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Point-Counterpoint

Antidepressant–Drug Interactions are Potentially but Rarely Clinically Significant

C Lindsay DeVane*,[1]
[1]*Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA*

The salient pharmacologic features of the selective serotonin reuptake inhibitors (SSRIs) discovered in the late 1980s included an *in vitro* ability to inhibit various cytochrome *P*450 enzymes (CYPs). Differences in potency among the SSRIs for CYP inhibition formed the basis of a marketing focus based largely on predictions of *in vivo* pharmacokinetic drug interactions from *in vitro* data, conclusions derived from case reports, and the extrapolation of the results of pharmacokinetic studies conducted in healthy volunteers to patients. Subsequently introduced antidepressants have undergone a similar *post hoc* scrutiny for potential drug–drug interactions. Concern for the untoward consequences of drug interactions led the FDA to publish guidance for the pharmaceutical industry in 1997 recommending that *in vitro* metabolic studies be conducted early in the drug development process to evaluate inhibitory properties toward the major CYPs. However, the prevalence of clinically significant enzyme inhibition interactions occurring during antidepressant treatment remains poorly defined despite millions of exposures. Although lack of evidence does not equate to evidence of absence, sparse epidemiological and post-marketing surveillance data do not substantiate a conclusion that widespread morbidity results from antidepressant-induced drug interactions. This commentary discusses points of uncertainty and controversy in the field of drug interactions, notes areas where inadequate data exist, and suggests explanations for a low prevalence of serious interactions. The conclusion is drawn that drug interactions from CYP inhibition caused by the newer antidepressants are potentially, but rarely, clinically significant.
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Point

When choosing a specific antidepressant for an individual patient, clinicians consider the possibility that harm may result from a drug–drug interaction. Given the statistics for drug-induced morbidity and mortality, this is a legitimate concern (Azaz-Livshits *et al*, 1998; Gandhi *et al*, 2003; Juntti-Patinen and Neuvonen, 2002). Widely quoted studies have estimated serious and fatal adverse drug reactions in hospitalized patients causing as high as 100 000 deaths per year (Lazarou *et al*, 1998; Moore *et al*, 1998). There is a presumption that drug interactions significantly contribute to this mortality.

Despite more than 10–15 years of extensive worldwide clinical use of the newer antidepressants (selective serotonin reuptake inhibitors (SSRIs), bupropion, venlafaxine), an uncertainty exists about their participation in harmful drug interactions and whether their use should be avoided in patients receiving potentially interacting medications. Serious and life-threatening events, as well as fatalities, have been documented when some drug pairs have been used in therapy. This issue is not in dispute. Thiazide diuretics added to a lithium regimen, azole antifungals combined with terfenadine or cisapride, and nitrates combined with sildenafil are documented examples (Crane and Shih, 1993; Kivisto *et al*, 1994; Krenzelok, 2000; Monahan *et al*, 1990). The risk of *Torsades de Pointes* occurring from drug interactions mediated by cytochrome *P*450 enzyme (CYP) inhibition has resulted in drug withdrawals from the market (terfenadine, astemizole, cisapride) and significant labeling revisions for thioridazine, mesoridazine, and pimozide (Alfaro, 2001). The issue addressed herein is if the newer antidepressants are malicious perpetrators of CYP inhibition, why a high prevalence of significant antidepressant–drug interactions is not better documented?

*Correspondence: Dr C Lindsay DeVane, Laboratory of Drug Disposition and Pharmacogenetics, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, 173 Ashley Avenue, Charleston, SC 29425, USA. Tel: +1 843 792 5448, Fax: +1 843 792 6318, E-mail: devanel@musc.edu
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HISTORICAL EVIDENCE FOR ANTIDEPRESSANT–DRUG INTERACTIONS

The availability of the SSRIs for clinical practice began with fluvoxamine in the mid-1980s in Europe and with fluoxetine

in 1988 in the US. Despite enthusiastic acceptance for their improved tolerability and safety, efficacy appeared to be similar, but perhaps no better, compared to the tricyclic antidepressants (TCA) (Danish University Antidepressant Group, 1990; Anderson, 1998). Thus, combining SSRI and TCA was an obvious therapeutic strategy for treatment of recalcitrant depression. Previously, recognition that some antipsychotics impaired TCA elimination had been studied extensively by Gram in Norway (Gram and Overø, 1972; Gram *et al*, 1974; Gram, 1975) and by Nelson and Jatlow (1980) in the US. As the *in vitro* data emerged of the SSRI's CYP inhibitory effects, initially on CYP2D6, it was reasonable to hypothesize that they could increase the plasma concentration of TCA (Fuller and Perry, 1989; Goodnick, 1989; Vaughan, 1988). At this time, *CYP2D6* was the most thoroughly studied of the genes encoding for CYPs (Gonzalez, 1992). It was of particular interest to learn if the SSRI could inhibit CYP activity, as functional polymorphisms of *CYP2D6* characterized genetically deficient metabolizers (poor metabolizers, PM) as accumulating higher plasma concentrations of various substrates (Eichelbaum *et al*, 1982; Schmid *et al*, 1985). The results across studies have been generally consistent in finding potent (ie $K_i = \sim \leqslant 1.0\,\mu M$) CYP2D6 inhibition for fluoxetine ($K_i = 0.17$–$3.0\,\mu M$; see Table 1) and paroxetine ($K_i = 0.15$–$3.2\,\mu M$; Table 1). The other SSRIs have not demonstrated as meaningful CYP2D6 inhibitory effects (Table 1); neither have *in vitro* reports shown potent CYP2D6 inhibition by mirtazapine ($K_i = 41 \pm 4$; Dahl *et al*, 1997; Störmer *et al*, 2000), venlafaxine ($K_i = 41.0 \pm 9.5\,\mu M$; Ball *et al*, 1997), or nefazodone (Schmider *et al*, 1996a). The initial *in vitro* data for bupropion suggested that it had a low inhibitory potency *versus* CYP2D6 ($IC_{50} = 58\,\mu M$; Hesse *et al*, 2000), but recent human volunteer studies have suggested a greater potency (GlaxoSmithKline, 2003; Kotlyar *et al*, 2005) underscoring the problematic interpretation of *in vitro* experimental data to predict accurately *in vivo* interactions. Sparse human data are available addressing the magnitude and significance of bupropion's CYP2D6 inhibition (Guzey *et al*, 2002; Pollock *et al*, 1996; Shad and Preskorn, 1997).

Subsequent work expanded the *in vitro* database to include SSRI effects on other major CYP isozymes. Most notable has been the substantial effect of fluvoxamine on CYP1A2, CYP2C19, and CYP3A4 (Brøsen *et al*, 1993; Daniel *et al*, 1994), and moderate effects of fluoxetine on CYP2C19 (Kobayashi *et al*, 1995). The potential contribution of norfluoxetine ($K_i = 1.04\,\mu M$) to CYP3A4 inhibition following fluoxetine administration has been the subject of speculation (von Moltke *et al*, 1998).

In vitro data and emerging case reports of SSRI–TCA interactions (Aranow *et al*, 1989; Balant-Gorgia *et al*, 1996; Preskorn *et al*, 1990; Vandel *et al*, 1992) stimulated two types of human studies. The first investigated the clinical advantages of SSRI–TCA treatment strategies in treatment-resistant or inadequately responding depressed patients (Nelson *et al*, 1991; Weilburg *et al*, 1989). The results were mixed and have not led to recommendations for the use of combined SSRI–TCA pharmacotherapy (American Psychiatric Association, 2000). Other studies, conducted mostly in young healthy male volunteers, investigated the inhibitory effects of SSRIs and newer antidepressants on CYP2D6 and other CYP probe substrates (Alfaro *et al*, 1999, 2000; Alderman *et al*, 1997; Barbhaiya *et al*, 1995; Bergstrom *et al*, 1997; Brøsen *et al*, 1993; Greenblatt *et al*, 1992; Kurtz *et al*, 1997; Otton *et al*, 1993; Preskorn *et al*, 1994; Sproule *et al*, 1997; Zussman *et al*, 1995). The results confirmed that

Table 1 Reports of *In Vitro* Inhibitory Constants of Selected Antidepressants for CYP2D6

Drug	K_i or IC_{50} (μM)	Reference
Citalopram (desmethyl citalopram)	5.1	Crewe *et al* (1992
	19 (1.3)	Skjelbo and Brøsen (1992)
	7 (6)	Otton *et al* (1993)
	34; 88 (11; 31)	Belpaire *et al* (1998)
	73	von Moltke *et al* (1996)
Fluoxetine (norfluoxetine)	0.6 (0.43)	Crewe *et al* (1992)
	0.92 (0.33)	Skjelbo and Brøsen (1992)
	0.17 (0.19)	Otton *et al* (1993, 1994)
	3.0 (3.5)	von Moltke *et al* (1994)
	1.6	Ball *et al* (1997)
	0.66; 0.93 (0.95; 1.2)	Belpaire *et al* (1998)
	0.24 (0.33)	Nielsen *et al* (1996)
	0.33 (0.55)	Hemeryck *et al* (2000)
Fluvoxamine	8.2	Crewe *et al* (1992)
	3.9	Skjelbo and Brøsen (1992)
	1.8	Otton *et al* (1993)
	8.0	Ball *et al* (1997)
	12; 16	Belpaire *et al* (1998)
	4.9	Olesen and Linnet (2000)
	1.3	Nielsen *et al* (1996)
	16.6	von Moltke *et al* (1995)
	1.45	Fogelman *et al* (1999)
Paroxetine	0.15	Crewe *et al* (1992)
	0.36	Skjelbo and Brøsen (1992)
	0.65	Otton *et al* (1993, 1994)
	1.47	von Moltke *et al* (1995)
	3.2	Ball *et al* (1997)
	0.44; 1.0	Belpaire *et al* (1998)
	0.17	Fogelman *et al* (1999)
	0.86	Nielsen *et al* (1996)
	0.54	Hemeryck *et al* (2000)
Sertraline/DMS	0.7	Crewe *et al* (1992)
	22.7/16.0	Skjelbo and Brøsen (1992)
	1.5	Otton *et al* (1993, 1994)
	22.7 (16.0)	von Moltke *et al* (1994)
	24.7	Ball *et al* (1997)
	19; 20 (18; 24)	Belpaire *et al* (1998)
	27	Nielsen *et al* (1996)
	1.15/4.32	Fogelman *et al* (1999)

fluoxetine and paroxetine were potent *in vivo* inhibitors of CYP2D6, whereas the effects of sertraline were marginal, although variable, owing to the presence of an occasional outlier, especially with doses higher than 50 mg (Zussman *et al*, 1995). The magnitude of SSRI CYP inhibition has been shown to be dose and concentration dependent (Alderman *et al*, 1997; Alfaro *et al*, 2000; DeVane, 1998a; Kurtz *et al*, 1997). The results from these human studies are consistent with competitive inhibition, although paroxetine has demonstrated mechanism-based inactivation (Bertelsen *et al*, 2003; Lin *et al*, 2001). This type of enzyme inhibition confers an additional complexity in reliably predicting *in vivo* interactions as the time for re-genesis of enzyme becomes an additional consideration. In contrast, competitive inhibition is transient and reversible and normal function of CYPs continues after the inhibitor has been eliminated from the body. Despite the *in vitro* data with paroxetine, our group found CYP2D6 inhibition by fluoxetine, sertraline, and paroxetine abated in 39 volunteers after steady-state dosing was discontinued, consistent with the elimination half-lives (Liston *et al*, 2002).

The *in vitro* and *in vivo* evidence suggesting fluoxetine and paroxetine can increase the plasma concentration of numerous drugs that are CYP2D6 substrates is indisputable. Product labeling cautions against combining SSRIs with CYP2D6 and/or other CYP substrate medications owing to potential metabolic drug interactions. In the mid-1990s, this scenario appeared to be a valid concern (Lane, 1996). Product labeling also implies that SSRI protein-binding displacement interactions are of concern. The evidence for this warning is likely based on the high degree of drug–plasma protein binding (90%). Authoritative reviews have repeatedly concluded that protein binding displacement interactions for drugs with pharmacokinetic characteristics of the SSRIs are of limited significance (Benet and Hoener, 2002; DeVane, 2002; Greenblatt *et al*, 1982; Rolan, 1994; Sansom and Evans, 1996; Sellers, 1979).

Recently, the role of drug transporters in the disposition of antidepressants has been reported (Rochat *et al*, 1999; Uhr *et al*, 2000). The discovery that paroxetine, venlafaxine, and citalopram are substrates of P-glycoprotein presents additional possibilities for SSRI–drug interactions (Uhr *et al*, 2003; Weiss *et al*, 2003).

PROBLEMS AND LIMITATIONS WITH EVIDENCE FOR ANTIDEPRESSANT–DRUG INTERACTIONS

As multiple mechanisms exist for drug interactions involving newer antidepressants, why are negative outcomes and serious adverse events, apart from the experience in occasional case reports, not more apparent when they are combined with other drugs in routine clinical care? Each of the major areas of evidence for interactions is considered below.

In Vitro Studies

In vitro models to study drug metabolism contribute substantially to our understanding of drug interactions (Bertz and Granneman, 1997; Carlile *et al*, 1999; Ekins *et al*, 2000). Given the enormous number of potentially interacting drug combinations, development of accurate *in vitro* models for *in vivo* predictions is a highly desirable scientific objective (Blanchard *et al*, 2004;Venkatakrishnan *et al*, 2003). The current models have several limitations beyond methodological considerations for extrapolation of results to the human situation. Multiple drugs are frequently taken by patients. The *in vitro* models lack sufficient ability to resolve the interactions of more than two drugs simultaneously. They cannot incorporate pharmacodynamic consequences of interactions. Generally, enzyme inhibition is more easily studied than enzyme inductive effects, yet therapeutic failure as a consequence of enzyme induction interactions is a legitimate concern (Grygiel and Birkett, 1981; Lin and Lu, 1998).

Without supporting *in vivo* evidence, the *in vitro* findings of antidepressant inhibition of a CYP enzyme are too often interpreted as indicating that the offending antidepressant will affect all substrates of the same enzyme equally (Crewe *et al*, 1992). Problems with *in vitro* models have been thoroughly discussed from the perspective of FDA guidance for drugs under development (Bjornsson *et al*, 2003; Yuan *et al*, 1999, 2002). The choice of test system can include microsomes, liver slices, hepatocyte cultures or suspension, cell lines, and recombinant *P*450 enzymes. Most systems do not represent the physiological environment of the liver containing multiple Phase II enzymes and transporters (Pelkonen *et al*, 1998; Liston *et al* (2001)). Experimental results rank order antidepressants on the basis of their K_i or IC_{50} values for inhibiting a particular CYP pathway. These determinations can be influenced by analytical considerations, test conditions, the choice of probe substrates to represent the same CYP enzyme reaction (Wang *et al*, 2000), time-dependent inhibition, concurrent induction, the formation of active metabolites, the choice of inhibitor and probe concentrations, and the methods of data analysis (Busby *et al*, 1999; Chauret *et al*, 1998; Eagling *et al*, 1998; Kakkar *et al*, 1999; Tran *et al*, 2002).

The variability in the outcome of *in vitro* studies can be appreciated by the several-fold differences in K_i values shown in Table 1 across studies for the same antidepressant. The attempts to predict *in vivo* clearance changes from *in vitro* data have had mixed success (Bertz and Granneman, 1997; Obach, 1996, 1997, 1999; von Moltke *et al*, 1994, 1998). An especially important variable is the appropriate hepatic drug concentration of the inhibitor. Many drugs are subject to active uptake or efflux by drug transporters and the relevant concentration at enzymatic sites may far exceed or be lower than their unbound drug concentration in plasma (Wang, 2001). There is a current debate of whether the most appropriate estimate of inhibitor concentration should be the total plasma concentration, intrahepatic concentration, unbound concentration at the inlet to the liver, or unbound concentration in hepatic cytosol around the enzymes (Houston, 1994; Neal *et al*, 2003; Venkatakrishnan *et al*, 2003). The outcome to be avoided is underestimation, that is, false negative, prediction of an *in vivo* interaction.

Accurate *in vitro–in vivo* predictions are needed to determine if follow-up human studies should be performed to provide further guidance during drug development (Bjornsson *et al*, 2003). For example, nefazodone was a moderately weak inhibitor of the CYP3A4-mediated N-dealkylation or C-hydroxylation of terfenadine *in vitro*

($K_i = 10 \pm 4$ and $41 \pm 4\,\mu M$, respectively), similar to sertraline ($K_i = 10 \pm 3$ and $67 \pm 13\,\mu M$, respectively; Jurima-Romet *et al*, 1998). I*n vivo*, nefazodone is substantially more potent as a CYP3A4 inhibitor than is sertraline (Barbhaiya *et al*, 1995; Green *et al*, 1995). As an opposing example, Crewe *et al* (1992) defined sertraline as a potent CYP2D6 inhibitor ($K_i = 0.7\,\mu M$) but *in vivo* studies did not confirm meaningful CYP2D6 inhibition (Alderman *et al*, 1997; Preskorn *et al*, 1994). Fortunately, positive *in vitro* results are likely to be further investigated in humans.

Case Reports

Apparent drug interactions described in case reports serve a useful purpose of developing hypotheses for unexplained events. This is an inherent purpose of the MEDWATCH reporting program (FDA, 2004). Rarely is proof of causality available in case reports. Numerous criticisms that apply to population-based studies of adverse drug effects apply to case reports of drug interactions (Ray, 2003). They represent historical and anecdotal experience that includes bias in the selection of the subject in the case and, potentially, bias in the measurement of results or outcome. Validated comparisons may not be possible with other treated or unaffected patients. Isolated case reports are unreliable for representing the variability that exists in the outcome from combining drugs in patients with diverse demographic and clinical features, different degrees of drug exposure, baseline CYP activity, and tolerability to drug effects. Despite these limitations, a major purpose of the MEDWATCH and similar programs is for developing suspicion for meaningful interactions that deserve formal investigation.

Pharmacokinetic Studies in Healthy Volunteers

Several variations in the experimental design are employed in drug interaction studies. Frequently, a probe substrate for an enzyme pathway is administered in a single dose, then combined with single or multiple doses of antidepressant. Less often used is a design where the substrate is also dosed to steady-state. This is unfortunate as outcomes based on single doses may underpredict the magnitude of a drug interaction.

The choice of probe CYP substrate is critical. Ideally, the enzyme pathway of interest would be the probe's near exclusive route of elimination. An increase in area under the plasma concentration *vs* time curve (AUC) is frequently used to reflect the magnitude of the inhibition. Desipramine and nortriptyline are common probes for CYP2D6 (Bertilsson *et al*, 1980; von Moltke *et al*, 1994). However, it is unlikely that these TCA are eliminated solely by CYP2D6 or the 5–10% of the population represented by PM devoid of CYP2D6 (see Alván *et al*, 1999) would quickly become toxic during chronic dosing. An additional pathway(s) must exist for elimination. Involvement of other CYPs or Phase I/II enzymes in elimination, or renal excretion of unchanged drug, will render less reliable any observed changes in pharmacokinetics for predicting impairment of other substrates. Ironically, it is this existence of parallel pathways of elimination that reduces the likelihood of serious CYP inhibitory interactions in clinical practice.

A statistically significant pharmacokinetic interaction does not necessarily lead to significant pharmacodynamic consequences. The outcome of an interaction is partly dependent upon the concentration–effect relationship of the inhibited substrate in that particular patient. Cimetidine produced a 50–60% increase in diazepam concentration, but no significant alterations in psychomotor performance (Greenblatt *et al*, 1984). Fluvoxamine's inhibition of theophylline (Rasmussen *et al*, 1995) is likely to result in significant clinical consequences owing to theophylline's steep concentration–response relationship. This contrasts with fluvoxamine's inhibition of alprazolam metabolism. Fleishaker and Hulst (1994) reported that fluvoxamine increased alprazolam concentration by 100% and extended its mean half-life from 20 to 34 h. The effects on psychomotor performance were minimally significant ($p < 0.05$ for digit symbol substitution and a continuous performance task) with no significant changes in sedation. Thus, the effects of pharmacokinetic changes for pharmacodynamic outcomes are highly dependent on the inhibited drug and less on the inhibited pathway. Unfortunately, pharmacodynamic effects have seldom been measured in the volunteer antidepressant–drug interaction studies, partly owing to difficulties in identifying relevant effects to measure.

An example of metabolic inhibition without serious adverse events is the Pfizer studies to evaluate ziprasidone as a cause of QTc prolongation (FDA, 2000). Outcomes were recorded from administering thioridazine 300 mg/day, a CYP2D6 substrate (Berecz *et al*, 2003), with dosing of paroxetine at 20 mg/day. This combination caused a mean change in the QTc of 28.0 ms (+ 7.2%), but fortunately none of the 30 completers had a QTc $\geqslant$ 500 ms, the cutoff for a potentially hazardous conduction effect. Additionally, 56 patients received SSRIs with ziprasidone and the mean change in QTc was 3.4 ms. In another study, paroxetine (20 mg/day) and ketoconazole (400 mg/day) were administered with haloperidol. The mean QTc increase was 8.9 ms, yet the plasma concentration of haloperidol increased by $>$50%. Thus, potent CYP2D6 inhibition, and in a rare experimental example, combined CYP2D6/3A4 inhibition, under circumstances of recognized hazard, led to no serious consequences. Whether a pharmacokinetic interaction is significant depends upon the magnitude of the interaction, the pharmacokinetic properties of the affected drugs, and the concentration–response relationship for the affected drug at the time of the interaction in the specific patient (Shader *et al*, 1996).

SSRI–drug interaction studies have mostly used healthy young males as study subjects (Alfaro *et al*, 2000; Alderman *et al*, 1997; Fleishaker and Hulst, 1994; Greenblatt *et al*, 1992; Kurtz *et al*, 1997; Liston *et al*, 2002; Preskorn *et al*, 1994; Sproule *et al*, 1997). This design increases homogeneity and the power to find a statistically significant effect, but it may limit the ability to generalize outcomes to women and patients of different ages. Sex is a major determinant of hepatic CYP3A4 expression although not in the small intestine where most drugs are absorbed (Paine *et al*, 2005; Wolbold *et al*, 2003). Hepatic *P*450 content declines after 40 years to remain stable until a further decline after 70 years (Sotaniemi *et al*, 1997).

The antidepressant–drug interaction studies reveal some unexplained inconsistencies. For example, Grimsley *et al* (1991) found that fluoxetine increased the plasma concentration of carbamazepine, a CYP3A4 substrate. The metabolism of diazepam, a partial CYP3A4 and CYP2C19 substrate (Schmider *et al*, 1996b), was also altered by fluoxetine, although no clinically significant alterations in psychomotor performance were found (Lemberger *et al*, 1988). Fluoxetine was reported to inhibit the oxidation of alprazolam *in vitro* (von Moltke *et al*, 1992), prolong its half-life, and reduce its clearance in male volunteers (48 *vs* 61 ml/min; Greenblatt *et al*, 1992; Lasher *et al*, 1991). These results suggest that fluoxetine or its active metabolite inhibit CYP3A4. However, fluoxetine had no effect on terfenadine (Bergstrom *et al*, 1997) or triazolam (Wright *et al*, 1992), other CYP3A4 substrates.

Epidemiologic Data

Many surveys of SSRI adverse events are available (Azaz-Livshits *et al*, 1998; Gandhi *et al*, 2003; Moore *et al*, 1998; Spigset, 1999). A *serious adverse event,* defined by the FDA, is one that results in a patient's death, is life-threatening, results in initial or prolonged hospitalization, disability, congenital anomaly, or requires intervention to prevent permanent impairment or damage (FDA, 2004). An *adverse event* is any undesirable experience associated with the use of a medical product in a patient. If SSRI–drug interactions were causing widespread and serious morbidity, a strong signal should appear in post-marketing surveillance reports. Deaths have been reported when SSRIs were involved in therapy (Ferslew *et al*, 1998; Preskorn and Baker, 1997; Sallee *et al*, 2000), but often under unusual circumstances, or with drug combinations that are widely documented to interact. The issue is not whether SSRI–drug interactions have resulted in serious adverse events, but the frequency of unanticipated drug interactions resulting in severe adverse events. While accurate estimates appear unavailable, several hundred million patients have taken an SSRI. In 2001, sales of the major antidepressants in the US totaled $9.3 billion (National Institute for Health Care Management, 2002). Documentation of highly prevalent SSRI–drug interactions causing adverse events could not be found. The post-marketing surveillance of fluvoxamine can be used as an example as it was the first available SSRI and possesses the broadest CYP inhibitory profile of the antidepressants.

Fluvoxamine has pronounced inhibition of CYP1A2, CYP2C19, and CYP3A4 (Brøsen *et al*, 1993; Perucca *et al*, 1994). Significant interactions have occurred with theophylline, olanzapine and clozapine (CYP1A2 substrates), carbamazepine, amitriptyline, clomipramine and imipramine (CYP2C, CYP3A4 substrates), although not desipramine (CYP2D6 substrate). Fluvoxamine robustly elevated haloperidol concentration (a multiple CYP substrate) in three patients (Daniel *et al*, 1994) but extrapyramidal side effects did not increase appreciably. For drugs with a steep dose concentration–effect relationship, the consequences of fluvoxamine's inhibition are significant. For drugs with a more shallow dose–effect relationship for adverse events, other evidence, albeit indirect, is not convincing of widespread adverse interactions. Reports by fluvoxamine's manufacturer (Wagner *et al*, 1992, 1994) of the drug's safety database of 34 587 predominantly depressed patients in 66 studies found the drug to be safe and well tolerated. The number of patients receiving other metabolized drugs was unavailable. A prescription-event monitoring of fluvoxamine was provided by Edwards *et al* (1994) of 10 401 patients. Fluvoxamine appeared safe with no unexpected or previously undetected drug-related events. Patients took a variety of concomitant medications from 14 drug classes. Fluvoxamine potently inhibits the *in vitro* metabolism of caffeine (Rasmussen *et al*, 1998) and it reduced caffeine clearance by 80% and extended the half-life in humans from 5 to 31 h (Jeppesen *et al*, 1996a, b). The magnitude of changes suggests that caffeine intoxication should be widespread among patients taking fluvoxamine. Despite fluvoxamine's inhibition of multiple CYPs, drug interactions producing serious adverse consequences are rare events.

In the mid-1990s, we hypothesized that pharmacokinetic interactions go undetected because the consequences have subclinical outcomes (DeVane *et al*, 2001). Interactions could be underreported as many drug concentration measures are unavailable in clinical settings. In a prospective study of 170 patients, we documented several predictable interactions (fluvoxamine–theophylline; fluvoxamine—clozapine; Markowitz *et al*, 1996; DeVane *et al*, 1997). However, screening of patients taking fluoxetine with over 20 different drugs, and paroxetine with over 33 different drugs, did not reveal any previously undocumented pharmacokinetic interactions or adverse events. Evaluative data from blood sampling of 101 patients were available.

Several reports (Burke *et al*, 1996; Davies *et al*, 2004; Juurlink *et al*, 2003), including our own (Markowitz and DeVane, 1997), have noted the potential for antidepressant–drug interactions. Such predictions have been primarily based on pharmacy dispensing records. There is lack of confirmatory data to support serious antidepressant–drug interactions as widespread reality. Epidemiologic reports of SSRI adverse events (Azaz-Livshits *et al*, 1998; Gandhi *et al*, 2003; Moore *et al*, 1998; Spigset, 1999) do not separate out drug interactions as a cause of morbidity.

An issue often overlooked in estimating the risk for drug interactions is options for management. Bergk *et al* (2004) evaluated drugs concurrently prescribed to 9481 adults aged 50–75 years. They concluded that only a small proportion of potential drug combinations offered no management options and should thus be avoided.

COMPENSATORY MECHANISMS FOR MINIMIZING DRUG INTERACTIONS

Explanations can be proposed for why highly significant antidepressant–drug interactions are rare occurrences by considering pharmacokinetic principles and patterns of clinical practice (Gibaldi and Perrier, 1982; Winkinson and Shand, 1975). Extensive continuing medical education efforts have been directed at physicians about drug interactions since the early 1990s (Nemeroff *et al*, 1996). Obvious interacting combinations are well publicized (SSRI–TCA), although confirmatory data that education reduces the prescribing of potentially interacting drug

combinations appear to be lacking. Whether efforts at publicizing the potential risks of drug interactions have caused patients to be deprived of needed antidepressant treatment is equally unknown.

Clinicians dose antidepressants by titration with a low initial dose. All antidepressant product labeling recommends this practice. The result minimizes unintended CYP inhibition on pre-existing pharmacotherapy. Should an interaction occur in the opposite direction, that is, the pre-existing drug therapy inhibiting the antidepressant's metabolism, dosing titration achieves the optimal antidepressant treatment at a lower daily dose than might otherwise be used if the antidepressants were given alone. This further reduces any antidepressant CYP inhibitory effects on pre-existing therapy as inhibition has been shown, by our group (DeVane, 1998a; Markowitz *et al*, 1996) and others (Alfaro *et al*, 2000; Alderman *et al*, 1997), to be dose dependent.

Pharmacokinetic evaluation of interactions in the human laboratory can assure 100% compliance with dosing. However, the reality is a low treatment adherence among depressed patients with prescribed pharmacotherapy. This favors minimizing an antidepressant's CYP inhibitory effects. Additionally, opposing influences may exist across patients, or within the same patient, such as induction and inhibition, to moderate the expression of a drug interaction.

Humans have developed multiple pathways of eliminating drugs, which serve to minimize the impact of impairment in any single pathway (Testa and Jenner, 1987). When a CYP inhibitory antidepressant is added to a drug regimen of susceptible substrates, two effects occur (Rowland and Matin, 1973). The degree to which metabolic blockade impairs total drug clearance will lead to increased steady-state concentration and prolongation of half-life under most circumstances. Drug clearance is an additive function of the various elimination pathways (Winkinson and Shand, 1975). Even though inhibition of a CYP metabolic pathway may be complete, the effect on steady-state plasma concentration may not be prominent, depending upon the proportion of total clearance normally contributed by the inhibited pathway. In addition to several parallel metabolic pathways existing for a drug's elimination, more than one enzyme may mediate the same pathway. For drugs eliminated by multiple pathways, as is the case for most drugs (Mitchell and Horning, 1987; Testa and Jenner, 1976), the inhibition of a single pathway will have a lesser effect on elevating concentration. This can be shown through model simulation.

The impact of parallel pathways of drug elimination was modeled by Ito *et al* (2005) and compared to the results of 44 drug interaction studies involving CYP2D6 substrates (Ito *et al*, 2004). A commonly used measure of a drug interaction is the AUC ratio of a substrate during coadministration with an inhibitor compared to the AUC of the drug administered alone. The crucial variable for predicting the extent of inhibition on the AUC ratio *in vitro* is the inhibitor concentration relative to the inhibition constant for that pathway, $[I]/K_i$ (Venkatakrishnan *et al*, 2003). Figure 1 shows the effect of increasing inhibitor concentration on the AUC ratio for a drug with varying proportions of total elimination by CYP2D6. A second, unaffected pathway is assumed to eliminate the proportion of the drug not metabolized by CYP2D6. It can be seen that for a drug totally eliminated by CYP2D6 (fm = 1), the AUC ratio rises dramatically when the $[I]/K_i$ ratio exceeds a value of 1.0. However, even a small fraction of the drug eliminated by a second pathway drastically reduced the maximum effect on the AUC ratio. When 50% of the drug is removed by an alternative pathway (fm = 0.5), then the maximum AUC ratio is 2.0, usually an insignificant drug interaction. The clinical significance of inhibition will depend upon the importance of the inhibited pathway to overall drug elimination, the activity of the various metabolites, and the concentration–response relationships for drug and metabolites in the individual patient. The variability between patients with regard to the role of primary and alternative pathways of drug elimination likely impacts the clinical importance of CYP inhibitory interactions among different patients (Guengerich, 1997; Gonzalez and Idle, 1994).

The relative importance of inhibiting a single drug elimination pathway can be considered in the context of the CYP2D6 polymorphisms that code for null enzyme activity (5–10% of Caucasian populations; for review see Alván *et al*, 1999; Meyer *et al*, 1990). These individuals are recognizable as a PM genotype. If the CYP2D6 pathway was essential to the elimination of xenobiotics, then intuitively PM, when chronically exposed to CYP2D6 substrates, would eventually experience profound toxicity from continuous drug accumulation in the body. However, there is a lack of evidence that being a PM translates into a 5–10% frequency of toxicity in patients given drugs considered CYP2D6 substrates.

A complete inhibition of CYP2D6 by an antidepressant produces a phenocopy of a PM genotype. The frequency of PM phenocopies reported in antidepressant–drug interaction studies is summarized for CYP2D6 in Table 2. No study reported a complete conversion of all volunteers, and some studies report no conversion. Even for the most potent CYP2D6 inhibitors, paroxetine and fluoxetine, the conversion was incomplete, implying that in patients given these drugs, the metabolic impact on the CYP2D6 pathway is compromised, but not rendered unfunctional, and with less

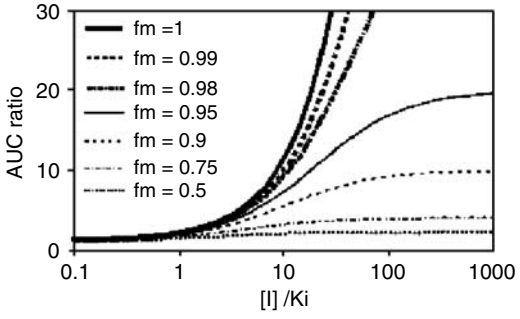

Figure 1 Effect of parallel pathways of drug elimination on predicted AUC ratio where a secondary pathway is unaffected by the inhibitor. Abbreviations: fm = fraction of substrate eliminated by the primary pathway; $[I]$ = inhibitor concentration; K_i = inhibitory constant for the primary pathway. From Ito *et al* (2005). Reprinted with permission from Figure 2A of Kiyomi Ito, David Hallifax, R Scott Obach, J Brian Houston (2005). Impact of parallel pathways of drug elimination and multiple cytochrome *P*450 involvement on drug–drug interactions: CYP2D6 paradigm. *Drug Metab Dispos* 33: 837–844.

Table 2 Selected Studies Reporting CYP2D6 Phenotype Changes in Pharmacokinetic Studies

Antidepressant	Dose	Test substrate	Results: number of subjects converted from EM to PM (%)	Reference
Citalopram	10, 20, 40, 80 mg single doses	Sparteine	0/6 (0)	Jeppesen *et al* (1996a, b)
Fluoxetine	20–80 mg/day	DM	?/19 incomplete inhibition	Otton *et al* (1993)[a]
	10, 20, 40, 80 mg single doses	Sparteine	0/6 (0)	Jeppesen *et al* (1996a, b)
	60 mg/day × 8 days	DM	5/8 (62.5)	Alfaro *et al* (1999)
	20 mg/day × 28 days	DM	2/14 (14)	Liston *et al* (2002)
Fluvoxamine	25, 50, 100, 200 mg single doses	Sparteine	0/6 (0)	Jeppesen *et al* (1996a, b)
	100 mg/day × 8 days	DM	0/8 (0)	Alfaro *et al* (1999)
Paroxetine	40 or 80 mg single doses	Sparteine	3/6 (50)	Jeppesen *et al* (1996a, b)
	20 mg/day × 8 days	DM	4/8 (50)	Alfaro *et al* (1999)
	20 mg/day × 10 days	DM	0/13 (0)	Liston *et al* (2002)
Sertraline	Zussman *et al* (1995)			
	50–150 mg/day × 21 days	DM	0/6 (0)	Sproule *et al* (1997)
	100 mg/day × 8 days	DM	0/7 (0)	Alfaro *et al* (1999)
	50 mg × 3 days, then 100 mg × 10 days	DM	0/6 (0)	Liston *et al* (2002)

[a]Dextromethorphan (DM) ratio fell within the antimode between extensive metabolizer (EM) and poor metabolizer (PM) status compared with a previously characterized population, indicating incomplete inhibition.

impairment than occurs naturally in 5–10% of the general population.

CONCLUSIONS

This commentary is not meant to exonerate antidepressants as a cause of clinically important drug interactions. What is in question is their prevalence. A sensitization to drug interactions has been inculcated into the formal education of psychiatric residents for over two decades stemming from recognition that a hypertensive crisis can result from combining monoamine oxidase inhibitors (MAOI) with other drugs, principally the TCA and sympathomimetics (Harrison *et al*, 1990; Kahn *et al*, 1989). This fear may have contributed to a lower utilization of MAOI in the US compared with England (Clary *et al*, 1990; Henry *et al*, 1995). The risk of drug interactions is often taken out of context, without regard for the intended or actual benefits of drug therapy, and the morbidity and mortality associated with under treatment or non-treatment. Perhaps research and education have been successful to some degree in that physicians may be aware of, and consequently avoid, the high-risk drug combinations. Fortunately, there are physiological mechanisms to compensate for enzyme inhibition. This commentary concludes that antidepressant drug interactions are potentially, but rarely, clinically significant. With the caveat that several predictable and well-documented interactions will occur with a high frequency, mostly involving drugs with a steep dose–response relationship (eg but not inclusive: fluoxetine–phenytoin (Shader *et al*, 1994); fluvoxamine–clozapine, theophylline, warfarin), a reasonable conclusion is that the risks of newer antidepressants causing highly prevalent and significant drug interactions are unfounded. While clinically unimportant interactions will occur occasionally, clinically important interactions are likely to be unusual, and severe adverse interactions are rare events.

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