Interactions Between Tamoxifen and Antidepressants via Cytochrome P450 2D6

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Objective: Women taking tamoxifen for the treatment or prevention of recurrence of breast cancer are likely to take antidepressants either for a psychiatric disorder or for hot flashes. Recent evidence suggested that some antidepressants inhibit the metabolism of tamoxifen to its more active metabolites by the cytochrome P450 2D6 (CYP2D6) enzyme, thereby decreasing the anticancer effect. This article reviews the literature on the interactions between newer antidepressants and tamoxifen via CYP2D6 and offers treatment recommendations.

Data Sources: A literature search of clinical and nonclinical studies published prior to September 2008 was conducted on PubMed. We performed 3 different searches combining the terms *tamoxifen* and *SSRIs*; *tamoxifen* and *CYP2D6 inhibitors*; and *antidepressant* and *breast cancer recurrence*. A fourth search with *CYP2D6 inhibition* and the generic names of individual antidepressants was carried out.

Study selection: Seven clinical research articles were selected. Nonclinical research articles about antidepressants were included if they mentioned in vitro or in vivo inhibition of CYP2D6.

Data Synthesis: There is consistent evidence that paroxetine and fluoxetine have a large effect on the metabolism of tamoxifen and should not be used. Indirect evidence indicates that bupropion may also have a large effect on the metabolism of tamoxifen. Venlafaxine has little or no effect on the metabolism of tamoxifen and may be considered the safest choice of antidepressants. Desvenlafaxine is not metabolized by the P450 system and may consequently be another option. Mirtazapine has not been extensively studied, but existing research suggests minimal effect on CYP2D6. The remaining commonly prescribed antidepressants have mild to moderate degrees of CYP2D6 inhibition.

Conclusions: Clinicians treating patients with breast cancer should review the prescription profiles of their patients to evaluate the need for treatment modification. There are safe options for the treatment of depression and clinicians and patients should bear in mind the health risks of untreated depressive states.

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Tamoxifen is a selective estrogen receptor modulator, having estrogenic and antiestrogenic properties on various tissues. In breast tissue, tamoxifen competes with estrogen for estrogen receptors (ERs) to inhibit the stimulatory effect of estrogen on tumor growth. Tamoxifen was approved by the US Food and Drug Administration in 1977 for use as an adjuvant in the treatment of postmenopausal women with ER positive breast cancer or ductal carcinoma in situ. It is also used in the treatment of ER positive metastatic breast cancer in both men and women, as well as for prophylaxis in women at very high risk of developing breast cancer.[1] Standard treatment consists of a 5-year course. Over the past 3 decades, tamoxifen has reduced breast cancer deaths by one-third and recurrences by one-half.[2] Unfortunately, 35% of women with advanced ER positive cancer do not respond to tamoxifen.[3] It has been postulated that genetic variation in enzymes involved in the metabolism of tamoxifen may account for tamoxifen failure in some patients.[4]

Metabolism of Tamoxifen

Tamoxifen has 3 major active metabolites.[4] It is converted to *N*-desmethyltamoxifen through CYP 3A4 and 3A5, which is then converted to 4-hydroxy-*N*-desmethyltamoxifen (endoxifen) through cytochrome P450 2D6 (CYP2D6). Tamoxifen is also converted to 4-hydroxytamoxifen through CYP2D6 and, subsequently, to endoxifen through CYP 3A4 and 3A5. The 4-hydroxytamoxifen metabolite is 100-fold more potent as an antiestrogen agent than tamoxifen and *N*-desmethyltamoxifen. Endoxifen is equivalent to 4-hydroxytamoxifen in terms of potency, but its steady state concentrations are 6 to 10 times higher than the latter. Endoxifen is also 30- to 100-fold more potent than tamoxifen for suppression of cell proliferation.[4]

Cytochrome P450 2D6

The CYP2D6 plays an important role in the metabolism of tamoxifen. The gene coding for this cytochrome is polymorphic, with at least 71 reported allelic variants,[5] many of which result in the loss of CYP2D6 enzyme function. CYP2D6 polymorphisms that result in poor metabolism are

found in 7% to 10% of Caucasians, 2% of African Americans, and 1% of Asians.[4]

P450 2D6 Phenotype and Tamoxifen Response

In 2005, Goetz et al[6] showed that women taking tamoxifen for breast cancer who were homozygous for the CYP2D6*4 allele, a nonfunctioning allele, had shorter relapse-free time and worse disease-free survival compared to women with either 1 or no *4 alleles. Serrano,[7] Borges,[8] Gjerde,[9] and their colleagues found that women with 1 or 2 nonfunctioning CYP2D6 alleles had lower plasma levels of tamoxifen metabolites. Schroth et al[10] and Kiyotani et al[11] also demonstrated that women treated with tamoxifen who have defective CYP2D6 alleles have significantly more recurrences of breast cancer, shorter relapse-free periods, and worse event-free survival rates in comparison with women with functioning alleles. Data from the Italian Tamoxifen Trial[12] furthermore suggest that healthy women with the CYP2D6 *4/*4 genotype are less likely to benefit from tamoxifen as a chemopreventive agent.

On the other hand, Wegman et al[13] found no statistically significant difference in the relapse-free survival between women homozygous or heterozygous for CYP2D6*4 and women homozygous for CYP2D6*1, whether they took tamoxifen for 2 or 5 years. In an earlier study,[14] they had shown that carriers of the CYP2D6*4 allele demonstrated a decreased risk of recurrence when treated with tamoxifen. Nowell et al[15] also found no significant association between CYP2D6 genotype and overall survival in breast cancer patients taking tamoxifen. It is not known, however, if these patients were taking concomitant CYP2D6 inhibitors, and the sample sizes may not have been sufficient to show a statistical difference.

On October 18, 2006, the US Food and Drug Administration Endocrinologic and Metabolic Drugs Advisory Committee recommended that the tamoxifen prescribing information be updated to include information about CYP2D6 genotypes, CYP2D6 genotyping tests, and the potential relationship between 2D6 genotype and clinical outcome. The members of the committee, however, did not reach a consensus as to whether testing should be recommended or considered as an option.[16] There is yet no consensus in the literature about the relationship between CYP2D6 genotype and tamoxifen efficacy.

Tamoxifen and Antidepressants

Antidepressants are the most prescribed class of medication in the United States.[17] Approximately 8% of civilian noninstitutionalized Americans and approximately one-third of patients visiting medical offices are taking an antidepressant.[17] Similarly, it is estimated that 20%–30% of patients taking tamoxifen are also taking antidepressants.[18,19] This includes women with breast cancer who are being treated for depression or anxiety as well as those receiving antidepressants for the treatment of vasomotor instability (hot flashes). According to the 2007 US retail market,[20] the 9 most commonly prescribed antidepressants were, in decreasing order: sertraline, escitalopram, fluoxetine, paroxetine, venlafaxine, citalopram, trazodone, duloxetine, and bupropion. Overall, approximately 62% of all antidepressants prescribed in the United States are selective serotonin reuptake inhibitors (SSRIs).[20]

The goal of this article is to review the interaction of the most prescribed antidepressants (SSRIs and newer antidepressants) with tamoxifen via the CYP2D6 enzyme and offer recommendations for the use of antidepressants in women taking tamoxifen. The review is divided into clinical and nonclinical studies. The clinical studies measure the effect of antidepressants on tamoxifen metabolites as well as changes in other substrates of the CYP2D6 enzyme. The nonclinical studies consist of in vitro studies of the inhibition of the CYP2D6 enzyme in human liver microsomes.

SEARCH METHOD

To identify clinical research studies, our search strategy began with *tamoxifen* and *SSRIs* with *clinical trial* as a limit, which resulted in 1 original article. Then *CYP2D6* was searched with *inhibitors* and *tamoxifen*, which retrieved 18 original articles. Four of these articles were retained as they were discussing antidepressants. *Tamoxifen* and *SSRI* provided 2 more pertinent original articles, while *antidepressant* and *breast cancer recurrence* gave 1 more pertinent article, for a total of 7 clinical research studies.

CYP2D6 inhibition was then searched with *fluoxetine*, *paroxetine*, *fluvoxamine*, *citalopram*, *escitalopram*, *sertraline*, *venlafaxine*, *desvenlafaxine*, *duloxetine*, *bupropion*, *nefazodone*, *monoamine oxidase inhibitors*, and *tricyclics*. Articles were included if they mentioned in vitro or in vivo inhibition of CYP2D6.

RESULTS

Clinical Studies of Tamoxifen and Antidepressants

Three prospective clinical studies,[3,8,21] 2 of which are based on the data from the same clinical trial,[3,8] have investigated the effect of antidepressants on the levels of endoxifen in women taking tamoxifen, taking into account their metabolizer status as defined by their CYP2D6 genotype (Table 1). All 3 studies found significant decreases in endoxifen levels with paroxetine in extensive metabolizers (EMs). One study investigating the effect of fluoxetine found a similar pattern of decreased endoxifen levels among EM patients.[8] The 2 studies examining the effect of venlafaxine found no change in endoxifen levels.[3,8] Meanwhile, the effect of sertraline and citalopram was observable but not as pronounced as that of the more strongly inhibiting antidepressants fluoxetine and paroxetine.[3,8] Interestingly, the levels of endoxifen of the EM patients taking strongly inhibiting drugs were comparable to those of the poor metabolizers (PM),[3,8] and there was no

Table 1. In Vivo Studies Involving Tamoxifen and Antidepressants

Reference	Type of Study/Subjects	Methods	Antidepressant	Results (according to presence of 2D6 inhibitor)	Results (according to genotype)
Stearns et al,[21] 2003	Prospective clinical trial; N = 12 with breast cancer (7 EMs and 5 IMs) on tamoxifen	Plasma levels of tamoxifen and metabolites measured before and after 4 wk of paroxetine	7 EMs on paroxetine	Plasma concentration of endoxifen significantly decreased from a mean of 12.4 ng/mL before paroxetine to 5.5 ng/mL afterward (n = 12)	Endoxifen concentration decreased, by 64% in EMs
			5 IMs on paroxetine		No statistically significant effect on endoxifen in IMs
Lehmann et al,[22] 2004	Case control study; N = 28 without recurrence of breast cancer matched with 28 with recurrence on tamoxifen	Charts reviewed for exposure to CYP 2D6, 2C9, and 3A inhibitors	2D6 inhibitors: fluoxetine, paroxetine, sertraline	No significant difference found for CYP inhibitor or substrate exposure between cases and controls (6 cases and 8 controls on 2D6 inhibitors)	
Jin et al,[3] 2005	Prospective trial; N = 78 with breast cancer (including 47 EMs, 28 IMs, and 3 PMs) on tamoxifen	Plasma levels of tamoxifen and metabolites measured at baseline and at 4 mo	6 EMs on paroxetine	Mean plasma concentration of endoxifen substantially lower compared to EMs not on an inhibitor (n = 34)	6 EMs obtained on average the same endoxifen concentration of PMs (average of 3 subjects)
			4 EMs on sertraline	Mean plasma concentration of endoxifen intermediate between that of EMs on paroxetine (n = 6) and subjects on venlafaxine (n = 3)	
			2 EMs + 1 IM on venlafaxine	Very little effect on plasma endoxifen concentration (n = 3)	
Borges et al,[8] 2006	Prospective trial; N = 158 with breast cancer (including 53 EMs and 7 PMs) on tamoxifen	Plasma levels of tamoxifen and metabolites measured at 4 mo	10 EMs on weak inhibitors (including sertraline or citalopram)	Trend toward a decrease in mean plasma endoxifen concentration compared with EMs not on inhibitors ($P = .15$)	
			5 EMs on potent inhibitors (fluoxetine or paroxetine)	Marked reduction in mean plasma endoxifen concentration of (23.5 ± 9.5 nmol/L) compared with EMs not on inhibitors (84.1 ± 39.4 nmol/L; $P < .0001$)	Mean plasma endoxifen concentration of 7 EMs on potent inhibitors comparable to that of 7 PMs (19.4 ± 6.1 nmol)
			6 subjects on venlafaxine (including 3 EMs)	No significant effect on mean plasma endoxifen concentration	
Chubak et al,[23] 2008	Retrospective cohort study; N = 1,306 with breast cancer users and nonusers of tamoxifen	Patients' charts examined for recurrence and death, pharmacy database checked for AD Rx	One-third of cohort used ADs (SSRIs, 18.6%; TCAs, 16.8%)	No association between AD use and the risk of recurrence either in general (HR = 0.8; 95% CI, 0.5–1.4) or for specific types of ADs; Risk of death from breast cancer did not differ between nonusers and users of ADs; ER positive patients on tamoxifen: use of fluoxetine and paroxetine associated with modest increase in risk of recurrence but number of observations too small	
Goetz et al,[24] 2007	Retrospective (chart review); N = 225 patients with breast cancer on tamoxifen	Patients' charts examined for 2D6 genotype, presence of inhibitor, and relapse-free survival	115 subjects Wt/Wt and not on an inhibitor	2-year relapse-free survival rate: 98%	
			32 subjects *4/Wt and not on an inhibitor + 8 subjects Wt/Wt on a weak/moderate inhibitor (including sertraline)	2-year relapse-free survival rate: 92%	
			13 subjects *4/*4 + 1 subject *4/Wt on a moderate/potent inhibitor + 1 subject Wt/Wt on a potent inhibitor (paroxetine or fluoxetine)	2-year relapse-free survival rate: 68%; greater than 3-fold higher risk of recurrence (HR = 3.12, $P = .007$) compared to group of Wt/Wt not on inhibitors	
Lash et al,[25] 2008	Retrospective; N = 184 cases of breast cancer recurrences versus 184 matched controls without recurrence on tamoxifen	Prescription histories taken from the National Health Service	Seventeen cases (9%) and 21 controls (11%) received at least 1 citalopram prescription while on tamoxifen (adjusted conditional odds ratio = 0.85, 95% CI, 0.42–1.7); No reduction of tamoxifen effectiveness among regular citalopram users		

Abbreviations: AD = antidepressant, EM = extensive metabolizer, HR = hazard ratio, IM = intermediate metabolizer, PM = poor metabolizer, Rx = prescription, SSRI = selective serotonin reuptake inhibitor.

effect of any antidepressants on the levels of endoxifen of nonextensive metabolizing patients in 1 study.[21]

Four retrospective clinical studies have investigated the risk of recurrence in relation to the use of antidepressants.[22–25] Goetz et al[24] retrospectively looked at the outcome of 256 postmenopausal women treated with tamoxifen. Extensive metabolizers with no CYP2D6 inhibitor had the best outcomes, followed by "intermediate metabolizers" (as defined by their CYP2D6 phenotype and thus including genotypical EM patients taking CYP2D6 inhibitors), and phenotypical "poor metabolizers" (which included anyone taking a potent CYP2D6 inhibitor) had the worst outcomes. In a recent study, Lash et al[25] suggested that citalopram does not lower the protective effect of tamoxifen on breast cancer recurrence. This study concluded that there was no reduction of tamoxifen effectiveness among regular citalopram users. However, it appears that the CYP2D6 genotype was not taken into consideration. Lehmann et al[22] retrospectively studied the effects of CYP 2D6, 2C9, and 3A inhibitors in 28 cases of breast cancer recurrence and 28 controls. The 2D6 inhibitors included fluoxetine, paroxetine, and sertraline. Lehmann et al[22] found no impact on the clinical outcome of women exposed to CYP isoform inhibitors and tamoxifen. However, the sample size was not sufficient to detect a significant difference if one truly existed. Chubak et al[23] conducted a retrospective cohort study of women with early stage breast cancer to assess the impact of antidepressant use on breast cancer recurrence. A third of these 1,306 women were taking antidepressants (mostly SSRIs [18.6%], especially paroxetine [10.3%]). There was no association found between antidepressant use after breast cancer diagnosis and the risk of recurrence either in general or for specific types of antidepressants. Among ER positive patients taking tamoxifen, the use of fluoxetine and paroxetine was associated with a modest increase in the risk of recurrence, but the number of observations was too small to achieve significance. Again, this study did not have sufficient power to detect small differences in the risk of recurrence.

We can also infer the potential interaction between antidepressants and tamoxifen by reviewing clinical studies[26–46] focusing on other medications that are metabolized by the CYP2D6 enzyme (Table 2). These studies demonstrated that paroxetine, fluoxetine, and bupropion convert approximately half of normal metabolizers to the poor metabolizer phenotype. Little or no effect was observed with venlafaxine, desvenlafaxine, and mirtazapine. Two studies[33,39] did not identify an effect of fluvoxamine, but significant increases in CYP2D6 enzyme substrates were reported with sertraline, citalopram, escitalopram, duloxetine, and moclobemide, indicating a mild to moderate degree of enzyme inhibition.

Nonclinical Studies of CYP2D6 Inhibition by Antidepressants

In the absence of further studies of the direct effects of antidepressants on levels of endoxifen in women taking tamoxifen or patients taking other medications, we may infer the possible pharmacodynamic effects by reviewing laboratory studies of this interaction carried out in vitro.

In vitro studies[31,47–70] of the inhibition of the CYP2D6 enzyme in human liver microsomes have measured the inhibitory constants of various antidepressants (Table 3). The probes used in these studies include psychiatric medications such as imipramine, clomipramine, venlafaxine, desipramine, and clozapine, as well as other medications such as dextromethorphan and metoprolol and other substrates including sparteine, bufuralol, propafenone, and mexiletine. Results are reported as inhibitory constants (K_i), with lower values indicating greater inhibition of the enzyme. Fluoxetine and its metabolites ($K_i = 0.15–4.08$) and paroxetine ($K_i = 0.065–4.85$) were the most potent inhibitors, while venlafaxine ($K_i = 33–41$), mirtazapine ($K_i = 41$), and desvenlafaxine ($K_i > 300$) were the least potent. Sertraline ($K_i = 0.7–27$), fluvoxamine ($K_i = 1.3–16.6$), and citalopram ($K_i = 7–88$) were intermediate in potency. Bupropion was not a strong inhibitor ($K_i = 21$), but its metabolites erythrohydrobupropion ($K_i = 1.7$) and threohydrobupropion ($K_i = 5.4$) were more so. Nefazodone is a mild inhibitor of 2D6 ($K_i = 18–50$). In vitro and in vivo studies have, however, shown that nefazodone is a strong inhibitor of CYP3A4/5,[68] although this property is of unknown significance in relation to tamoxifen metabolism.

DISCUSSION

Many women with breast cancer are prescribed antidepressants for the treatment of common psychiatric disorders, such as major depression or anxiety, or for symptoms of vasomotor instability (hot flashes). However, most antidepressants, such as many of the SSRIs, have CYP2D6 inhibition properties, which affects the metabolism of tamoxifen to its more potent metabolite, endoxifen. Medications that have CYP2D6 inhibitory action can decrease the plasma concentrations of endoxifen in people who would otherwise respond to tamoxifen, "turning" those with genotypes of extensive metabolizers into poor metabolizers.[3,8,21,71] Consequently, CYP2D6 inhibitors may increase their risk of relapse of breast cancer and death.[71]

We reviewed the evidence from clinical and nonclinical studies regarding the effects of antidepressants on the CYP2D6 enzyme. There is consistent evidence from all sources that paroxetine[3,8,21,71] and fluoxetine[3,8,71] have a large effect and should not be used in women taking tamoxifen. Indirect evidence regarding bupropion from in vitro studies (Table 3) and research of the effects on other medications (Table 2) suggest that bupropion is also likely to have a large effect on the metabolism of tamoxifen and should not be used. Clinical[3,8] and nonclinical studies (Tables 2 and 3) report that venlafaxine has little or no effect on the metabolism of tamoxifen and may be considered the safest choice of antidepressants. Clinical studies with

Table 2. In Vivo Measures of Inhibition of CYP2D6 by Antidepressants[a]

Antidepressant	Dose	Test Substrate	Results (subjects converting from EM to PM)	Notes	Reference
Citalopram	40 mg/d × 10 d	Imipramine	NA/8	No significant change in concentration of imipramine; 50% increase in AUC of desipramine	Gram et al,[26] 1993
	10, 20, 40, 80 mg single doses	Sparteine	0/6 (0%)	"Modest increase" in sparteine MR	Jeppesen et al,[27] 1996
	40 mg/d × 22 d	Metoprolol	…	200% increase in the plasma levels of metoprolol	Package insert from Forest,[28] 1998; info from Lundbeck,[29] 2000
Escitalopram	20 mg/d	Desipramine	…	40% increase in Cmax 100% increase in AUC of desipramine	Unpublished, in a 2005 package insert from Forest, reported by Preskorn et al,[30] 2007
	20 mg/d	Metoprolol	…	50% increase in Cmax 82% increase in AUC of metoprolol	Unpublished, in a 2005 package insert from Forest, reported by Preskorn et al,[30] 2007
	10 mg/d × 3 d, 20 mg/d × 14 d	Metoprolol	NA/15	86% increase in AUC of metoprolol	Preskorn et al,[30] 2007
Fluoxetine	…	Dextromethorphan	NA/208	*O*-demethylation ratio of DX in antimode region between EM and PM for 19/208 EMs	Otton et al,[31] 1993
	20 mg/d × 3 wk	Desipramine	NA/18	400% increase in Cmax 480%-fold increase in AUC of desipramine	Preskorn et al,[32] 1994
	10, 20, 40, 80 mg single doses	Sparteine	0/6 (0%)	"More pronounced" increase in sparteine MR compared to citalopram and fluvoxamine	Jeppesen et al,[27] 1996
	60 mg/d × 8 d	Dextromethorphan	5/8 (63%)	Mean DX/DR increased from 0.020 to 0.364	Alfaro et al,[33] 1999
	…	Dextromethorphan	5/12 (42%)	Mean DX/DR increased from 0.017 to 0.313	Alfaro et al,[34] 2000
	20 mg/d × 28 d	Dextromethorphan	Day 7: 1/11 (9%) Day 28: 3/12 (25%)	DX/DR increased by 9.1-fold on day 7, 17.1-fold on day 28	Amchin et al,[35] 2001
	20 mg/d × 28 d	Dextromethorphan	2/14 (14%)	Day 28: 2 subjects had MR of 0.299 and 0.25	Liston et al,[36] 2002
Sertraline	50 mg/d × 3 wk	Desipramine	…	31% increase in Cmax 23% increase in AUC of desipramine	Preskorn et al,[32] 1994
	50–150 mg/d × 21 d	Dextromethorphan	0/6 (0%)	…	Sproule et al,[37] 1997
	50 mg/d × 10 d, 100 mg/d × 3 d	Desipramine	NA/17	44% increase in Cmax 37% increase in AUC of desipramine	Alderman et al,[38] 1997
	100 mg/d × 8 d	Dextromethorphan	0/7 (0%)	No significant difference in mean DX/DR	Alfaro et al,[33] 1999
	…	Dextromethorphan	0/12 (0%)	No significant change in DX/DR urinary ratio	Alfaro et al,[34] 2000
	50 mg/d × 3 d, 100 mg/d × 10 d	Dextromethorphan	0/6 (0%)	…	Liston et al,[36] 2002
	50 mg/d × 3 d, 100 mg/d × 14 d	Metoprolol	NA/16	48% increase in AUC of metoprolol	Preskorn et al,[30] 2007
	50 mg/d × 1 d, 100 mg/d × 16 d	Metoprolol	NA/7	67% increase in AUC of metoprolol	Preskorn et al,[30] 2007
Fluvoxamine	50–100 mg/d × 5–43 d	Dextromethorphan	0/8 (0%)	No significant effect on log *O*-demethylation ratio of DX	Ozdemir et al,[39] 1998
	100 mg/d × 8 d	Dextromethorphan	0/8 (0%)	No significant difference in DX/DR	Alfaro et al,[33] 1999
Paroxetine	40 mg, 80 mg single doses	Sparteine	3/6 (50%)	…	Jeppesen et al,[27] 1996
	20 mg/d × 10 d, 30 mg/d × 3 d	Desipramine	NA/17	358% increase in Cmax 421% increase in AUC of desipramine	Alderman et al,[38] 1997
	20 mg/d × 10 d	Perphenazine	NA/8	200%–13,000% increase in Cmax of perphenazine	Ozdemir et al,[40] 1997
	10–20 mg/d × 5–74 d	Dextromethorphan	0/13 (0%)	Log *O*-demethylation ratio of DX changed from 2.28 to 1.13	Ozdemir et al,[39] 1998
	20 mg/d × 8 d	Dextromethorphan	4/8 (50%)	Mean DX/DR ratio increased from 0.028 to 1.085	Alfaro et al,[33] 1999
	…	Dextromethorphan	10/12 (83%)	Mean DX/DR ratio increased from 0.017 to 0.601	Alfaro et al,[34] 2000
	20 mg/d × 10 d	Dextromethorphan	0/13 (0%)	…	Liston et al,[36] 2002

(continued)

Table 2 (continued). In Vivo Measures of Inhibition of CYP2D6 by Antidepressants[a]

Antidepressant	Dose	Test Substrate	Results (subjects converting from EM to PM)	Notes	Reference
Duloxetine	60 mg bid×21 d	Desipramine	N=16	170% increase in Cmax 290% increase in AUC of desipramine	Skinner et al,[41] 2003
	30 mg/d×1 d, 60 mg/d×16 d	Metoprolol	NA/16	180% increase in AUC of metoprolol	Preskorn et al,[30] 2007
Mirtazapine	30 mg/d until steady state	Paroxetine 40 mg/d	…	Pharmacokinetics of paroxetine not affected	Van Lookeren-Campagne, 1998 (quoted by Timmer et al,[42] 2000)
Venlafaxine	…	Dextromethorphan	0/12 (0%)	No significant change in DX/DR	Alfaro et al,[34] 2000
	37.5 mg bid×7 d, then 75 mg bid×21 d	Dextromethorphan	0/14 (0%)	DX/DR increased by 1.2-fold on day 7, 2.1-fold on day 28	Amchin et al,[35] 2001
Bupropion	…	Dextromethorphan	Close to half of 16 EMs became PMs	…	Kotlyar et al,[43] 2005
Moclobemide	400 mg/d×4–6 wk	Sparteine	2/29 (7%)	Sparteine MR increased by 1- to 103-fold (median: 4.7)	Gram et al,[26] 1993
	300 mg/d×1 d, 600 mg/d×9 d	Sparteine	0/15 (0%)	Median sparteine MR increased by 4.4-fold	Gram et al,[44] 1995
	300 mg bid×9 d	Dextromethorphan	1/3 (33%)	Mean DX/DR increased by 23.5-fold (range 7.0- to 55.7-fold)	Hartter et al,[45] 1998

[a]A strong inhibitor is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.[46]
A moderate inhibitor is one that causes a > 2-fold increase in the plasma AUC values or 50%–80% decrease in clearance.[46]
A weak inhibitor is one that causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20%–50% decrease in clearance.[46]
Abbreviations: AUC = area under the concentration curve, Cmax = maximal concentration, DX = dextromethorphan, DX/DR = metabolic ratios of dextromethorphan/dextrophan (a ratio of ≥ 0.3 defines poor metabolizer status), EM = extensive metabolizer, IM = intermediate metabolizer, MR = metabolic ratio, NA = not available, PM = poor metabolizer.

desipramine demonstrated that desvenlafaxine at twice the recommended therapeutic dose does not inhibit the activity of CYP2D6 in a clinically meaningful way.[72–74] The effect of mirtazapine on tamoxifen has not specifically been studied, but indirect evidence[59] suggests that it is likely to have minimal or no effect on the CYP2D6 enzyme. Citalopram appears to have mild[8,25] and sertraline has moderate effects[3,8,71] on the metabolism of tamoxifen. Although they have not been tested directly with respect to tamoxifen, other research (Tables 2 and 3) indicates that escitalopram has mild and fluvoxamine and duloxetine have moderate inhibitory effects on the CYP2D6 enzyme. These antidepressants may be considered as secondary options in which the risk of not treating depression needs to be weighed against the possibility of some reduction in the metabolism of tamoxifen. At this time, it is difficult to assess the possible clinical consequences of this mild to moderate inhibitory effect of these antidepressants, but 1 retrospective study[25] in women taking tamoxifen reported no association with breast cancer recurrence with the use of citalopram. Nefazodone is a mild inhibitor of 2D6 in vitro and in vivo[68] and a strong inhibitor of 3A4.[68] There is insufficient evidence at this time to advise against using inhibitors of 3A4/5. A clinical trial[75] looking at levels of tamoxifen in the blood of women with breast cancer and in women at high risk of breast cancer who are receiving tamoxifen together with venlafaxine, citalopram, escitalopram, gabapentin, or sertraline is currently underway and may help us gauge the risks associated with these medications when prescribed concomitantly with tamoxifen.

Not all of the commonly prescribed antidepressants have been studied with respect to their possible effect on the metabolism of tamoxifen, and the clinical implications of mild and moderate degrees of inhibition of CYP2D6 enzyme have not been well established. Given that antidepressants are among the most commonly prescribed medications, and women with breast cancer have high rates of depression and are likely to be prescribed antidepressants, clarifying these issues should become research priorities in breast cancer. Clinicians treating patients with breast cancer should review the prescription profiles of their patients to identify those who may need to modify their treatment based on a careful risk assessment (Table 4). Psychotherapy may be considered as an alternative or adjunct to antidepressant medications if clinically indicated.

Other selective estrogen receptor modulators, such as raloxifene, may be considered as alternatives to tamoxifen. Raloxifene is metabolized by glucuronide conjugation and not by the P450 enzymes.[76,77] Raloxifene has been approved in the United States for breast cancer prevention in postmenopausal women at increased risk of invasive breast cancer and in postmenopausal women with osteoporosis.[78] Hence, interactions between raloxifene and commonly used antidepressants may be less problematic. Moreover,

Table 3. In Vitro Inhibitory Constants of Antidepressants for CYP2D6

Antidepressant/Metabolites	K_i μmol (or IC_{50})	Mean	Median	Reference
Citalopram	7–88	27.33	15	Otton et al,[31] 1993; Crewe et al,[47] 1992; Yu et al,[48] 2003; Skjelbo and Brosen,[49] 1992; Belpaire et al,[50] 1998
	(IC_{50} > 100)			Hemeryck et al,[51] 2000
Desmethylcitalopram	1.3–31	12.33	8.5	Skjelbo and Brosen,[49] 1992; Otton et al,[31] 1993; Belpaire et al,[50] 1998;
Escitalopram	(IC_{50} = 70–80)			von Moltke et al,[52] 2001
Fluoxetine	0.15–4.08	1.05	0.6	Otton et al,[53] 1994; Otton et al,[31] 1993; Nielsen et al,[54] 1996; Hemeryck et al,[51] 2000; Fogelman et al,[55] 1999; Yu et al,[48] 2003; Crewe et al,[47] 1992; Hara et al,[56] 2005; Belpaire et al,[50] 1998; Skjelbo and Brosen,[49] 1992; Ball et al,[57] 1997; von Moltke et al,[58] 1994; Verhoeven et al,[59] 1996; Delbressine and Vos,[60] 1997
	(IC_{50} = 0.72)			Hemeryck et al,[51] 2000
R-fluoxetine	1.38			Stevens and Wrighton,[61] 1993
S-fluoxetine	0.22			Stevens and Wrighton,[61] 1993
Norfluoxetine	0.19–3.5	0.90	0.55	Otton et al,[31] 1993; Skjelbo and Brosen,[49] 1992; Nielsen et al,[54] 1996; Fogelman et al,[55] 1999; Crewe et al,[47] 1992; Hemeryck et al,[51] 2000; Belpaire et al,[50] 1998; Yu et al,[48] 2003; von Moltke et al,[58] 1994
	(IC_{50} = 1.5)			Hemeryck et al,[51] 2000
R-norfluoxetine	1.48			Stevens and Wrighton,[61] 1993
S-norfluoxetine	0.31			Stevens and Wrighton,[61] 1993
Fluvoxamine	1.3–16.6	7.59	5.85	Nielsen et al,[54] 1996; Fogelman et al,[55] 1999; Otton et al,[31] 1993; Skjelbo and Brosen,[49] 1992; Olesen and Linnet,[62] 2000; Ball et al,[57] 1997; Crewe et al,[47] 1992; Yu et al,[48] 2003; Belpaire et al,[50] 1998; von Moltke et al,[63] 1995
	(IC_{50} = 10.7)			Hemeryck et al,[51] 2000
Paroxetine	0.065–4.85	1.58	0.54	Otton et al,[53] 1994; Crewe et al,[47] 1992; Fogelman et al,[55] 1999; Skjelbo and Brosen,[49] 1992; Belpaire et al,[50] 1998; Hemeryck et al,[51] 2000; Nielsen et al,[54] 1996; Hara et al,[56] 2005; von Moltke et al,[63] 1995; Ball et al,[57] 1997, Bertelsen et al,[64] 2003
	(IC_{50} = 1.0)			Hemeryck et al,[51] 2000
Sertraline	0.7–27	14.93	16	Crewe et al,[47] 1992; Fogelman et al,[55] 1999; Otton et al,[53] 1994; Otton et al,[31] 1993; Hara et al,[56] 2005; Nielsen et al,[54] 1996; Belpaire et al,[50] 1998; von Moltke et al,[58] 1994; Skjelbo and Brosen,[49] 1992; Ball et al,[57] 1997
	(IC_{50} = 9.3)			Hemeryck et al,[51] 2000
Desmethylsertraline	4.32–24	15.66	16	Fogelman et al,[55] 1999; von Moltke et al,[58] 1994; Skjelbo and Brosen,[49] 1992; Belpaire et al,[50] 1998
	(IC_{50} = 10.8)			Hemeryck et al,[51] 2000
Mirtazapine	41	41	41	Verhoeven et al,[59] 1996; Delbressine and Vos,[60] 1997
	not substantial			Stormer et al,[65] 2000
Venlafaxine	33–41	37	37	Otton et al,[66] 1996; Ball et al,[57] 1997
R-venlafaxine	52			Otton et al,[66] 1996
S-venlafaxine	22			Otton et al,[66] 1996
Bupropion	21			Reese et al,[67] 2008
Erythrohydrobupropion	1.7			Reese et al,[67] 2008
Threohydrobupropion	5.4			Reese et al,[67] 2008
Nefazodone	18–50			Schmider et al,[68] 1996
Moclobemide	140			Skjelbo and Brosen,[49] 1992
	minor inhibition			Polasek et al,[69] 2006
Amitriptyline	4			Crewe et al,[47] 1992
Clomipramine	2.2–16	9.1	9.1	Crewe et al,[47] 1992; Skjelbo and Brosen,[49] 1992
Desipramine	2.3–3.2	2.75	2.75	Crewe et al,[47] 1992; Hara et al,[56] 2005
Phenelzine	mechanism-based inhibition			Polasek et al,[69] 2006
Tranylcypromine	367			Salsali et al,[70] 2004

Table 4. Proposed Risk of Decreased Metabolism of Tamoxifen by Antidepressants Inhibiting the CYP2D6 Enzyme

Antidepressant	Degree of Decreased Tamoxifen Metabolism	Recommendations
Venlafaxine	Minimal	Use preferentially
Desvenlafaxine	Minimal, direct studies with tamoxifen lacking	Consider use based on risk-benefit assessment
Mirtazapine	Minimal, direct studies with tamoxifen lacking	
Citalopram	Mild	
Escitalopram	Mild, direct studies with tamoxifen lacking	
Sertraline	Moderate	
Fluvoxamine	Moderate, direct studies with tamoxifen lacking, moderate 3A4 inhibitor	
Duloxetine	Moderate, direct studies with tamoxifen lacking	
Nefazodone	Mild 2D6, direct studies with tamoxifen lacking, strong 3A4 inhibitor	
Paroxetine, fluoxetine, bupropion	Severe	Avoid use

third-generation aromatase inhibitors can be substituted to selective estrogen receptor modulators in postmenopausal women with breast cancer. Anastrozole and letrozole are approved for the first-line treatment of hormone-sensitive advanced breast cancer in postmenopausal women. Anastrozole, letrozole, and exemestane are all indicated for the second-line treatment of advanced breast cancer in postmenopausal women.[79] The main target of aromatase inhibitors is CYP19. The aromatase inhibitors are not metabolized by CYP2D6 and do not appear to inhibit it,[80] thus limiting the potential for drug interactions with current antidepressants.

This review indicates the need to consider the possible pharmacokinetic interactions between antidepressants and tamoxifen. However, clinicians and patients may be reassured that there are safe options for the treatment of depression and should bear in mind the health risks of untreated depressive states.

Drug names: amitriptyline (Limbitrol and others), anastrozole (Arimidex), bupropion (Aplenzin, Wellbutrin, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), clozapine (FazaClo, Clozaril, and others), desipramine (Norpramin and others), desvenlafaxine (Pristiq), dextromethorphan (Bromfed, Prometh, and others), duloxetine (Cymbalta), escitalopram (Lexapro), exemestane (Aromasin), fluoxetine (Prozac, Sarafem, and others), fluvoxamine (Luvox and others), gabapentin (Neurontin and others), imipramine (Tofranil, Surmontil, and others), letrozole (Femara and others), metoprolol (Lopressor, Toprol, and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), propafenone (Rythmol and others), raloxifene (Evista), sertraline (Zoloft and others), tranylcypromine (Parnate and others), venlafaxine (Effexor and others).

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