing the complexity of diagnosis and treatment in ambulatory settings, or in extending the length or expense of hospitalization. Interactions that cause only "minor" morbidity (e.g., side-effects) can lead to patient non-adherence and loss to follow-up care. Because chronic depression requires extended periods of treatment, the probability of co-administration of additional medications is high. Moreover, the increased prevalence of depression in the elderly population lead to antidepressant drugs being added to complex medication regimens. Some of the antidepressant drugs marketed in the last two decades have been associated with serious drug-drug interactions. As a consequence, newly marketed antidepressants have been subject to careful scientific examination. An understanding of how drug interactions can occur and familiarity with the pharmacokinetic and metabolic profiles of the newer antidepressant medications will help clinicians anticipate and prevent adverse interactions with these medications. The recent Institute of Medicine Report clearly delineates that our healthcare system is not documenting the full extent of errors committed, preventing errors, nor have in place the ongoing programs to reduce medical errors [Kohn, 1999]. Further, in a study component of the IOM report, 3.7% of hospitalized patients experienced clinically important adverse events, of which 20% are adverse drug events (ADEs), defined as injury resulting from medical intervention related to a drug [Leape et al., 1991]. Other studies report similar rates of ADEs with 28% of these events considered preventable. This preventable subset of ADEs should be a priority for our health system in developing corrective interventions [Bates et al., 1993, 1995].

This article reviews clinically meaningful aspects of the physiology and pharmacology of drug-drug interactions, with a focus on drug interactions associated with drug metabolism. The metabolic profiles and pharmacokinetics of the newer antidepressant medications are reviewed with special emphasis on venlafaxine.

VENLAFAXINE PHARMACOKINETICS

Venlafaxine is rapidly absorbed after oral administration with food or fasting dietary conditions minimally affecting the rate or extent of absorption [Troy et al., 1997; Wyeth Laboratories Inc., 1997]. Venlafaxine is widely distributed in the body with only limited protein binding. Protein binding interactions with venlafaxine are improbable, because the percent bound to albumin is ≤30% for both parent and metabolite. Upon absorption, venlafaxine undergoes extensive first pass metabolism to a major metabolite, (*O*-desmethylvenlafaxine), that is equal in antidepressant activity to the parent compound and to two minor metabolites (*N*,*O*-didesmethylvenlafaxine and *N*-desmethylvenlafaxine). Figure 1 shows the metabolic pathways of venlafaxine in humans. Formation of the *O*-desmethyl metabolite is mediated by the CYP-2D6 isoenzyme [Otton et al., 1996], whereas the majority of N-demethylation formation seems to be via CYP3A4. In vitro data suggest that CYP2C9 and 2C19 isoenzymes could play a minor role in both *O*- and *N*-demethylation [Fogelman et al., 1999]. Venlafaxine and its active metabolite exhibit a linear relationship between dose and plasma concentration for doses ranging from 75–450 mg/day [Klamerus et al., 1992]. Thus, dose adjustments do not lead to unexpected disproportionate increases in plasma concentration of the active moieties. Table 1 lists pharmacokinetic parameters for selected antidepressants including their dose versus plasma concentration linearity. Venlafaxine and *O*-desmethylvenalfaxine are significantly cleared by the kidneys with 87% of a single 50 mg ^{14}C-venlafaxine dose excreted in the urine after 48 hr [Troy et al., 1994]. The half-life of venlafaxine is 5 ± 2 hr and that of *O*-desmethylvenlafaxine is 11 ± 2 hr. Although once daily administration of immediate release venlafaxine (Effexor) has been reported, the most commonly recommended administration schedule is twice (b.i.d.) daily [Troy et al., 1995; Amsterdam et al., 1998; Patat et al., 1998].

The use of the extended-release formulation of venlafaxine (Effexor-XR) on a once-daily administration schedule is the preferred dosage form for this antidepressant. The extended-release formulation of venlafaxine has a delayed absorption profile (maximum concentration achieved at 6 hr post-dose) that results in lower peak plasma concentrations when compared with the immediate release formulation (peak concentration achieved in 2 hr). The extent of absorption does not significantly vary between the two formulations and switching to the extended-release product can be completed by selecting the nearest equivalent daily dose (mg/day). Fluctuations in plasma concentration are reduced when switching to the extended release formulation enhancing the tolerability of the product. Therefore, peak plasma concentration related

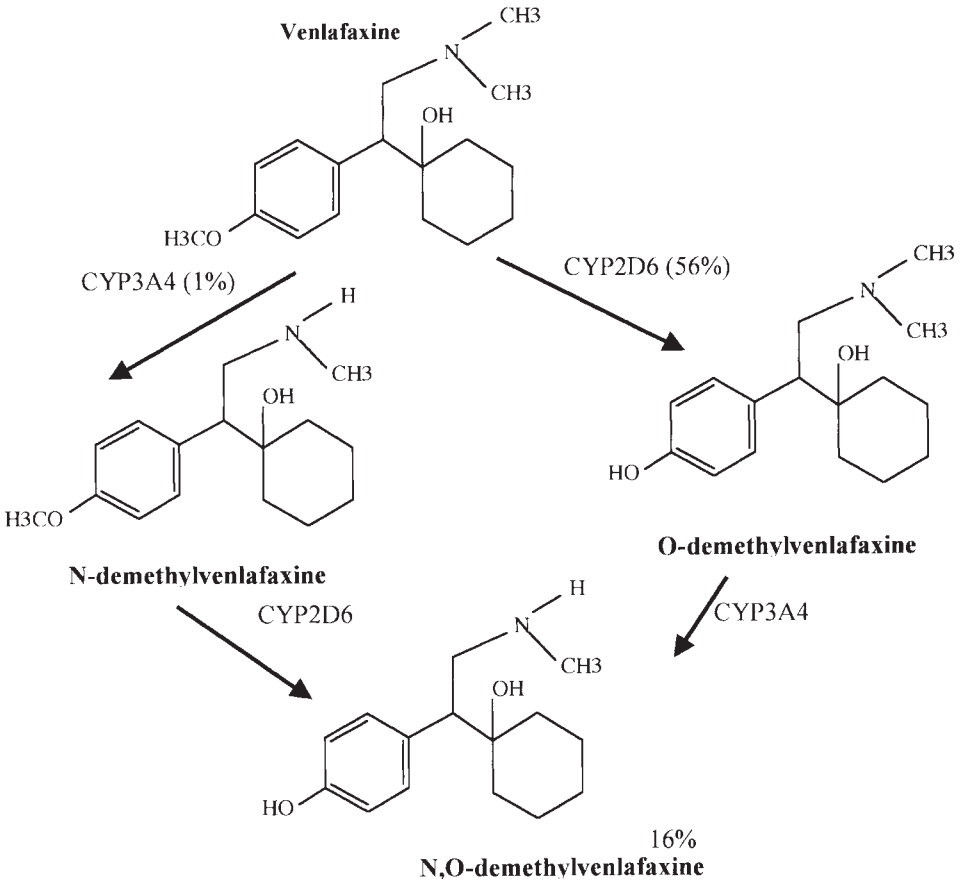

Figure 1. The metabolic disposition of venlafaxine.

side effects, e.g., nausea, are minimized with this strategy. The favorable pharmacokinetic profile for venlafaxine extended release when used at a starting dose of 37.5 mg/day, with upward titration to 75–150 mg/day, results in extremely favorable tolerability and a low rate of early side effects [Wyeth Laboratories Inc., 1997; Amsterdam et al., 1996; 1999b]

The half-life of an antidepressant and its active metabolites determine the time to steady-state, and the time until washout. As illustrated in Figure 2, differences in these half-lives amongst the antidepressants can have a prominent effect on the time-course of metabolic drug interactions. Metabolic drug interactions with most antidepressants will be apparent within 3–5 days. In contrast fluoxetine treated patients, (half life of fluoxetine: 2–3 days; norfluoxetine: 7–9 days), may manifest early- or delayed-onset drug interactions depending on the potency of the interaction. For instance, rapid increases in secondary tricyclic antidepressant concentrations can occur within the first week, whereas effects on haloperidol, clozapine, or carbamazepine might not become obvious until the second month of therapy. These delayed onset

TABLE 1. Pharmacokinetic profiles of select newer antidepressants*

	Sertraline	Fluoxetine	Paroxetine	Citalopram[a]	Nefazodone	Mirtazapine	Venlafaxine[a]
Half-life (hr)	~24	48–72	~24	~35	2–4	20–40	~5
Metabolite Activity (% of parent)	20–30%	Equal	No	No	Several active	10%	Equal
Metabolite half-life (hr)	48–96	168–216	—	—	1.5–18	20–40	~11
Time to steady state	7–14	28–42	~7	~7	<5	~7	<5
Dose vs. concentration relationship	Linear	Non-linear	Non-linear	Linear	Non-linear	Linear	Linear

**Adapted from: Ereshefsky et al., 1995; Ereshefsky, 1996; Rickels and Schweizer, 1990; DeVane, 1992; Grimsley and Jann, 1992.*
[a]Very low protein binding.

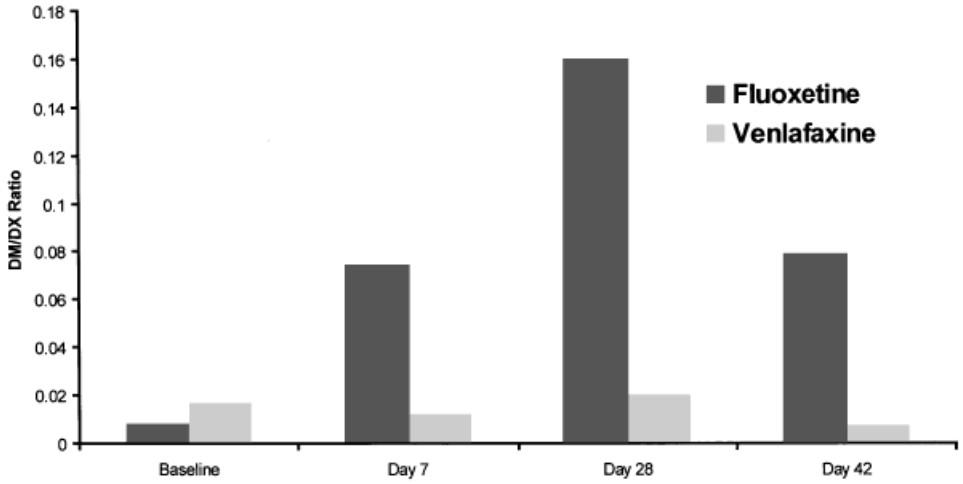

Figure 2. In vivo inhibition of CYP2D6 by venlafaxine and fluoxetine. Dextromethorphan is metabolized to dextrorphan by CYP2D6. The ratio of dextromethorphan to dextrorphan (DM/DX) in the urine therefore is a specific marker of CYP2D6 activity. Twenty-six volunteers were randomized to 28-day treatment with fluoxetine 20 mg/day or venlafaxine 75 mg × 7 days, then 150 mg × 21 days. Although the venlafaxine treated arm showed no significant change in metabolic capacity from baseline at each assessment, fluoxetine was associated with significant increases in DM/DX ratio from baseline at both of the active treatment assessments (Days 7 and 28) and two weeks after discontinuation (Day 42). Consistent with the slow accumulation of fluoxetine and norfluoxetine in the body, maximal inhibition of CYP2D6 is observed ≥4 weeks after initiation and inhibition persists ≥2 weeks after discontinuation. Adapted from Amchin and Ereshefsky [1996].

drug interactions can mislead clinicians into misinterpreting these ADEs as unrelated to drug-drug interactions. Table 1 presents a review of key pharmacokinetic factors of selected newer antidepressant drugs. These differences in metabolic half-lives and time to steady-state for venlafaxine and fluoxetine are accentuated in the elderly patient, where norfluoxetine's half-life may approach 14 days, and time to steady state greater than 2 months [Ereshefsky 1996; 1999b].

Pharmacokinetic investigations of venlafaxine in special populations have been reported. Klamerus and colleagues examined steady state venlafaxine pharmacokinetic profiles of 18 elderly (ages 60–80) and 18 young adults (ages 21–44) and concluded that no dosage adjustment is necessary in the elderly on the basis of age alone [Klamerus et al., 1996]. On the other hand, Troy and co-investigators found that venlafaxine and metabolite disposition is altered in patients with renal disease and that dialysis does not significantly improve clearance [Troy et al., 1994]. They recommend a 50% reduction in venlafaxine dose for patients with creatinine clearance rates of less than 30 mL/min. In patients with clinically significant hepatic impairment, careful titration should be undertaken with a 50% reduction in the initial dose [Wyeth Laboratories Inc., 1997] recommended. Carefully controlled studies of venlafaxine during human pregnancy do not exist and limited animal data is equivocal. Venlafaxine has a pregnancy-risk category of C, and should only be used when the benefits clearly outweigh the risks to the fetus. Ilett et al. [1998] reported that detectable levels of the *O*-desmethylvenlafaxine were found in three infants nursing from mothers taking venlafaxine. Examination of plasma and milk concentrations revealed that venlafaxine and *O*-desmethylvenlafaxine were concentrated in the milk (milk/plasma concentration ratio of 4:1 for VFX and 3:1 for ODV). Total infant exposure was calculated at 7.6% of the weight adjusted maternal dose. No adverse effects were observed in these nursing infants.

DRUG INTERACTIONS

Drug interactions can occur as a result of pharmacodynamic or pharmacokinetic events or may be of mixed etiology. Pharmacodynamic interactions include those in which there is an additive, subtractive, or potentiating effect on an affected organ system due to the actions of another substance. Pharmacokinetic drug interactions on the other hand, involve alterations in the amount of a drug or metabolite that is available at a site of drug action. Many drug interactions in clinical practice are of mixed etiology, with pharmacokinetic and pharmacodynamic factors each contributing to an adverse (or favorable) outcome. Constitutional susceptibility to an adverse event (e.g., altered physiology due to genetic or disease state determinants) can play a significant role in the development or outcome of a drug-drug interaction.

PHARMACODYNAMIC

One common example of a serious pharmacodynamic interaction is delirium or paralytic ileus that can

be experienced by patients when anticholinergic toxicity results from a combination of drugs each possessing only moderate anticholinergic properties. For instance the use of an antimuscarinic agent such as traditional antihistamines (e.g., diphenhydramine) with a tricyclic antidepressant can lead to combined anticholinergic toxicity greatly exceeding the expected risk of either drug alone at therapeutic doses. The elderly seem to be especially susceptible to additive anticholinergic effects of medications [Feinberg, 1993]. A common pharmacodynamic interaction is the additive sedative effects between two or more psychoactive medications or with ethanol. Another illustration is tricyclic antidepressants, that increase pressor response of direct acting sympathomimetic drugs such as epinephrine and dobutamine, while inhibiting the pressor effects of such indirect acting pressors as dopamine and ephedrine. The mechanism of these interactions is a blockade of uptake into the presynaptic nerve terminals at the noradrenergic transporter site. Thus, the direct acting sympathomimetics have a prolonged duration at their site of action whereas indirect sympathomimetics are blocked from their site of action [Risch et al., 1981; Michelson, 1998]. These potential drug interactions are also likely to be seen with venlafaxine, reboxetine and other drugs that share significant blockade of the norepinephrine transporter. Note that this adrenergic effect for venlafaxine confers, along with its potent inhibition of the serotonin transporter, a dual mechanism of action for depression [Harvey et al., 2000].

Pharmacokinetics is best understood as the science that examines how the body acts on a drug. Pharmacokinetic drug interactions can occur at any point in the absorption, distribution, metabolism or excretion of a drug. Drug absorption interactions include changes in the extent or rate of drug absorption after oral administration. Interactions that alter the actual extent of absorption are rare and those that alter only the rate of absorption do not usually have clinical significance for antidepressant drugs, as these do not change the overall bioavailability of the object drug. Examples of drug absorption interactions with significant alterations in the extent of absorption often involve physical incompatibilities between two reacting substances. Drugs that commonly precipitate such reactions include antacids, bile acid sequestrants, and sucralfate.

Interactions involving protein or tissue binding (drug distribution interactions) generally involve drugs that are tightly bound to plasma proteins. When two such drugs compete for protein binding sites, the object drug can be displaced by a precipitant drug. The unbound fraction of the object drug increases resulting in an increase in concentration and is more freely available to sites of action where toxicity may develop (Fig. 3). Protein displacement interactions leading to changes in available drug level can precipitate serious clinical consequences if the object drug has both a narrow therapeutic index and toxicity that is apparent with acute exposure (e.g., digoxin, warfarin). In most instances, protein binding interactions tend to be self-limiting because displacement of a drug from a binding site increases the rate of metabolism and elimination. A new equilibrium for unbound drug concentration is established that is approximately the same as in the original condition, even though the unbound fraction of drug is now higher due to the interaction, e.g., total drug levels are now lower due to increased clearance.

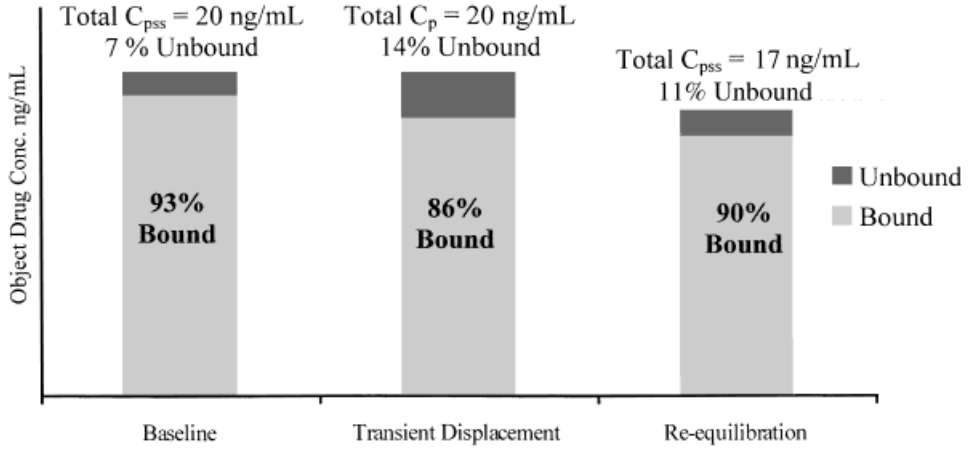

Figure 3. Illustration of protein binding displacement drug interactions. At baseline (a), steady state plasma concentration (C_{pss}) of the object drug is 20 ng/mL, with 93% protein binding. A transient displacement period (b) may be observed within hours after the addition of a drug that displaces the object drug from protein binding sites. Unbound concentrations of the object drug have doubled, whereas total concentration has not changed. Adverse effects of a protein binding interaction may be transiently observed during this period until re-equilibration occurs over a period of hours to days depending on the object drug's half-life. At re-equilibration (c), a new steady state is observed with a lower total concentration of the object drug and slightly increased unbound concentration. The amount of object drug at the site of action in the three periods may be summarized as follows: a >> b and a ≅ c.

Most of the newer antidepressants are at least 90% protein bound although protein binding displacement interactions are rare in physically healthy adults. These antidepressants could precipitate an ADE in special populations such as the very old, the debilitated/malnourished, and in those with renal or hepatic failure. Drugs unlikely to pose a protein binding interaction risk are venlafaxine (least likely to interact with less than 30% protein bound), bupropion (80% protein bound), and fluvoxamine, (70% protein bound).

Metabolic drug–drug interactions involve two or more drugs or metabolites and the enzymes responsible for metabolism. The process of metabolism yields more hydrophilic active (or inactive) metabolites from a parent compound. In a few cases this process yields an active drug from an inactive prodrug. Although most drug metabolism takes place in the liver, drug metabolizing enzymes in the gastrointestinal epithelium, as well as in other organs including the kidney, lung, and brain can contribute significantly to a drug's disposition [Tsunoda et al., 1999]. Phase I (oxidative) reactions usually precede Phase II (conjugative) reactions, because oxidation of the molecule lends to its conjugation. The best characterized metabolic drug-drug interactions with antidepressant drugs are those involving the Phase I reaction enzymes of CYP enzyme family. Beyond the scope of this review are non-CYP drug-drug interactions including aldehyde oxidase, flavin mono-oxygenase (FMO) system, a variety of reductase systems, and changes in P-glycoprotein and other transporter protein activities by medications.

Due to the infrequency of making the connection between observed clinical phenomenon and metabolic drug interactions, skepticism is frequently expressed about the relevance of this topic. On the other hand, adverse events, side effects, patient non-adherence, and therapeutic failures with medications of every class are a routine aspect of every medical practice. Altered drug metabolism often is a possible physiologic mechanism for any these undesirable outcomes. As the science of drug metabolism continues to mature, evidence accumulates that the interindividual variance in metabolic capacity, as genetically determined, for the various drug metabolizing enzymes accounts for a substantial portion of the heterogeneity of response observed to medications (genotype). Drug interactions, other environmental factors, disease processes, and aging, are all significant sources of the observed inter-individual variance in metabolic capacity (phenotype). Familiarity with known drug interactions can alert clinicians to more carefully monitor therapy, or to select medications that avoid the complexities of these interactions.

THE CYTOCHROME P450 ENZYME SYSTEM

The cytochrome P450 (CYP) enzyme system is a group of around 50 heme-containing isoenzymes embedded in the lipid bilayer of smooth endoplasmic reticulum of hepatocytes and other cells. The nomenclature for CYP enzymes is based on the amino acid sequence similarities and differences identified in groups and subgroups of isoenzymes (reviewed in Ereshefsky, 1996a). Most of the CYP enzymes have a limited role in drug metabolism, but rather are involved in the creation and metabolism of endogenous substances such as steroids, prostaglandins, cholesterol and other substances. The CYP subfamilies responsible for drug and xenobiotic metabolism and involved in clinically significant drug interactions include CYP 3A, 2D, 1A, and 2C. Recent investigations have explored the role of the isoenzyme 2E1 in drug and alcohol metabolism and suggest some potential for interactions at this pathway. Table 2 presents selected CYP isoenzymes, substrates, inhibitors, and inducers considered relevant in psychiatry, as well as examples of probes (test drugs) utilized in research.

Individual metabolic capacity at specific enzyme pathways can be tested in the clinic. A simple sampling of a biological tissue or fluid can yield genetic material for CYP automated genotyping at enzymes where polymorphism has been detected, e.g., CYP-2D6. Additionally, phenotyping can be employed to provide an accurate current state of metabolic capacity. This is accomplished by the administration of a minimally invasive probe (drug) that is metabolized by a well characterized pathway to yield a known metabolic product. See Table 2 for a list of common probes for each CYP pathway. Subsequent urine (or plasma) collection at specified times captures parent compound and metabolite for quantitative assay. The ratio of parent to metabolite is a phenotypic marker of the activity of the examined metabolic pathway. The urine (or plasma) of poor metabolizers will have high amounts of parent compound with low amounts of metabolite. On the other hand, extensive metabolizers will have the opposite profile. Our laboratory has standardized a procedure utilizing numerous probes to test multiple CYP isoenzyme pathways at once [Lam and Rodriguez, 1993; Ereshefsky L, 1999; Ereshefsky B et al., 1999; Gewertz et al., 1999]. These techniques reliably quantify both absolute and relative effects of antidepressant drugs on CYP systems. Drug interactions caused by antidepressants can cause a genotypically extensive metabolizer to mimic the poor metabolizer genotype, i.e., the phenotype has been altered by the drug interaction.

The interindividual differences in drug metabolizing capacity observed in probe-phenotype investigations can in part be explained by genetic polymorphisms of specific CYP isoenzymes. Clinically relevant genotype polymorphisms in CYP 2D6, 2C9 and 2C19 isoenzymes have been documented. Polymorphisms in CYP 1A2, 2E1 and 3A4 have also been demonstrated, but the clinical relevance of these has not yet been clarified

TABLE 2. Drug substrates, inhibitors, inducers and probes of the cyrochrome P450 isoenzymes*

	CYP1A2	2C9[a]	2C19[a]	2D6[a]	2E1	3A4
Antidepressant substrates	fluvoxamine imipramine clomipramine amitriptyline	sertraline fluoxetine amitriptyline	citalopram sertraline amitriptyline clomipramine imipramine	venlafaxine fluoxetine fluvoxamine secondary amine tricyclics		venlafaxine imipramine mirtazapine nefazodone reboxetine sertraline
Other important substrates	olanzapine clozapine caffeine tacrine theophylline warfarin	phenytoin s-warfain rosiglitazone glipizide tolbutamide fluvastatin NSAIDS	diazepam pheytoin primidone propranolol r-warfarin omeprazole lansoprazole indomethacin nelfinavir Antiarrythmics	risperidone olanzapine phenothiazines codeine hydrocodone tramadol propranolol timolol s-metoprolol ondansetron tamoxifen	acetaminophen ethanol halothane isoflurane	pimozide buspirone tamoxifen sildenafil amiodarone Short-activating triazolobenzodiazepines Calcium Channel Blockers Protease inhibitors 'Statins'
Antidepressant inhibitor ranking[b]	fluvoxamine+++ fluoxetine+ paroxetine+ sertraline+ mirtazepine 0 citalopram 0 venlafaxine 0	fluvoxamine+++ fluoxetine++ sertraline+ citalopram 0 venlafaxine 0	fluvoxamine+++ fluoxetine+ sertraline+ venlafaxine 0	paroxetine+++ fluoxetine+++ bupropion++ sertraline+ citalopram+ mirtazepine 0/+ fluvoxamine 0/+ venlafaxine 0/+	fluvoxamine+++	nefazodone+++ fluvoxamine++ norfluoxetine+ mirtazepine 0 sertraline 0 paroxetine 0 citalopram 0 venlafaxine 0
Other important inhibitors	cimetidine floroquinolones	isoniazid lovastatin trimethoprim fluconazole fluvastatin	cimetidine omeprazole lansoprazole	haloperidol thioridazine quinidine cimetidine ticlodipine	disulfiram	ciprofloxacin macrolide antibiotics grapefruit juice ketoconazole cimetidine protease inhibitors
Inducers	tobacco smoke omeprazole broccoli brussel sprouts chargrilled meats	rifampin phenobarbital	carbamazepine norethindrone rifampin	dexamethazone rifampin	ethanol isoniazid	St. John's Wort carbamazepine barbiturates phenytoin rifampin ritonavir
Substrate probe	caffeine	phenytoin	s-mephenytoin	dextromethorphan debrisoquine	chlorzoxazone	alprazolam dapsone erythromycin breath test
Inhibitor probe	furafylline	sulphaphenazole	omeprazole	quinidine	diethyl-dithiocarbamate	ketoconazole

**Product labeling for all drugs listed, Ereshefsky, 1998; Greenblatt et al., 1998; Ereshefsky, 1996b; Owen 1998; Ereshefsky, 1999b.*
[a]Some individuals are poor metabolizers of substrates of these pathways due to genetic polymorphisms.
[b]Relative strength of antidepressant inhibition: negligible, 0; low, +; moderate, ++; high, +++.

[Human Cytochrome P450 (CYP) Allele Nomenclature Committee]. Patients who are genotypically poor metabolizers do not demonstrate drug-drug interactions at the deficient CYP isoenzyme because there is minimal enzymatic activity to inhibit. If a second drug, however, is co-administered along with the drug that relies on a poor metabolizer's deficient pathway, then an interaction at a secondary metabolic pathway (caused by the added drug), might significantly increase the risk of a serious adverse reaction. Thus, a poor metabolizer at one CYP isoenzyme, (e.g., 2D6) might experience greater than expected drug interaction effects if an antidepressant inhibits alternate enzyme pathways, e.g., CYP3A4 [Ereshefsky, 1996]. Additionally, these inhibitory CYP-mediated drug interactions are not 'all or none.' Rather there is tremendous inter-patient variability in the observed shift in metabolic capacity, plasma concentrations of the affected drug, and in the observed clinical consequences [Lam et al., 1999].

INHIBITORS, INDUCERS AND SUBSTRATES

Substrate molecules interact with CYP isoenzymes in the same way that drugs bind to receptors (e.g., lock and key, competitive binding). Therefore, drugs and their metabolites are substrates for specific isoenzymes and these specific isoenzymes can be blocked, induced, or remain fully active in the presence of a second drug. Some drug molecules fit as substrates to numerous CYP isoenzymes that can effect biotransformation, whereas others undergo metabolism by one or a limited number of pathways. All of the newer antidepressant drugs are substrates of one or more CYP isoenzymes. It is important to realize that a drug can be substrate at a CYP but not an inhibitor, and conversely, a drug can inhibit a CYP enzyme without being a substrate.

An inhibitor is a molecule that diminishes the activity of a CYP pathway either by competitive displacement of substrates from the active site on the isoenzyme or, rarely, by binding and causing a conformational change in the active site. The potential to inhibit an isoenzyme exists on a spectrum with some molecules having very little potential to inhibit an isoenzyme, and other molecules acting as potent inhibitors. The binding affinity (K_i) can predict, from in vitro testing, if a potential interaction might occur in patients. Inhibition of an isoenzyme is also a concentration dependent phenomenon. Thus significant inhibition of an enzyme pathway may be achieved by a potent inhibitor at relatively low concentration (and dosage) or by a moderate inhibitor at higher concentrations. This also explains the significance of time to steady state in understanding the time course of when interactions or ADEs are observed, as well as the increasing risk of using several medications at a time. Other variables beyond the scope of this article include the effect of aging on CYP activity, and the inhibitory effects caused by disease, e.g., inflammatory processes inhibit CYP gene expression [reviewed in Ereshefsky, 2000].

Drugs and environmental chemicals can act as inducers of CYP isoenzymes by increasing mRNA concentration for the CYP isoenzyme via increased gene expression. A CYP pathway that is induced may enzymatically inactivate an object drug at an accelerated rate thus increasing that drug's clearance. This can result in a therapeutic failure. Conversely, a CYP can activate a prodrug, (e.g., codeine's conversion to morphine), accounting for efficacy. The onset of enzyme induction is generally observed to be 5–14 days after initiation of drug therapy, because induction of CYP pathways is dependent on protein synthesis and accumulation. Although it is assumed that none of the newer antidepressant medications act as enzyme inducers, this has not been systematically studied. Familiarity with each of the CYP isoenzymes and the newer antidepressants that are substrates for these pathways will aid clinicians in anticipating and responding to clinically relevant drug-drug interactions.

CYP2D6

This is the major pathway for venlafaxine metabolism (Fig. 1), and this enzyme system metabolizes a multitude of other drugs including the secondary amine tricyclic antidepressants, antipsychotics such as phenothiazine derivatives and risperidone, the more lipophilic beta-adrenergic antagonists such as metoprolol, type 1C antiarrhythmic drugs such as encainide, dextromethorphan, and the opioid analgesics codeine, hydrocodone, and oxycodone. Venlafaxine although a substrate for CYP2D6, is among the weakest inhibitors of this enzyme, when compared to marketed antidepressants. Administration of venlafaxine to patients that are metabolically impaired at CYP2D6 (by genetic predisposition or by coadministration of a CYP2D6 inhibitor) leads to increased plasma concentration of the parent compound with an equal decrease in the concentration of the metabolite. Because both are considered equally active, the net result is no change in the active moiety. Labeling information for venlafaxine, based on small studies in extensive versus poor metabolizers, indicates that there is no significant impact of CYP2D6 status on the pharmacologic effects of venlafaxine [Wyeth Laboratories Inc., 1997]. There are, however, four cases of toxicity associated with venlafaxine administration in possible poor metabolizers at CYP2D6, though details for these patients is limited [Lessard et al., 1999]. Although the authors summarize the symptoms of these patients as "cardiovascular toxicity", electrocardiogram readings were reported for only one patient, and plasma concentrations of venlafaxine were not reported. It is unlikely that a CYP2D6 interaction accounts for this phenomena. Moreover, a recently completed double blind study of venlafaxine, fluoxetine, and placebo in 300 elderly patients with depression demonstrated the cardiac safety for both antidepressants (1/100 EKG abnormality for venlafaxine vs. 2/100 for fluoxetine) [Mark Cantillon, M.D., personal communication].

Polymorphisms of CYP2D6 lead to significant variability in individual metabolic capacity that can be further altered by the presence of several of the newer antidepressants (Table 2). Four different metabolic subgroups by genotype can be discerned at the 2D6 pathway [Dalen et al., 1998]. Poor metabolizers have two inactive alleles and so have no/little 2D6 metabolic capacity. Five to 10% of Caucasians and 1–2% of African Blacks and Asians are poor metabolizers [Bertillison et al., 1997] and are expected to more frequently experience ADEs with standard doses of medications. Extensive metabolizers at CYP2D6 have two active alleles and metabolize drugs at a normal rate, whereas ultra rapid metabolizers have three or

more active alleles (gene amplification). One to 5% of Caucasians, 0–2% of Asians, 2% of Black Africans and 10–16% of Ethiopians and Saudi Arabians are ultrarapid metabolizers at this enzyme system with CYP-2D6*2_n (where n is the number of gene copies). Individuals with greater than two active alleles at CYP2D6 showed a 5–17-fold increase in the rate of clearance of nortriptyline when compared to genetically typed poor metabolizers [Dalen et al., 1998]. Recent findings provide evidence for polymorphisms in CYP2D6 also leading to an intermediate metabolizer state. People with the CYP2D6*10 allele, for instance, seem to have slower (but not deficient) metabolism at the 2D6 pathway [Fukuda et al., 1999], accounting for the observed reduced metabolic capacity for many Asians. Genetic polymorphisms at CYP2D6 may have significant effects on outcomes of treatment with psychotropic agents and with codeine derivatives [Bertilsson et al., 1997; reviewed in Coutts and Urichuck, 1999].

Fluoxetine and paroxetine are potent inhibitors of CYP2D6 and have demonstrated the propensity to shift a subject's metabolic status from extensive metabolizer to poor metabolizer [Alfaro et al., 1999]. Citalopram and sertraline acts as a moderate to weak antagonist at this enzyme system, whereas venlafaxine and nefazodone are weak inhibitors. Based on probe methodology using dextromethorphan conversion to dextrorphan, we can reliably rank the following medications in order of potential drug interaction risk (from greatest to least at CYP2D6): paroxetine > fluoxetine = bupropion >> sertraline > citalopram > fluvoxamine = venlafaxine = nefazodone. This ranking of antidepressants is based on in vivo data where available, or existing in vitro data. The rankings are probability statements, because even drugs ranked high do not always significantly interact with substrates. Conversely, drugs ranked low might rarely interact significantly in susceptible individuals. In a trial of adjunctive sertraline, [Solai et al., 1997] in 14 elderly patients treated with nortriptyline, the SSRI raised TCA blood levels in some patients, whereas others were unaffected (median increase in nortriptyline plasma concentration was 2% with a range of –26% to +117%). In this case a moderate inhibitor of the CYP2D6 isoenzyme had no effect on TCA metabolism in the majority of patients, although it doubled levels in one patient. A more potent inhibitor, a combination of inhibitors, or higher doses of sertraline could be expected to have elicited a more robust response.

It is important to exercise caution in dosing drugs that are substrates of the CYP2D6 pathway when coadministered with paroxetine, fluoxetine and high doses of sertraline or in patients that are known to be poor metabolizers. These patients may experience increased adverse side effects from substrate drugs when compared with patients who are extensive metabolizers. A study with single-dose perphenazine in 8 healthy extensive metabolizers given paroxetine 20 mg daily for 10 days, demonstrated a 2–13-fold increase in peak perphenazine plasma concentrations after paroxetine. These increased levels were associated with worsened side effects of perphenazine including increased sedation, extrapyramidal symptoms and impaired performance on psychomotor and memory tasks [Ozdemir et al., 1997]. Similarly, inhibition of dextromethorphan or secondary TCA metabolism increases the rate of side effects observed.

Failure to achieve a therapeutic effect through the inhibition of the 2D6-mediated conversion of the inactive prodrug codeine to its active metabolite morphine has been documented in case reports and demonstrated in some, but not all, clinical investigations. A similar effect may occur with hydrocodone and oxycodone, though clinical trials have shown ambiguous pharmacodynamic responses when these drugs were coadministered with peripherally active 2D6 inhibitors; CNS CYP2D6 is not inhibited by medications such as quinidine that do not readily cross the blood brain barrier [Heiskanen et al., 1998]. Despite the clinical ambiguity associated with analgesia trials in general, and with drug interaction studies at CYP2D6, it is recommended that medications that do not inhibit this enzyme be selected when codeine or its derivatives are to be administered.

CYP3A4

The CYP3A subfamily of enzymes include the isoenzymes CYP3A3, CYP3A4, CYP3A7, and CYP-3A5. These isoenzymes share 85% homology of their amino acid sequence and seem to be unevenly distributed in the body with CYP3A4 predominating in the liver and gastrointestinal tract [Tsunoda et al., 1999; Dresser et al., 2000]. About 30% of all CYP isoenzymes in the body are CYP3A4 and 50% of drugs cleared from the body by P450 enzyme system are acted on by CYP3A [Ingelman-Sundberg et al., 1999]. Metabolic activity of CYP3A4 varies greatly in individuals with as much as a 10-fold difference between the lowest and highest capacity metabolizers. Despite numerous investigations, genetic polymorphisms that account for the high variability of CYP3A4 activity in individuals have not been identified. It seems that environmental factors and disease processes can dramatically alter the expression of this gene, accounting for the wide range of observed enzymatic activity.

CYP3A4 acts as the minor pathway (*N*-demethylation: Fig. 1) in venlafaxine metabolism and metabolizes a large number of the newer antidepressants, including citalopram, mirtazapine, nefazodone, sertraline, trazodone, and reboxetine. Numerous other psychotropics are chiefly metabolized through this pathway, specifically the short acting triazolobenzodiazepines, many anticonvulsants, diazepam, buspirone, donepezil, haloperidol (one of many pathways), pimozide, zolpidem, zopiclone, sildenafil, and sibutramine (Table 2). Other important medications that are metabolized through CYP3A4 include the immunosuppressive agents tacrolimus and cyclosporine, the non-sedating antihista-

mines astemizole, terfenadine and loratidine, cisapride, the protease inhibitors, calcium channel antagonists, antiarrhythmics, HMG-CoA reductase inhibitors, antibiotics and synthetic opioid compounds like fentanyl [Ereshefsky, 1996; Dresser et al., 2000].

CYP3A4 is densely located in the cells lining the small intestine and the liver, and therefore plays an important role in first pass metabolism. First pass metabolism has a profound effect on the oral bioavailability of some drugs into systemic circulation. For instance, drugs with high extraction ratios will have low bioavailabilities, e.g., quetiapine and buspirone, and be more sensitive to CYP3A4 drug interactions when an inhibitor is simultaneously coadministered. Grapefruit juice has been shown to significantly inhibit gastrointestinal CYP3A4 with less dramatic effects on hepatic isoenzymes. In a study with 10 healthy volunteers, the combination of grapefruit juice and a single dose of buspirone 10 mg was compared to buspirone and water. Although buspirone maximum concentrations were 2–15.6 times greater (mean: 4.3) in persons receiving grapefruit juice, the elimination half-life was only slightly affected. The authors conclude that first-pass metabolism of buspirone in the gut was significantly reduced by the administration of grapefruit juice [Lilja et al., 1998].

Newer antidepressants that have demonstrated inhibition of CYP3A4 metabolism in vivo include nefazodone, fluvoxamine, and fluoxetine (through the metabolite norfluoxetine). In our own investigation of these three antidepressants, a single 10 mg oral dose of midazolam was used as a CYP3A4 probe in 40 healthy volunteers both before and after randomization to steady-state treatment with ketoconazole 200 mg/day, nefazodone 400 mg/day, fluvoxamine 200 mg/day or fluoxetine 60 mg/day for 5 days followed by 20 mg/day for 6 days (this was to 'load' patients to approximate steady state conditions). Mean area under the curve, (a measure of total drug exposure), for midazolam was increased 556.4% by ketoconazole, 355.6% by nefazodone, 39.4% for fluvoxamine and 16.3% by fluoxetine administration. Fluoxetine and fluvoxamine had minimal inhibitory activity, whereas nefazodone was observed to be a potent inhibitor of this pathway. It is important to note that norfluoxetine concentrations in this study did not fully approximate steady state levels despite the modified loading dose technique utilized [Ereshefsky and Lam, 1998]. In addition to this comparative trial, studies for individual antidepressants have been reported in the literature [Ereshefsky, 1996]. For instance, venlafaxine was demonstrated to have no appreciable effect on the metabolism of alprazolam and terfenadine in normal volunteers [Amchin et al., 1998a,b]. Interestingly, venlafaxine in a recent report by Levin et al. [1999] demonstrated a 38% reduction in indinavir concentrations after chronic venlafaxine administration. The relative strength of each of the newer antidepressants to act as inhibitors at CYP3A4 has been summarized as follows: nefazodone >> fluvoxamine > norfluoxetine > paroxetine > desmethylsertraline > fluoxetine > sertraline > mirtazapine >>> venlafaxine [Owens and Nemeroff, 1998]. Clinically important inhibitors of CYP3A4 include the antifungals, ketoconazole and itraconazole, the protease inhibitors, saquinavir, ritonavir, indinavir, and nelfinavir, the macrolide antibiotics as well as ciprofloxacin, cimetidine and grapefruit juice.

Significant interactions between inhibitors of CYP3A and terfenadine, astemizole, cisapride and pimozide have led to potentially life threatening ventricular arrhythmias due to accumulation of unmetabolized drugs [Delpon et al., 1999; Dresser et al., 2000]. Terfenadine, astemizole, and cisapride have recently been voluntarily removed from the US market due to concerns over CYP3A4-mediated drug-drug interactions. Rhabdomyolysis has been associated with use of a CYP3A inhibitor during therapy with HMG-CoA reductase inhibitors (statins). Other effects that may be observed at usual doses when an antagonists at the 3A4 pathway is part of therapy include hypotension with calcium channel blockers, excessive sedation with the triazolobenzodiazepines, and toxicity with carbamazepine and immunosuppressants. Inhibition of the CYP3A4 by nefazodone and other strong inhibitors of this enzyme pathway have been associated with adverse effects with numerous CYP3A4 substrates [Greene and Barbhaiya, 1997; Campo, 1998; Alderman, 1999]. ADEs from interactions involving CYP3A4 substrates and co-administered fluoxetine (dosed for 28 days) and fluvoxamine have also been reported [Grimsley et al., 1991].

There is growing evidence that St. John's Wort, an herbal product frequently used as an over the counter treatment for mild depression, might be (or at least mimic the effects) of an inducer at CYP3A4. In three clinical trials, plasma concentrations of digoxin and indinavir have been reduced and the conversion of dextromethorphan to 3-methoxymorphinan (via CYP3A4 pathway) was increased with chronic coadministration of St. John's Wort [Ereshefsky et al., 1999; Johne et al., 1999; Piscitelli et al., 2000]. The addition of St. John's Wort has been associated with 2 cases of acute transplant rejection due to decreased cyclosporine concentrations. Other case reports associate St. John's Wort with reduced theophylline plasma concentration as well as altered INRs with warfarin therapy [Ernst E, 1999; Nebel et al., 1999; Ruschitza et al., 2000; Yue et al., 2000]. These reports and studies are all consistent with CYP3A4 induction (increased gene expression). Many patients may fail to disclose the use of herbal products to the clinician, further complicating the monitoring of therapy. Growing evidence reveals that herbal products are potential sources of drug interactions, and care in their use is warranted. Whereas induction of CYP3A4 is a compelling theory for the observed drug interactions, induction of P-glycoprotein has also been theorized as an alternative hypothesis [Johne et al., 1999].

P-glycoprotein is a drug efflux pump expressed on the apical aspect of the intestinal epithelium, at the

blood brain barrier, and in other organs. P-glycoprotein coded, for by the multiple drug resistance gene-1, can reduce the bioavailability of orally administered medications as a result of increased efflux of drug from the gastrointestinal wall back into the lumen, or can alter effectiveness and safety by reducing CNS concentrations via increased efflux from CNS. Induction of intestinal CYP3A4 has been associated with induction of P-glycoprotein. Further, Hochman and colleagues have demonstrated enhanced pre-absorption metabolism of indinavir by CYP3A4 in part explained by the increased activity of P-glycoprotein [Hochman et al., 2000]. Induction of either or both CYP3A4 and P-glycoprotein by St. John's Wort could be expected to reduce plasma concentrations of substrate drugs. Studies evaluating currently marketed antidepressants and their effects on P-glycoprotein are essential to further categorize drug interactions.

CYP1A2

Metabolizing capacity at CYP1A2 varies widely in people. The activity of CYP1A2 can be increased by environmental factors such as exposure to cigarette smoke. This induction has been noted to decrease plasma concentrations of CYP1A2 substrates requiring adjustment in dosing for drugs with narrow therapeutic index. Induction of CYP1A2 due to arylhydrocarbons consumed with burnt or blackened meats have also been demonstrated. Until recently, investigations into genetic determinants of heterogeneity of CYP1A2 activity have failed to demonstrate a polymorphism that predicted activity of this enzyme in the population. One recent investigation, however, determined that the capacity for induction of CYP1A2 by environmental factors is variably expressed in Caucasians due to a polymorphism in the promoter region of the CYP1A2 gene [Sachse et al., 1999]. In an investigation of 236 Caucasians, 46% were found to have two copies of the allele that led to high inducibility of the CYP1A2 isoenzyme in smokers. This finding suggests a complex interplay between environmental and genetic factors in determining individual CYP1A2 activity.

Drug interactions involving the CYP1A2 isoenzyme pathway are important in psychiatry. This pathway is key to the biotransformation of imipramine, clozapine, olanzapine, tacrine, methadone, caffeine, cyclobenzaprine, haloperidol, and theophylline (Table 2). Fluvoxamine is a potent inhibitor of CYP 1A2 activity [Brosen et al., 1993], and interactions with 1A2 substrates are well documented [Xu et al., 1996; Kuo et al., 1998; Spigset, 1998; Alderman and Frith, 1999; Larsen et al., 1999] The addition of fluvoxamine to steady-state clozapine therapy has caused 5- to 10-fold increases in clozapine plasma concentration [Heeringa et al., 1999] . In our own experience, this interaction can be very potent. One patient treated with stable clozapine 900 mg/day with plasma concentrations of 200–300 ng/mL had a 10-fold increase in clozapine concentration 1 week after the addition of 25 mg of fluvoxamine. In contrast, CYP1A2 is not involved in the disposition of venlafaxine [Fogelman et al., 1999], nor does this medication act as an inhibitor of this enzyme. During in vitro and in vivo testing, venlafaxine had no effect on the disposition of probes (phenacetin and caffeine) at CYP1A2 [von Moltke et al., 1996; Amchin et al., 1999].

One preventable mixed pharmacodynamic and pharmacokinetic interaction is that of caffeine consumption complicating a clinical presentation of insomnia with serotonergic antidepressant therapy. Serotonergic stimulation has been shown to alter deep sleep, REM, and have a negative effect on sleep latency. Caffeine is a well characterized stimulant that increases monoamine transmission leading to increased arousal states. The combination of caffeine and serotonergic drugs may lead to new onset, or exacerbation of insomnia. Caffeine metabolism and inactivation is accomplished chiefly by CYP1A2. Inhibition of this isoenzyme pathway by fluvoxamine has been shown to extend the normally short elimination half-life of caffeine from 5–31 hr [Jeppesen et al., 1996a]. This can result in caffeinism. Insomnia, nervousness and symptoms resembling akathisia, apparently induced by fluvoxamine can sometimes be eliminated by reductions of caffeine intake.

CYP2C9/19

The CYP2C subfamily of isoenzymes include CYP-2C9, 2C10 and 2C19. CNS substrates of the CYP-2C9/19 isoenzymes include citalopram, imipramine, amitriptyline, clomipramine, diazepam and phenytoin (Table 2). Other important substrate drugs include S-warfarin (the more active enantiomer), omeprazole, mephenytoin and tolbutamide. Fluvoxamine is a potent inhibitor at both CYP2C9 and CYP2C19, whereas fluoxetine shows moderate inhibition at CYP2C9 and minimal inhibition of CYP2C19. Sertraline, desmethylsertraline and citalopram are not significant inhibitors of either enzyme system [Preskorn et al., 1997; Hemeryck et al., 1999]. Venlafaxine does not act as an inhibitor of CYP2C9 and CYP19-mediated metabolism.

Poor metabolizer status at CYP2C19 is conferred by 2 variant alleles: CYP2C19*2 and CYP2C19*3. Poor metabolizers at CYP2C19 represent 13–23% of Oriental populations and only 2–5% of Caucasians and Africans [Ibeanu et al., 1998]. In a recent report, it was found that 61% of a sample population of >5,000 Pacific Islanders were poor metabolizers at CYP2C19 [Kaneko et al., 1999]. Patients with poor metabolizer at CYP2C19 are probably at greater risk of toxicity if CYP3A4 inhibitors are co-administered, because many medications utilize both of these pathways for drug clearance.

Polymorphisms in CYP2C9 that cause significantly reduced enzyme activity arise from two different point mutations in the CYP2C9 gene. The allelic variant

CYP2C9*3 is less than 5% as efficient as the normal enzyme, whereas the CYP2C9*2 variant has about 12% of the wild-type activity. In one recent survey of 36 patients treated with low-dose warfarin and 100 healthy controls, one or more variant alleles were detected in 40% of the control population and in 80% of patients selected for sensitivity to warfarin [Guruprasad et al., 1999]. It was reported that these low-dose warfarin patients were four times more likely to experience major bleeding events than a random selection of warfarin clinic patients. Fluvoxamine and fluoxetine therapy may be expected to cause similar responses in patients treated with warfarin and therefore should be avoided or carefully monitored for ADEs. A pharmacodynamic interaction with all serotonin transporter inhibitor drugs is also possible, because platelet aggregation is reduced by down-regulation of 5-HT_2 receptors with antidepressant therapy. This later effect is relatively modest, though reports of epistaxis and bruising are in the literature.

ILLUSTRATIVE CASES

Four cases illustrate the potential for using phenotyping or genotyping in the clinical setting. The first case involves a 65-year-old women referred to our group for metabolic evaluation due to inability to tolerate most antidepressant therapies. This woman demonstrated dramatic decreases in metabolic capacity at CYP 2D6 and 3A4 when grapefruit juice was coadministered with dextromethorphan (probe). Subsequent dosing of medications was made with fractional increments until clinical effects were achieved, e.g., 12.5, 25, 37.5 mg desipramine. This patient could not tolerate potent antidepressant inhibitors of CYP-2D6 such as fluoxetine or paroxetine.

In the second case, a workman's compensation case was referred to us for the evaluation of chronic pain syndrome not responsive to codeine and hydrocodone. This patient was a poor metabolizer at CYP2D6, and therefore would not produce significant amounts of morphine. This patient required antidepressant therapy as well, and a recommendation to use venlafaxine was made to the referring physician Alternative analgesia included the use of tramadol at lower than usual doses (substrate at CYP2D6).

The third patient was in two of our drug interaction studies had undetectable dextromethorphan in urine despite a state of the art sensitive HPLC assay system. Moreover, she had undetectable paroxetine levels while on 20 mg/day for 8 days and demonstrated no inhibition at CYP2D6 via probe methodology. Upon phenotyping, this Caucasian female was determined to have the CYP2D6*2N allele, with multiple copies of the gene.

In a fourth patient, chronic moderate pain was successfully treated with hydrocodone and acetaminophen. The patient became depressed and paroxetine was initiated at 20 mg/day. One week after the start of antidepressant therapy, pain worsened necessitating a return to the clinic. The patient was switched to venlafaxine extended release 75 mg/day, and within 5 days reported the restoration of analgesia [Ereshefsky and Lam, data not published)].

Clearly these cases indicate that improved outcomes are possible by considering drug interactions or genetic polymorphisms as potential reasons for care that does not yield the desired results. Controlled studies further evaluating these issues are needed.

APPARENT PAUCITY OF SIGNIFICANT DRUG INTERACTIONS REPORTING

Significant drug-drug interactions are rarely spontaneously documented in clinical practice. Patients frequently receive and tolerate combinations of medications, including drugs that may compete for limited metabolic pathways. There are numerous factors to consider in understanding the apparent low frequency of drug interactions; including pharmacodynamic, pharmacokinetic, and other factors (Fig. 4).

Drugs with a small or narrow therapeutic index are poorly tolerated by most patients at a concentration that is slightly higher than the upper limit of the therapeutic range and drug interactions that raise the concentration of these drugs are of significant concern. Fortunately, most medications have a wide therapeutic index. These drugs are well tolerated and drug interactions that raise the concentrations by 30–50% do not elicit ADEs in many patients. Therefore one factor leading to an apparent infrequency of drug-drug interactions is the wide margins of tolerable concentrations we have with most drugs. Large changes in concentrations are reported when substrate drugs with a single predominant metabolic pathway are coadministered with drugs that potently inhibit that CYP system. Alternately, a drug administered in usual doses can already be at concentrations in the sub-threshold range for ADEs, e.g., the elderly or those with the CYP2D6*10 intermediate metabolizer gene. The addition of an inhibitor drug might be sufficient to increase the substrate drug's effects and cause toxicity. Yet, if a patient has greater than average metabolic capacity, the same drug interaction could lead to an improved clinical effect for the substrate drug.

Most clinicians and patients focus on tolerability rather than on optimal therapy. The lack of spontaneous ADEs reports does not mean an absence of side effects or optimal efficacy. Large scale population studies are needed to study the impact of drug interactions on health care costs and outcomes. The Institute of Medicine report and large scale health care system surveillance suggests that thousands of lives are lost and billions of dollars are wasted due to inappropriate medication utilization [Bootman and Harrison, 1997a; Kohn, 1999]. More importantly by addressing inap-

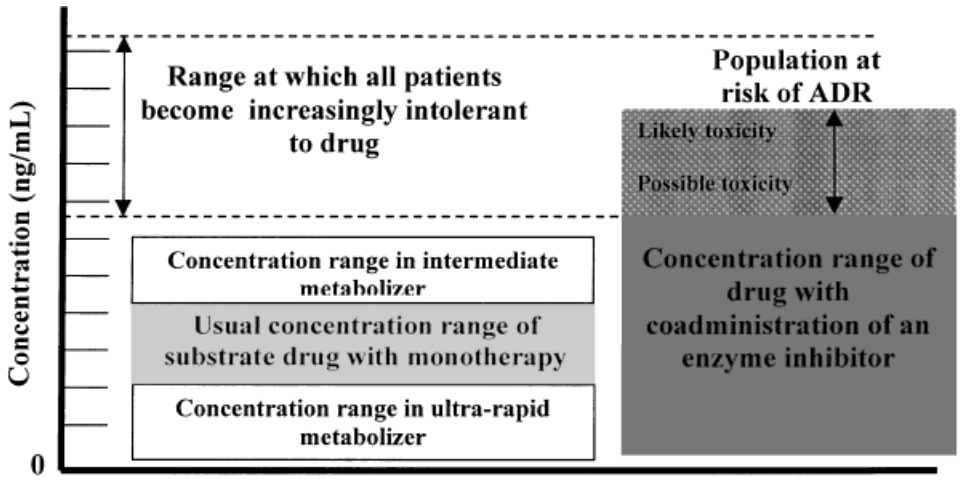

Figure 4. The interface of patient-specific variables in determining the presentation of an adverse event due to a drug-drug interaction. Patients treated with a substrate drug as monotherapy have plasma concentrations usually in the range depicted by the light gray (e.g., 80–90% of the population for CYP2D6). 1–10% of subjects are intermediate or poor CYP2D6 metabolizers with higher than expected concentrations, whereas 1–10% of the patients have lower than expected concentrations due to ultra-rapid CYP2D6 metabolizer status. At CYP systems, environmental (smoking), disease states (inflammation, cirrhosis), and other influences can lead to a 10–15-fold variation in concentrations. The majority of patients on a potent inhibitor will have a significant increase in plasma concentrations of 3–5-fold, but a few patients (rarely) will have no or catastrophic effects. For most patients there is movement towards higher concentrations but still within the range of tolerability. A significant minority, e.g., 2–10% will have extreme concentrations in the range where toxicity is likely to occur, whereas a larger number of patients, e.g., 20–25% will be above usual concentrations but experience only mild to moderate adverse effects. Concurrent disease, aging, other genetic differences such as race and gender will shift the starting population's relative weighting across the observed concentration range, resulting in a shift in susceptibility to inhibitor drug interactions (increased or decreased).

propriate drug therapy including drug-drug interactions, Medicare could save more than $30 billion per year in skilled nursing facilities alone [Bootman et al., 1997, 1998].

For a drug interaction to be detected, a patient must seek care and provide accurate information to a clinician. Patients may fail to seek care for drug–drug interactions due to incorrect attribution of adverse events to a disease condition or due to non-adherence to a poorly tolerated drug regimen, never returning to clinic. When a patient seeks care, it may be in an acute setting that does not have access to the patient's full history and again, incorrect attribution of an adverse event to non-drug factors can be made. Thus an additional layer of behavioral and social variables may play a role in the apparent infrequency of reported drug–drug interactions. Through a more systematic research program using both pharmacogenetic and genomic tools a more precise characterization of potential risk to patients could be determined, before administering the first dose of medication. Future efforts to minimize drug–drug interaction risks could involve the application of investigational technologies such as genetic profiling of patient metabolic capacity in the clinical setting [Ereshefsky, 1999a; Ingelman-Sundberg, 1999]. In the meantime, increased application by clinicians of the pharmacokinetic and pharmacodynamic basis of drug interactions could minimize the risk of ADEs. Fortunately, the past ten years have seen increased "pharmacovigilance" on the part of the clinicians [Meyboom et al., 1999]. Efforts to provide patients with sufficient information and skills to minimize drug-interaction risks are also a part of the current patient-empowerment movement [Alderman, 2000].

SUMMARY

A variety of factors contribute to drug-drug interactions. Disease, patient demographics and genetics, drug, and environmental factors all play a role in determining therapeutic outcomes. Drug interactions can result in increased or decreased toxicity or efficacy. In the current health-care landscape where less time is available to evaluate a patient for all potential drug therapy considerations, selecting an antidepressant that is well characterized and low in its drug interaction potential across the largest number of possible systems is highly desirable. Although antidepressant drug interactions and their impact on outcome are probabilistic by virtue of the large interpatient variability observed, the application of drug interaction and pharmacokinetic principles to avoid potential problems or to identify at risk patients for increased monitoring can improve outcomes in our patients with depression.

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