Tamoxifen-Paroxetine

Tamoxifen is a prodrug that is metabolized in the liver by the cytochrome P-450 (CYP) system to a primary active metabolite 4-hydroxy-N-desmethyltamoxifen, which is termed endoxifen. Polymorphisms in the CYP2D6 gene lead to variations in the circulating concentrations of endoxifen. More than 80 different major alleles of the CYP2D6 gene have been identified, many of which confer diminished or absent CYP2D6 activity. Most individuals have 2 alleles, so the combined activity level of the alleles determines the metabolic rate of CYP2D6. Phenotypic subpopulations are categorized as persons with poor (PM), intermediate (IM), extensive (EM), or ultrarapid (UR) ability to metabolize drugs by CYP2D6. Poor metabolizers have 2 nonfunctional alleles. Intermediate metabolizers have 2 alleles with decreased function or 1 allele with decreased function and 1 nonfunctional allele. Extensive metabolizers, have standard or usual CYP2D6 metabolism. Ultrarapid metabolizers have active gene duplication of a functional allele. Some variants are more common in certain populations. Table 1 lists the common CYP2D6 variants and the frequency of phenotypes among African Americans, Asians, and Caucasians. While genotyping is not typically conducted prior to prescribing tamoxifen, there is likely reduced or no benefit to taking tamoxifen for patients who are poor or intermediate metabolizers. Likewise, concurrent administration of medications known to inhibit CYP2D6 should be avoided as well.

Table 1: Common CYP2D6 Variants, Phenotypes, and Frequency[42]

Metabolizer Phenotype	Common CYP2D6 Variant Alleles	Frequency of Phenotype		
		African Americans	Asians	Caucasians
Ultrarapid	*1, *2, gene duplication *35 enhanced activity	<1%	<1%	2%-10%
Extensive	*1	37%	52%	71%
Intermediate	*9, *10, *17, *29, *41	30%	30%	11%
Poor	*3, *4, *5, *6	7%	1%-2%	7%

Prospective randomized clinical trials have demonstrated the efficacy of SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) in decreasing vasomotor symptoms among healthy peri- or postmenopausal women, and women with breast cancer on or off endocrine therapy. Antidepressants have variable effects on CYP2D6 activity: 1) strong inhibitors: fluoxetine, paroxetine, and bupropion; 2) moderate inhibitor: duloxetine; and 3) weak or non-inhibitors: citalopram, escitalopram, fluvoxamine, sertraline, venlafaxine, desvenlafaxine, milnacipran, mirtazapine, reboxetine, vilazodone. Paroxetine is a potent CYP2D6 inhibitor that can significantly decrease endoxifen levels especially among extensive metabolizers. An observational study of women treated with tamoxifen showed low endoxifen concentrations among those receiving strong inhibitors of CYP2D6 (e.g., fluoxetine, paroxetine) and intermediate endoxifen concentrations among those receiving weak inhibitors CYP2D6 (e.g., sertraline, citalopram).

Type of Anti-depressant	Weak or non-inhibitors: sertraline, citalopram, escitalopram, venlafaxine, fluvoxamine, desvenlafaxine, milnacipran, mirtazapine, reboxetine, vilazodone	Moderate inhibitors: Duloxetine	Strong Inhibitors: Paroxetine,[5,6] fluoxetine,[5] bupropion[3]	
Tamoxifen treatment	○[1]	■[1]		◆[2]

○ = No special precautions. ■ = Assess risk and take precautions as necessary. □ ◆ = Take measures to reduce risk.

Changes in Area Under the Curve with Antidepressants

Medication	Substrate Medication	Percent increase in AUC	Source
Citalopram	Metoprolol	200%	Desmarais and Looper, J Clin Psychiatry 2009; 70(12):1688-97 (citing product labeling by Forest and Lundbeck)
Desvenlafaxine	Desimpramine	36%	Nichols et al. J Clin Pharmacol 2009; 49:219-228
Duloxetine	Metoprolol	180%	Preskorn et al. J Clin Psychopharmacol 2007;27:28-34
Duloxetine	Desimpramine	290%	Skinner et al. Clin Pharmacol Thera 2003; 73:170-177
Escitalopram	Metoprolol	89%	Preskorn et al. J Clin Psychopharmacol 2007;27:28-34
Escitalopram	Desipramine	100%	Lexapro product label: (https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4a08b6cf-7ba0-54a9-14e0-a6e8d1e4854e
Fluoxetine	Desipramine	480%	Preskorn et al. J Clin Psychopharmacol 1994; 14:90-98
Sertraline	Desipramine	23%	Preskorn et al. J Clin Psychopharmacol 1994; 14:90-98
Sertraline	Metoprolol	48%	Preskorn et al. J Clin Psychopharmacol 2007;27:28-34 (Study 1)
Sertraline	Metoprolol	67%	Preskorn et al. J Clin Psychopharmacol 2007;27:28-34 (Study 2)
Paroxetine	Desipramine	421%	Alderman et al. J Clin Psychopharmacol 1997; 17:284-291
Venlafaxine	Metoprolol	30-40%	Spina et al. CNS Drugs 2012; 26:39-67 (citing package insert but could not find in package insert)

Footnotes:

1. An analysis of 2430 women receiving tamoxifen and a single SSRI found no significant increase in the recurrence of breast cancer for patients taking fluoxetine (OR 0.97, 95% CI: 0.86-1.10), sertraline (OR 1.02, 95% CI: 0.93-1.18), fluvoxamine (OR 1.05, 95% CI: 0.93-1.18), citalopram (OR 0.98, 95% CI: 0.86-1.12), or venlafaxine (OR 0.96, 95% CI: 0.80-1.15) 25% of the time concurrently. If the proportion of concurrent use increases, no significant differences are observed. Source: Kelly et al. BMJ 2010:340:c693.
2. The same study mentioned in footnote 1 found the odds of recurrence with paroxetine to be 1.12 (95% CI: 1.02-1.23). Higher risk with was observed with greater concurrent use of tamoxifen and paroxetine. It is recommended that paroxetine be avoided in women receiving tamoxifen. While the evidence to date suggests no significant increase in risk with fluoxetine, it is advisable to use another SSRI/SNRI to avoid the interaction. Source: Kelly et al. BMJ 2010:340:c693. However, another large cohort study conducted in Southern California studying 8099 women taking paroxetine found no significant risk in recurrent of breast cancer. Odds ratios for 25% concurrent use were 1.06 (95% CI: 0.98 to 1.14) for paroxetine. Source: Haque et al. J. Natl Cancer Inst 2015:108(3):djv337.
3. Bupropion is a moderate inhibitor in vitro studies, but clinical doses produces substantial inhibition because plasma doses are high. (see Spina et al. CNS Drugs 2012:26:39-67.
4. Lehmann et al. used a case-control study to evaluate long-term cancer recurrence in tamoxifen users (cases). Controls were patients without cancer recurrence. Antecedents of interest was chronic exposure to a CYP inhibitor. No significant differences exposure to inhibitors was observed between cases and controls.
5. Alfaro et al. studied CYPD26 inhibition in extensive metabolizers for treatment with fluoxetine, paroxetine, sertraline, and venlafaxine in cross-over study. The outcome was ratio of dextromethorphan/dextrophan (DM/DX). Significant changes were observed with fluoxetine (0.313) and paroxetine (0.601) but not with sertraline (0.026) and venlafaxine (0.023). Alfaro et al. J Clin Psychopharmacol 2000;40:58-66.

6. In vitro studies with paroxetine inhibition of tamoxifen have shown that plasma levels of 4-hydroxy-tamoxifen to change from 12.4 ng/ml prior to paroxetine administration to 1.1 ng/ml after paroxetine administration. Stearns et al. J Natl Cancer Inst 2003:95:1758-64.
7. A study examining CYP2D6 status among patients taking tamoxifen found that exposure to a 2D6 inhibitor (paroxetine, fluoxetine, sertraline, citalopram, amiodarone, metaclopromide) found a 58% lower concentration of endoxifen than those not using an inhibitor. Desta et al. J Natl Cancer Inst 2005;97:30-9.