THE INFLUENCE OF ETHNICITY AND ANTIDEPRESSANT PHARMACOGENETICS IN THE TREATMENT OF DEPRESSION

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CONTENTS

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SUMMARY

Antidepressant disposition can be influenced by a variety of CYP isozymes and their effects in the treatment of depression are reviewed. The CYP isozymes 2D6, 3A4, 1A2 and 2C are discussed in regard to antidepressant drug pharmacokinetics, clinical relevance and variability in activity for each isozyme. Polymorphism has been identified with CYP 2D6 and 2C19. Disposition of antidepressants which are substrates of these two isozymes can also be influenced and contributes towards the wide interpatient and interethnic variability found with these drugs. Antidepressants (especially SSRIs) can be CYP isozyme inhibitors and produce significant drug-drug interactions.

KEY WORDS

ethnicity, CYP isozymes, metabolism, drug interactions, antidepressants

INTRODUCTION

Depression ranks as one of the world's major illnesses that impairs a person's daily activities. In the 1990s depression ranks fourth among the world's diseases that affect the global burden. It was forecasted that by 2020, depression would be ranked second only to ischemic heart disease in global burden /1/. Yet, despite these alarming numbers, depression is often underrecognized and undertreated by clinicians /2/. The neurobiology of depression is well described and involves a variety of neurotransmitters (serotonin, norepinephrine, etc.) and neuropeptides in different brain regions /3/. Genetic factors have long been recognized to play a major role in depression /3/. The role of ethnicity in the assessment and treatment of depression is now attracting attention. For example, in a recent lifetime and 12-month study of depression among Chinese-Americans, the prevalence was found to be 6.9% of 1,747 adults /4/. Other ethnic populations can have different prevalence rates of depression dependent upon not just biological factors but also sociocultural factors that are not yet clearly understood /5/. It is beyond the scope of this article to present these

sociocultural factors and the reader is referred to other review articles that discuss this topic /5/.

The main pharmacological treatment for depression is with antidepressant medications. Although cultural differences may be a factor in explaining interpatient/interpopulational differences in the pharmacology of these drugs, most of the variability in drug disposition and pharmacodynamics appears to be genetically based /6/. The role of ethnicity has long been recognized to influence drug disposition in many different types of medications /7-9/.

The term "pharmacogenomics" has emerged to represent this field of translating functional genomics to rational therapeutics /10/. The genetic basis for drug metabolism occurs via Phase I oxidative pathways; the majority of these pathways involve the cytochrome P-450 isozymes /10/. Dr. Aitchison's article in this issue clearly describes the influence of ethnicity and the variability of P-450 isozymes among different populations and this article will not repeat those discussions. Another set of metabolic enzymes showing genetic differences is those responsible for Phase II conjugation reactions which are being studied for the genetic basis influencing drug metabolism and therapeutics /10/.

Most of the work on CYP 450 and antidepressants focuses extensively upon Phase I reactions and this article will present its latest findings. As no single CYP 450 is solely responsible for antidepressant disposition, this article presents a general discussion about antidepressants and then presents specific CYP isozymes and their impact upon the disposition of drugs in different ethnic populations and the pharmacokinetics related to CYP 450 genotype and phenotype.

1. ANTIDEPRESSANT DRUG DISPOSITION

Antidepressants include a variety of medications, such as tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and other miscellaneous compounds based upon their chemical structure (see Table 1). The pharmacokinetic parameters (clearance, protein binding, etc.) of these agents have been previously described /11/. However, clinical studies have identified a "therapeutic" plasma concentration for routine patient care for only four of the TCA agents /12/. The vast

majority of the determination of clinical response to antidepressant pharmacotherapy remains in the clinical evaluation of the patient by their clinicians.

TABLE 1

Antidepressants available in the USA

Tricyclic antidepressants	
Amitriptyline	Imipramine
Clomipramine	Nortriptyline
Desipramine	Protriptyline
Doxepin	Trimipramine
Selective serotonin reuptake inhibitors	
Citalopram	Paroxetine
Fluoxetine	Sertraline
Fluvoxamine	
Monoamine oxidase inhibitors	
Isocarboxazid	Tranycypromine
Phenelzine	
Other miscellaneous agents	
Amoxapine	Nefazodone
Bupropion	Trazodone
Maprotiline	Venlafaxine
Mirtazapine	

The role of CYP 450 isozymes as substrates or inhibitors has been evaluated for various antidepressants including the TCAs, SSRIs, and other miscellaneous agents. Although therapeutic plasma concentrations have not been determined for most of these agents, CYP 450 information has provided a genetic basis for understanding the wide interpatient variability in drug disposition and greatly expanded the

knowledge of drug-drug and drug-food interactions that can influence drug dosing among different ethnic populations. Since studies with CYP 450 isozymes have been evaluated for most of the antidepressants except the MAOIs, this article will not discuss these agents as they relate to drug disposition and ethnicity.

A general scheme for the metabolic profile of TCAs is shown in Figure 1, which examines imipramine disposition. Imipramine conversion via demethylation to desipramine (an active antidepressant) can occur by the different CYP isozymes 1A2, 2C, and 3A4 /12,13/. Both imipramine and desipramine are metabolized to their respective 2-hydroxy metabolites by CYP 2D6 /12/. With slight differences among the TCAs, conversion from the parent drug by demethylation and hydroxylation to metabolites generally occur. Subsequent sections on the specific CYP isozymes describe the latest findings with TCAs.

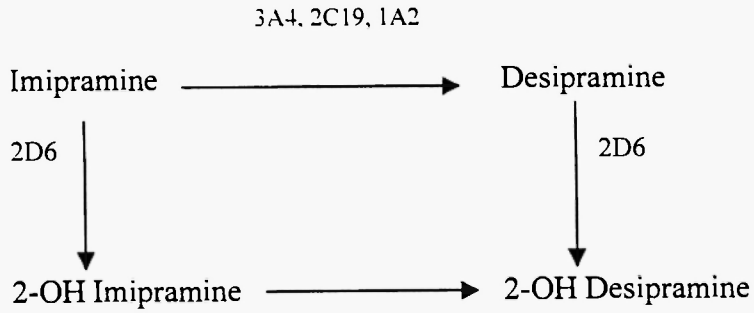

Fig 1: Metabolism of imipramine and CYP isozymes known to influence the disposition of imipramine and its metabolites.

Unlike the TCAs, a general metabolic scheme for SSRIs and other miscellaneous agents does not exist due to their different chemical structures. These agents present a more complex issue in pharmacogenetics. These compounds can be substrates for CYP 1A2, 3A4, 2D6, 2C9 and 2C19, as shown in Table 2 /14/. Conversely, SSRIs can also inhibit the same or different CYP isozymes, creating a complicated effect for these agents when prescribed alone or in combination with other drugs or food /14,15/.

TABLE 2

Summary of SSRIs, antidepressants and other miscellaneous agents and CYP isozymes*

Drug	CYP Substrate	CYP Inhibitor				
		1A2	2C9	2C19	2D6	3A
Fluoxetine	2C9, 2D6, 3A4**	+	++	+/++	+++	+
Norfluoxetine	Same	+	++	+ ++	+++	++
Citalopram	2C19, 3A, 2D6	+	0	0	0	0
Fluvoxamine	1A2, 2D6	+++	++	+++	+	++
Paroxetine	2D6	+	+	+	+++	+
Sertraline	2C9, 2B6, 2C19, 2D6, 3A4	+	+	+/++	+	+
Mirtazapine	3A, 1A2**, 2D6**	N/R	N/R	N/R	N/R	N/R
Nefazodone	3A	0	0	0	0	+++
Venlafaxine	2D6, 3A, 2C19	0	0	0	0	0

*Adapted from /14/
** = small quantitative importance
N/R = not reported

2. CYP 2D6

This isozyme is among the best studied of the cytochromes. As previously mentioned, the CYP 2D6 isozyme is polymorphic and contains four levels of activity that range from ultrarapid metabolizers (UMs) to poor metabolizers (PMs). Extensive metabolizers (EMs) and intermediate metabolizers (IMs) fit between the UMs and PMs. These activities are based upon the use of specific metabolic probes such as debrisoquine (D) or dextromethorphan (DM). The frequency of PMs in Africans, Afro-Americans and Asians is lower than in Caucasians and specific alleles have been identified (see article by Aitchison *et al.* in this issue).

2.1 Tricyclic antidepressants - Variability in CYP 2D6 activity

2.1a Desipramine

The use of metabolic probes (phenotyping) occurred earlier than analyzing specific DNA blood samples (genotyping) due to the later development of the polymerase chain reaction (PCR) technique which allows for rapid determination of genomic data. Many of the early studies with TCAs identified CYP pathways by using single dose studies in healthy volunteers who were given either D or DM. Very few studies examined depressed patients treated with TCAs. The following two studies are examples utilizing the D probe in desipramine disposition in both depressed patients and healthy volunteers. Ten depressed patients treated with desipramine 75 mg twice a day for at least two weeks were selected for evaluation with D /16/. The plasma desipramine levels in these patients had a wide interpatient variability that ranged from 113-1594 nmol/l. The D/4-hydroxy-debrisoquine (4-OHD) ratio was found to correlate with desipramine plasma concentrations ($r=0.92$, $p < 0.01$). These findings suggested the clinical utility of D phenotyping when dosing depressed patients with desipramine. When D was used to determine PMs versus EMs and desipramine disposition in healthy volunteers, it was found that EMs (mean D/4-OHD = 1.33) had a mean desipramine clearance (CL) of 0.97 l/h/kg which was significantly greater than the PMs' (mean D/4-OHD = 70.33) mean desipramine CL of 0.20 l/h/kg ($p < 0.005$) /17/.

D was given to Chinese and Caucasian volunteers (N=10 each group) who were also administered a single 100 mg dose of desi-

pramine /18/. All subjects in both groups were EMs; however, it was found that the mean fraction of the D dose (10.9% versus 6.3%) and 4-OHD (15.9% versus 9.7%) was higher in the Caucasians versus the Chinese. Significant correlations between desipramine hydroxylation and D hydroxylation were not found in either ethnic group. The fact that single dose studies may differ from clinical situations under steady-state dosing conditions was a suggested explanation for the lack of findings from previous studies.

Both phenotype and genotype were evaluated in EMs (N=89) and PMs (N=23) who participated in a study on the metabolism of desipramine /19/. Restriction fragment length polymorphism (RFLP) analysis of the *CYP 2D6* gene showed that 52% of PMs were homozygous for the Xba I 29 kb fragment whereas only 8% had two mutant alleles. Allele-specific PCR analysis revealed that every PM except one had two mutant alleles of *CYP 2D6A* or *CYP 2D6B* or both. EMs were heterozygous for the wild-type (wt) and *CYP 2D6B* gene and had higher D and desipramine metabolic ratios than homozygous subjects for the wt gene. PMs with the *CYP 2D6B* mutation displayed the RFLP pattern of 16 + 9 kb Xba. Three UMs had the 44 kb Xba I fragment but did not have either *CYP 2D6A* or *CYP 2D6B* mutations. PCR allele-specific genotyping was found to be 99% accurate in predicting D phenotype in EMs and PMs.

2.1b Other TCAs

Like desipramine, nortriptyline is converted to its 10-hydroxylated metabolite via the CYP 2D6 isozyme. In 20 depressed patients treated with nortriptyline, 100-150 mg/day, D phenotype was shown to be significantly correlated with nortriptyline steady-state plasma levels ($r=0.77$, $p < 0.01$) /20/. Significant correlation between the 10-hydroxy metabolite and the D/4-OHD ratio was not found ($r= -0.31$, p =n.s.). Similar results were described in a single dose nortriptyline and D study, and when tested in Swedes and Ghanaians /21/. Total nortriptyline CL significantly correlated with 10-hydroxy-nortriptyline CL in both groups (Swedes $r=0.89$ and Ghanaians $r=0.97$, $p < 0.001$). Amitriptyline metabolism in non-smoking healthy volunteers was found to significantly correlate with the D/4-OHD ratio ($r=0.78$, $p < 0.01$) /22/. Its disposition as measured by total plasma CL, CL by demethylation and CL by pathways other than demethylation also correlated with D/4-OHD ratios ($r= -0.89$, $r= -0.78$, and $r= -0.83$,

respectively). Significant correlations between amitriptyline disposition and D phenotyping were not found in smokers.

Recent *in vitro* studies with human hepatic microsomes reported that the metabolic scheme of clomipramine resembled other TCAs such as imipramine /23/. Clomipramine's conversion to desmethylclomipramine occurs by CYP 1A2, 2C19 and 3A4. Metabolism from clomipramine and desmethylclomipramine to their 2-hydroxy and 8-hydroxy metabolites takes place by CYP 2D6. D phenotyping has not yet been reported with clomipramine. Like clomipramine, imipramine metabolism to its desmethyl metabolite (desipramine) occurred by CYP isozymes other than 2D6. However, using human cell lines AHH-1 and TK +/- in following the metabolism of imipramine to desipramine and 2-OH desipramine, it was shown that CYP 2D6 does catalyze this reaction and could be involved in TCA demethylation as well as hydroxylation pathways /24/. Further *in vivo* studies are needed to confirm these *in vitro* findings.

2.2 Clinical relevance

A small number of in-depth clinical pharmacokinetic studies have been completed with TCAs in different ethnic groups. One of the first studies compared a single desipramine dose of 100 mg in Caucasians and Chinese healthy volunteers /25/. Although a ten-fold range of total desipramine CL was observed (range 18-221 l/h) in the study population, mean desipramine CL was significantly lower in Chinese subjects compared to Caucasians (73.5 l/h versus 123.0 l/h, $p < 0.05$). The mean CL of the 2-hydroxy metabolite did not significantly differ between the two ethnic groups (Chinese 29.6 l/h versus Caucasians 39.7 l/h). Another study with desipramine was conducted in a larger number of Asians (N=18; 9 Vietnamese, 7 Chinese and 2 Japanese) and Caucasians (N=19), in which a single dose of 1.0 mg/kg was administered /26/. Both median desipramine and 2-hydroxy metabolite CLs were significantly lower in the Asians compared to the Caucasians (desipramine CL: 64.0 l/h versus 101.4 l/h, $p < 0.05$; 2-hydroxy metabolite CL: 35.9 l/h versus 45.5 l/h, $p < 0.05$). Saliva desipramine concentrations were also evaluated in both ethnic groups /27/. A wide interpatient variation was observed in saliva concentrations as well as differences in sampling time. Due to these variabilities, significant differences in saliva/plasma desipramine ratios in Asians and Caucasians were not found. Measurement of drugs in saliva is also

influenced by pH, protein binding, and secretion rates from salivary glands.

Imipramine and doxepin plasma concentrations were evaluated in Saudi patients under steady-state conditions /28/. Total apparent drug CL (TCL) was determined as: TCL = D / T × Css where D = dose, T = time interval between doses, Css = steady-state drug concentration. The mean TCL values for doxepin and imipramine were 2.529 l/kg/h and 1.620 l/kg/h, respectively. These two mean values were compared to other published CL values by other investigators for doxepin and imipramine. Significant differences between Saudi patients and other previously published studies for doxepin CL were not found (range 2.92-3.81 l/kg/h). However, mean imipramine CL was found to be significantly lower in Saudi patients than in one study (mean 4.649 l/kg/h, $p = 0.025$) but not in two other studies (means 2.31 l/min and 1.487 l/kg/h).

A single 75 mg nortriptyline dose study was conducted in Hispanic and Caucasian healthy volunteers in which pharmacokinetic parameters were compared /29/. Significant differences in CL, area under the plasma concentration time curve (AUC), elimination half-life ($t_{½}$), or volume of distribution (Vd/F) were not found between the two groups. Information regarding metabolic status (either PMs or EMs) can assist clinicians to determine appropriate dosing for nortriptyline. A case report describes a 41 year-old female patient who needed nortriptyline doses of 300-500 mg/day to maintain a therapeutic plasma concentration of 50-150 ng/ml /30/. The urinary D/4-OHD ratio of 0.10 and 0.07 tested on two different occasions revealed an UM phenotype. The patient tolerated the high nortriptyline doses with only mild anticholinergic side effects.

Clomipramine disposition was evaluated in a single dose study of 25 mg and 50 mg in Asians (Indian) and Caucasians (English) /31/. The mean AUC for Asians were consistently lower than that for Caucasians at both drug doses. At the 25 mg dose, the mean AUC for the Asians was 224 compared to 183 for the Caucasians (units not provided; $p = 0.220$). However, at the 50 mg dose, the AUC for the Asian group was significantly greater than that for the Caucasians (572 versus 352, $p < 0.001$). The peak plasma drug concentration (Cmax) was also higher in the Asians (50 mg dose: 45.1 ng/ml versus 28.3 ng/ml, $p < 0.02$). The Asians reported a higher incidence and severity of adverse side effects than the Caucasians. Plasma clomi-

pramine and its metabolites were measured in Japanese psychiatric patients (N=92) /32/. A large interpatient variability of plasma concentrations for clomipramine and its metabolites was found and only one possible PM identified. Although D phenotyping was not conducted, the metabolic hydroxylation ratio of clomipramine to its hydroxylated metabolite in this particular male patient was 18.30 (mean male value 2.40). Steady-state plasma clomipramine and desmethylclomipramine levels were compared in Japanese and Swedish patient populations /33/. Higher mean clomipramine plasma levels were found in the Japanese group, but the difference was not statistically significant (135 ng/ml versus 80 ng/ml). A significant difference in mean clomipramine concentration/daily dose (ng/ml per mg) ratio was found between the two ethnic groups as the Japanese population had higher values (1.75 versus 0.65, $p < 0.05$). Mean desmethylclomipramine plasma levels did not differ between the groups (Japanese 138 ng/ml versus Swedish 149 ng/ml). Overall, clomipramine studies tend to support that Asians have higher plasma drug concentrations than Caucasians when comparable doses of the drug are given.

In summary, some pharmacokinetic studies with TCAs tend to show that Asians have differences compared to Caucasians but these differences were not found with other ethnic groups such as Hispanics /34/. Fewer data are available from the Afro-American population in which methodological problems prevent an accurate evaluation of TCA disposition /35/. There is some evidence that Afro-Americans respond better than Caucasians to TCAs /5/, but carefully designed studies have not been reported. Based upon these findings with TCAs, one suggestion in dosing non-Caucasians is to begin with 25 mg at bedtime (except protriptyline) and to increase the dose every 2-3 days by 25 mg/day until the patient reaches 100 to 150 mg/day, unless adverse side effects occur which prevent further dosage increases. When the patient reaches 150 mg/day, if the patient does appear to respond or has significant side effects, a plasma concentration should be measured to determine further dosage adjustments /6/. Cardiac monitoring (ECGs) may be needed in non-Caucasians who could be more sensitive to adverse cardiotoxic effects /35/.

2.3 Selective serotonin reuptake inhibitors (SSRIs)

The metabolic profile of SSRI antidepressants with CYP isozymes shown in Table 2 is based upon *in vitro* and *in vivo* studies with human hepatic microsomes and clinical studies. SSRIs are a complex set of antidepressants regarding their metabolic profile as these agents can be substrates for various CYP isozymes and yet also be inhibitors of the same or different CYP isozymes. All of the SSRIs listed in Table 2 are substrates for CYP 2D6 (usually with another CYP isozyme - except paroxetine) /14/. For example, paroxetine is a substrate of CYP 2D6 but also a potent inhibitor of CYP 2D6 /14, 15,36/. *In vitro* studies have shown that fluoxetine and its desmethyl metabolite norfluoxetine are similar to paroxetine for CYP 2D6 inhibition while citalopram and fluvoxamine are much less potent inhibitors /37,38/. A recent *in vitro* study with citalopram showed this agent was actually a very weak CYP2D6 inhibitor /39/. Other SSRI metabolites (paroxetine, citalopram and sertraline) had weak inhibitory potency /15,38/. TCAs such as cloimpramine, desipramine, and amitriptyline were also weak inhibitors, similar to citalopram and fluvoxamine /37,38/.

2.4 Clinical relevance

A nonlinear pharmacokinetic profile for paroxetine was described in two EMs and PMs (sparteine oxidation phenotyped) when given single drug dosages ranging from 10 mg to 50 mg /40/. Serum paroxetine concentrations in PMs were dramatically elevated with increasing drug doses. Paroxetine concentrations were only minimally increased in EMs when drug doses were increased. Although therapeutic plasma paroxetine concentrations have not been established, these results indicate that paroxetine dosing in PM subjects must proceed very slowly and be carefully monitored for potential adverse side effects. Conversely, EMs can be dosed more aggressively to maximize clinical drug response in depressed patients.

The CYP 2D6 status of EMs was investigated by D phenotyping prior to and during SSRI dosing in healthy volunteers /41/. Phenotyping was conducted on three occasions prior to SSRI dosing to determine a consistent pre-dose D/4-OHD ratio. Subjects were randomized into four groups that received drug for eight consecutive days: paroxetine 20 mg; fluvoxamine 100 mg; sertraline 100 ıng; and

fluoxetine 60 mg. A loading dose method was used for fluoxetine due to the drug and its active metabolite's long elimination half-life in which this method approximates a 20 mg/day dose at steady-state. Phenotyping was repeated at the 8th day after SSRI dosing. The results showed that D/4-OHD ratios remained unchanged with fluvoxamine and sertraline. Mean ratios of D/4-OHD were significantly increased with paroxetine (0.028 to 1.085, $p < 0.001$) and fluoxetine (0.020 to 0.364, $p < 0.01$). Interestingly, four subjects in each group converted from EM status to PM status with D/4-OHD ratios greater than the D anitmode of 0.3. Unfortunately, genotyping was not conducted to determine whether a change in the allele status correlated with the change in phenotype status. The authors suggested that SSRI dose and plasma concentrations may be correlated with the extent of CYP 2D6 inhibition.

Paroxetine's effect upon D/4-OHD was evaluated in depressed patients (N=6) and healthy volunteers (N=6) with doses of 10 mg/day (N=3) and 20 mg/day (N=9) /42/. These investigators found significant changes in mean log O-demethylation ratios upon paroxetine use from –2.28 to –1.13 ($p < 0.001$). In another study, paroxetine was given as a single dose of 10-80 mg to healthy volunteers (N=24) /43/. Sparteine ratios were determined prior to and three hours after paroxetine dosing. Three of six EMs converted from EM status to PM status after 40 mg or 80 mg paroxetine dose.

Fluoxetine and paroxetine are potent CYP 2D6 inhibitors compared to other SSRIs, as shown in Table 2, based upon *in vitro* and *in vivo* data /15,41/. This knowledge can assist clinicians in predicting clinically significant drug-drug interactions (see Section 6). It is beyond the scope of this article to describe every drug-drug interaction study with SSRIs based upon CYP 2D6 status, but selected studies are presented in subsequent sections.

The influence of ethnicity has not yet been reported in SSRI disposition. Despite the low frequency of PMs among non-Caucasian populations (i.e. Asians, Afro-Americans, Africans, etc.), some non-Caucasians might be more sensitive to the SSRIs' inhibitory effects on CYP 2D6 and may be more prone to adverse side effects /6/. Anecdotal evidence has suggested that some Afro-American depressed patients had an adequate therapeutic response to SSRIs at half the usually recommended dose, but without carefully designed studies this comment should be interpreted cautiously /6/.

2.5 Other miscellaneous agents

Maprotiline (not listed in Table 2) is a noradrenergic specific antidepressant /44/. In 12 healthy Caucasian volunteers who were phenotyped by D (6 PMs and 6 EMs), the peak plasma drug concentration (Cmax) was 2.7 fold greater ($p = 0.004$) and the AUC was 3.5 times higher ($p = 0.0003$) in the PMs than in the EMs /44/. The mean $t_{½}$ in PMs was significantly greater than in EMs (88.3 h versus 30.4 h, $p < 0.0001$). These results support that maprotiline appears to co-segregate with CYP 2D6 polymorphism hydroxylation.

Mirtazapine and venlafaxine are newer antidepressants approved in the USA, listed in Table 2, that are CYP 2D6 substrates /15,45,46/. However, their effects upon CYP 2D6 oxidation are much less potent than SSRIs /47/. Mirtazapine's inhibitory action upon CYP 2D6 was reported to be 10 times less potent than fluoxetine /43/. Similar to a previous study /41/, D phenotyping changes were evaluated in healthy volunteers (N=12) comparing SSRIs and venlafaxine /48/. Subjects received each antidepressant for eight days in a crossover design: paroxetine 20 mg; sertraline 100 mg; fluoxetine 60 mg (loading dose method); and venlafaxine 150 mg. All subjects completed the study with the four different agents. Phenotyping was completed prior to antidepressant dosing and at the end of eight day period. D/4-OHD ratios did not change significantly with sertraline and venlafaxine, but were elevated with paroxetine and fluoxetine. Again, paroxetine and fluoxetine demonstrated potent CYP 2D6 inhibition while sertraline and venlafaxine lacked inhibitory action for CYP 2D6.

3. CYP 3A4

This isozyme represents the largest amount found in the human body (liver, gut wall, etc.) that is involved with Phase I drug metabolic reactions /10/. CYP 3A isoforms (3A3, 3A4, and 3A5) are partially or entirely responsible for the metabolism of many different drugs besides antidepressants, including antipsychotic (see article by Aitchison *et al.* in this issue), cardiovascular, immunosuppressive, antineoplastic and protease inhibitor agents /15/. Polymorphism similar to CYP 2D6 has not been established with 3A isoforms. This section presents relevant information regarding the effects of antidepressants upon CYP 3A4. Specific metabolic probes are available to

assess CYP 3A4 activity (such as midazolam); however, their use in a large number of study subjects has not been reported due to the drug's safety profile and/or the need for technical assay development.

3.1 Tricyclic antidepressants

TCAs such as amitriptyline, imipramine and clomipramine have been shown to be demethylated to their desmethyl metabolites via CYP 3A4. The example of imipramine is shown in Figure 1. Conversion to these desmethyl metabolites can yield agents that contain equal pharmacological activity to the parent drug, such as the transformation from imipramine to desipramine. However, it must be remembered that TCA demethylation is also influenced by other CYP isozymes, 1A2 and 2C19 and possibly 2D6. TCAs have been shown to lack inhibitory effects upon CYP 3A isoforms.

3.2 Selective serotonin reuptake inhibitors

Only three SSRIs, listed in Table 2, have been reported to be substrates of CYP 3A4. CYP 3A4 appears to play a minor role in drug disposition for fluoxetine and sertraline /15/. Citalopram, like other SSRI antidepressants, can be used for other psychiatric disorders, such as panic, social phobia and obsessive-compulsive disorder /49/. Like TCAs, these SSRIs are demethylated by CYP 3A4 /15/. Other CYP isozymes can be involved in this conversion; however, CYP 3A4 has been shown with *in vitro* models to be the major isozyme that metabolizes citalopram to desmethylcitalopram /39,50/. SSRIs (including norfluoxetine) have been shown to possess moderate (++) to low (+) potency in inhibition of CYP 3A4 activity, as shown in Table 2 /15,48/.

3.3 Other miscellaneous agents

Nefazodone is solely metabolized while mirtazapine is predominantly metabolized by CYP 3A4, as listed in Table 2 /45,46/. As a CYP 3A4 inhibitor, mirtazapine was reported to be 250 times less potent than ketoconazole, which implies that the likelihood of significant drug-drug interactions are minimal /46/. Nefazodone was reported to be the most potent CYP 3A4 inhibitor of the antidepressants and numerous drug-drug interactions can potentially occur (see Section 6).

4. CYP 1A2

The detoxification of many drugs and the conversion of various prodrugs to their pharmacologically active metabolites takes place via this isozyme /51/. CYP 1A2 is one of two isozymes in the CYP 1A subfamily and although it comprises only a small portion of the hepatic isozyme system /10/, a wide intra- and interindividual variability occurs in CYP 1A2 activity /51/. Cigarette smoking produces a marked induction of CYP 1A2 activity; to date, evidence for genetic polymorphism has not been demonstrated.

4.1 Tricyclic antidepressants

The conversion of imipramine and cloimpramine to the desmethyl metabolite (see Fig. 1) has been shown to be partially influenced by CYP 1A2 /23,51/. Caffeine has been shown to be a relatively specific metabolic probe for CYP 1A2 activity /52/. However, due to the multiple CYP isozymes involved in the metabolism of imipramine and other TCAs, use of the caffeine phenotyping method becomes unfeasible for correlating TCA disposition and CYP 1A2 activity.

4.2 Selective serotonin reuptake inhibitors

Fluvoxamine was shown to be the only SSRI to have substrate affinity for CYP 1A2; however, this evidence was indirectly demonstrated by clinical case reports of theophylline toxicity when fluvoxamine was co-administered /15/. Other SSRIs were shown not to influence theophylline disposition. Theophylline is metabolized by CYP 1A2 and also 2E1, but none of the SSRIs including fluvoxamine were shown to inhibit CYP 2E1 /15/. In *in vitro* studies, fluvoxamine was clearly shown to be a very potent CYP 1A2 inhibitor with a Ki of 0.2 μM, whereas other SSRIs had Ki values greater than 45 μM /53/. In a healthy volunteer study, smokers were shown to have significantly lower mean AUC values than non-smokers (771 $nmol^{-1}$/h versus 1110 $nmol^{-1}$/h, $p = 0.012$), indicating the influence of CYP 1A2 upon fluvoxamine disposition /54/.

Caffeine urinary ratios were determined in patients and healthy volunteers treated with fluvoxamine /42,43/. A caffeine test dose of 100 mg was given and the caffeine metabolic ratio (CMR) determined prior to and after fluvoxamine 50-100 mg/day usage /42/. All subjects

were previously phenotyped as CYP2D6 EMs prior to caffeine phenotyping. Fluvoxamine produced a significant decrease in mean CMR from baseline (5.1 to 2.7, $p < 0.01$). These findings show that even low to modest fluvoxamine doses can inhibit CYP 1A2 activity. Single fluvoxamine doses of 25-200 mg were given to healthy volunteers in which CMRs were calculated at each dosage increment /43/. At the 25 mg dose, median CMR decreased from 4.3 to 2.8 ($p = 0.2$); however, at the 50 mg dose, median CMR ratios were unable to be determined due to the metabolites being below the limits of quantification. Caffeine CL decrease from 107 ml/min to 21 ml/min ($p < 0.05$) and CYP 1A2 activity were shown to be almost completely abated with 50 mg fluvoxamine. CMR ratios were shown to be unaltered with other SSRIs.

4.3 Other miscellaneous agents

Mirtazapine's disposition was mainly influenced by CYP 3A4 with only a small contribution of CYP 1A2, as listed in Table 2 /14/. Mirtazpine was reported to be 900 times less potent than fluvoxamine in CYP 1A2 inhibition /45/. The likelihood of significant drug-drug interactions and effect of smoking with mirtazapine would therefore be minimal.

5. CYP 2C

CYP 2C has several isoforms but the most predominant isozymes studied in drug metabolism involve the 2C9 and 2C19 isozymes /55/. CYP 2C19 like CYP 2D6 has been shown to possess polymorphism and its genes identified. The highest incidence of PMs of 2C19 occurs in the Asian population (about 20%) whereas the Caucasian prevalence is much lower at 2-5% /55/. Specific metabolic probes have been identified to examine CYP 2C19 status in PMs versus EMs. The two most accepted probes used for phenotyping are mephenytoin and omeprazole /55/. PCR based methods have determined two mutations for the CYP 2C19 genotype, defined as M1 and M2 alleles, which are defective in PMs /55/. Substrates for CYP 2C9 have not included the antidepressants and this isozyme will not be discussed in this article. However, one of the most well known drugs to be metabolized by CYP 2C9 is warfarin /15/, for which the many drug interaction studies

have usually focused on a protein binding displacement type of interaction. Recent evidence suggests that CYP 2C9 activity may be involved (see Section 6).

5.1 Tricyclic antidepressants

As previously mentioned in the CYP 3A4 and 1A2 sections, the demethylation of TCAsm such as imipramine's conversion to desipramine, is mediated by various CYP isozymes. The other CYP isozyme involved in this metabolic pathway is CYP 2C19 (see Fig. 1). Besides imipramine, clomipramine and amitriptyline demethylation via CYP 2C19 has been shown /55/.

5.2 Clinical relevance

Imipramine metabolism was evaluated in PMs versus EMs of mephenytoin /56/. Each subject was given a single dose of imipramine 100 mg and desipramine 100 mg on two separate study days. Imipramine demethylation mean CL was significantly lower in PMs versus EMs (0.74 l/min versus 1.43 l/min, $p = 0.01$). These subjects were also previously phenotyped by sparteine (s) as EMs of CYP 2D6. Subjects who were EMs of mephenytoin [EM(m)] and EM(s) had an imipramine mean total CL of 2.55 l/min, which was slightly greater than the mean imipramine total CL of 1.83 l/min in subjects who were PMs of mephenytoin [PM(m)] and EM(s)s. One subject who was a PM(m) and a PM(s) had the lowest imipramine total CL of 0.66 l/min. The desipramine mean CL of 0.20 l/min was lowest in the EM(m)/PM(s) group when compared to other groups (PM(m)/EM(s) 1.93 l/min). These results also suggested that about 50% of imipramine's demethylation pathway was mediated by CYP 2C19. Similar findings were reported with clomipramine mean total CL and its demethylation to desmethylclomipramine in PM(m)/EM(s) versus EM(m)/EM(s) /57/. Again one subject who was a PM(m)/PM(s) had the lowest clomipramine CL in the study.

In a large population study (N=106) previously classified as EM(s)s, a single dose of 25 mg imipramine was given and one blood sample obtained three hours later /58/. The desipramine/imipramine ratio and 2-OH-desipramine/2-OH-imipramine ratio reflects the demethylation of imipramine and 2-OH-imipramine. A negative correlation was found for both of these two ratios and mephenytoin

metabolic status. Also, correlations between the hydroxylation of imipramine and desipramine metabolites were not found with mephenytoin metabolic ratios. These findings support previous studies that the demethylation pathway of imipramine to desipramine is partially mediated by CYP 2C19.

Phenotyping for both CYP 2D6 (using metoprolol [mt]) and CYP 2C19 (mephenytoin) metabolic status was conducted in an Asian population (3 Japanese, 13 Koreans) who were given a single 25 mg dose of imipramine /59/. Subjects were divided into three groups: EM(mt) (extensive metabolizer of metoprolol)/PM(m); EM(mt)/ EM(m); and PM(mt)/EM(m). The mean imipramine AUC was significantly greater for the EM(mt)/PM(m) group versus the EM(mt)/ EM(m) group (375 ng/ml-h versus 215 ng/ml-h, $p < 0.01$) but not for the PM(mt)/EM(m) group (365 ng/ml-h). Desipramine mean AUC was nine-fold greater in the PM(mt)/EM(m) than the other two groups ($p < 0.01$). Conversely, the 2-OH-desipramine metabolite mean AUC was 4-6 fold less in the PM(mt)/EM(m) group ($p < 0.05$). This study demonstrates in an Asian population that imipramine's conversion to its metabolites is under pharmacogenetic influence. A similar study was conducted in depressed Japanese patients who were phenotyped with metoprolol and mephenytoin prior to imipramine treatment /60/. Two patient groups were identified: EM(mt)/PM(m) and EM(mt)/ EM(m). Imipramine and imipramine + desipramine plasma concentrations were 2.4 and 1.8 times greater in the PM(m) group versus the EM(m) group ($p < 0.01$). Since the Asian population has a greater frequency of PM(m) of CYP 2C19, the authors suggest that TCA dosing (at least with imipramine) should proceed slowly to avoid adverse effects and maximize therapeutic efficacy.

5.3 Selective serotonin reuptake inhibitors

The only two SSRI antidepressants identified as substrates for CYP 2C19 are sertraline and citalopram, for their metabolic conversion from parent drug to desmethyl metabolites, listed in Table 2. Since CYP 2C19 was listed with four other CYP isozymes for sertraline, it has been recently reported that the contribution of any individual isoform was less than 40% (2C19 13%) based upon *in vitro* cDNA expressing cells /61/. Citalopram conversion to its desmethyl metabolite is partially influenced by CYP 2C19 but by a much smaller amount than by CYP 3A4 /39,50/. As metabolic inhibitors based upon

in vitro models, only fluvoxamine possesses potent action on CYP 2C19 /14/, while other SSRIs had mild to modest effects, shown in Table 2. Citalopram was reported to have the least inhibitory effect with Kis 20-40 fold greater than paroxetine, fluoxetine, and sertraline /39,62/. Therefore, based upon *in vitro* findings, significant drug-drug interactions with CYP 2C19 would only occur with fluvoxamine.

5.4 Clinical relevance

Healthy volunteers were given citalopram 40 mg/day for ten days in which the drug's disposition was determined /63/. Each subject was previously phenotyped with sparteine and mephenytoin and three groups were identified: EM(s)/EM(m); PM(s)/EM(m); and EM(s)/PM(m). The median citalopram AUC was significantly greater in the EM(s)/PM(m) group versus the other two groups (i.e. 8,145 nM/h EM(s)/PM(m) versus 4,700 nM/h PM(s)/EM(m), $p < 0.001$). The mean desmethylcitalopram AUC in the PM(s)/EM(m) group was also significantly greater than in the other two groups (i.e. PM(s)/EM(m) 2,400 nM/h versus EM(s)/EM(m) 1,768 nM/h, $p < 0.03$). These findings show that CYP 2C19 status can influence citalopram disposition in PM(m)s versus EM(m)s. Citalopram, fluoxetine, fluvoxamine, and paroxtine in single doses ranging from 10-80 mg were given to healthy volunteers (except fluvoxamine 25-200 mg) and with repeated mephenytoin phenotyping at each dose /43/. The mephenytoin metabolic ratio changed modestly with fluoxetine and fluovamine ($p < 0.01$). However, even at the highest drug doses, the metabolic ratio did not exceed 0.6 and not a single subject's status changed from EM(m) to PM(m). Citalopram and paroxetine produced no significant changes in mephenytoin metabolic ratio.

6. DRUG INTERACTIONS

Drug-drug and drug-food interactions have become increasingly complex from a mechanistic profile as the information regarding CYP isozymes increases. Presently, significant drug-food interactions have not yet been reported and this section will focus only on drug-drug interactions. It is beyond the scope of this article to review every published article on antidepressant drug-drug interactions and the reader is referred to other publications for in-depth review. This

section presents relevant information about drug-drug interactions in general terms with CYP isozymes. Other biochemical mechanisms could be involved with antidepressant disposition (e.g. drug transport mechanisms - phophoglycoproteins, etc.) but have not been presently investigated.

6.1 Tricyclic antidepressants

In vitro models have been used to predict drug-drug interactions with TCAs based upon CYP isozyme effects. For example, the transformation of amitriptyline to nortriptyline was evaluated by a variety of known CYP metabolic inhibitors /64/. SSRIs (except citalopram) listed in Table 2 were CYP 3A4 inhibitors and inhibited the formation of nortriptyline with the following Kis: sertraline 4.37; fluvoxamine 9.22; norfluoxetine 12.26; paroxetine 15.76; and fluoxetine 43.55. Ketoconazole's Ki was very potent - 0.11 - and also inhibited nortriptyline formation. These results support that inhibition of CYP 3A4 can elevate amitriptyline levels while inhibiting nortriptyline formation. In the clinical environment with monitoring nortriptyline plasma levels routinely in 578 patients, it was found that concomitant drugs known to inhibit CYP2D6 resulted in a major increase in drug concentration /65/. Demographic factors, age, and body weight had only minor effects upon nortriptlyine CL and were unaffected by treatment duration.

6.2 Selective serotonin reuptake inhibitors

Numerous review articles have been recently published that examine the variety of drug-drug interactions with SSRIs and other drugs /10,14,15,66-69/. These drug interactions are based upon *in vitro* and *in vivo* studies involving the different CYP isozymes where SSRIs listed in Table 2 have been shown to be potent inhibitors. Therefore, other drugs that are substrates of these CYP isozymes could potentially interact with SSRIs. An example of this type of interaction is between SSRIs and TCAs. SSRIs (such as paroxetine) are potent CYP 2D6 inhibitors and increase desipramine plasma levels by inhibition of the aromatic hydroxylation pathway influenced by this isozyme. An important distinction in the clinical arena is that this interaction would occur only in EMs of CYP 2D6 and not in PMs (PMs lack the isozyme and therefore, no enzyme is available for the

interaction). Polymorphism of CYP 2D6 should be kept in mind when considering drug-drug interactions with CYP 2D6, and also the prevalence of PMs among different ethnic populations. Additional factors to consider are the possibility of EMs being converted to PM status during SSRI therapy, and these drugs' non-linear pharmacokinetics with increasing doses upon long-term treatment.

SSRIs are listed as low to modest metabolic inhibitors of CYP 3A4 in Table 2. Both fluoxetine and fluvoxamine (modest inhibitors) were reported to significantly increase mean alprazolam concentration (CYP 3A4 substrate) by 26% and 96%, respectively /15/. However, significant drug-drug interactions with CYP 3A4 may be partially dependent upon their Ki values. For example, many clinicians became aware of the deadly drug-drug interaction between antifungals and terfenadine /70/. SSRIs were shown to have Kis for CYP 3A4 several fold higher than ketoconazole in inhibiting both desalkyl and hydroxy terfenadine metabolites /70/. Due to this difference, SSRIs should not produce a significant interaction with terfenadine, but most clinicians should use their clinical judgement and carefully monitor patients when using this drug combination.

Fluvoxamine is the only SSRI listed as a potent CYP 2C19 inhibitor and a significant interaction with diazepam was shown in healthy volunteers /71/. Diazepam's mean elimination half-life was prolonged from 51 hours to 118 hours ($p < 0.01$). Desmethyldiazepam mean AUC was also significantly increased from 7.3 ng-h/ml to 10.3 ng-h/ml ($p < 0.01$). Citalopram's conversion to its desmethyl metabolite is partially influenced by CYP 2C19 (see previous section). Fluvoxamine was shown to increase plasma citalopram levels in depressed patients in a small preliminary study /72/. However, since fluvoxamine also inhibits CYP 3A4, this contribution must be considered as an additional mechanism for this interaction. Phenytoin is primarily metabolized by CYP 2C9 and every SSRI (except citalopram) showed a potent inhibition based on *in vitro* models which resulted in clinically significant increased drug levels in seizure patients /66,73/. CYP 2C9 was reported to be one of the major isozymes involved with warfarin metabolism, in which sertraline and citalopram were suggested as least likely to interact /74/.

6.3 Other miscellaneous agents

Venlafaxine was reported not to produce significant interactions with alprazolam, carbamazepine, and diazepam /75/. It was also reported that venlafaxine did not alter EM status in subjects who were phenotyped with D /48/. The lack of interactions with venlafaxine and other drugs could be forecasted due to its lack of CYP inhibitor status listed in Table 2. The incidence of depression among HIV patients could be as high as 45% /76/. Protease inhibitors are primarily substrates for CYP 3A4 /76/ and theoretically could interact with some SSRIs. A small pilot study in healthy volunteers showed that venlafaxine did not alter indinavir pharmacokinetics /77/. Nefazodone is a potent CYP 3A4 inhibitor and produced significant interactions with alprazolam and triazolam /46/. Clinicians are cautioned with nefazodone when used concomitantly with other drugs that are CYP3A4 substrates.

7. CONCLUSIONS

Information regarding CYP isozymes is increasing exponentially in the scientific literature. CYP isozymes are involved with Phase I oxidative metabolic processes in drug metabolism. Numerous CYP isozymes and their subtypes have been identified; however, the main CYP isozymes involved with drug metabolism are 2D6, 3A4, 1A2, 2C9 and 2C19. The amount of CYP isozymes differs: in hepatic tissue the most abundant is 3A4 with decreasing quantities of 2D6, 2C9, 2C19 and 1A2 /10/. Of these isozymes, polymorphism has been found with 2D6 and 2C19 and their genetic alleles identified. The prevalence of metabolic status known as PM versus EM differs among various ethnic populations. A wide interpatient variability in the same ethnic population as well as interethnic variability in antidepressant drug disposition can be attributed to CYP isozyme differences and polymorphism. Many antidepressant drug-drug interactions can be traced back to their ability to produce CYP isozyme inhibition. Some SSRIs can alter an individual's metabolic status from EM to PM for CYP 2D6. Although some CYP isozymes exist in relatively small amounts, for example, CYP3A4 versus CYP1A2, inhibition of CYP 1A2 by fluvoxamine can have profound effects in causing drug-drug interactions. The incidence of significant drug-drug interactions could

differ among ethnic populations due to polymorphism and differing prevalences of PMs. Therefore, clinicians must always consider the individual patient in evaluating the antidepressant clinical response and impact of a drug-drug interaction /78,79/.

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