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Invited Editorial

Do antidepressants reduce the effectiveness of tamoxifen?†

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Because of the relatively significant incidence of both clinical depression and debilitating hot flashes (20%–30%), clinicians caring for women with breast cancer who are taking tamoxifen for the treatment or prevention of cancer recurrence are often faced with the need to prescribe antidepressant medications concurrently with tamoxifen. Over the past 5 years, a growing number of studies have raised questions regarding the interaction of antidepressants and tamoxifen, particularly the following question: 'Do antidepressants reduce the effectiveness of tamoxifen treatment?' At issue is the extent of the clinical impact of cytochrome P450 2D6 (CYP2D6) inhibitors, in the form of several antidepressants (particularly several of the serotonin reuptake inhibitors, or SSRIs) on the effectiveness of tamoxifen.

Tamoxifen and breast cancer

Tamoxifen is a selective estrogen receptor modulator (SERM) used as adjuvant therapy for early-stage, estrogen receptor–positive (ER+) breast cancer in premenopausal women. Other uses for tamoxifen include treatment of metastatic ER+ breast cancer in pre- and postmenopausal women, as well as chemoprevention in women at risk for breast cancer [1,2].

The Early Breast Cancer Trialists' Collaborative Group [3] demonstrated that early-stage breast cancer patients with ER+ disease given tamoxifen for 5 years had a significant reduction in recurrence (almost 47% proportional reduction) and in new breast cancers in the opposite breast (also 47% proportional reduction). The investigators observed fewer deaths in tamoxifen recipients than in women who did not receive the drug (26% proportional reduction). The survival advantage for women treated with tamoxifen continues to increase up to at least 10 years. In a large chemoprevention trial [4] involving 13,175 women who were determined to be at high risk for breast cancer, tamoxifen significantly reduced the incidence of invasive and noninvasive breast cancer, especially ER+ tumors in both pre- and postmenopausal women.

A woman with depression on tamoxifen therapy

S.M. is a 41-year-old divorced premenopausal woman who was diagnosed with estrogen receptor–positive, invasive ductal carcinoma, treated with surgery, adjuvant chemotherapy, and radiotherapy. Tamoxifen therapy was begun to reduce chances of breast cancer recurrence. S.M. tolerated tamoxifen therapy poorly, primarily complaining of severe depressive symptoms. These depressive symptoms were so severe that she contemplated discontinuation of tamoxifen therapy after 3 months.

The patient had a history of recurrent depressive episodes. The first occurred 12 years earlier during the postpartum period after the birth of her daughter, and the second occurred after a bitter divorce and custody battle 2 years ago. Both prior episodes of depression had been successfully treated with antidepressant therapy. The first episode resolved with fluoxetine at 20 mg/d, which she continued to take for 18 months. The second episode was successfully treated with sustained-release bupropion at 300 mg/d. Prior to the bupropion, trials of mirtazapine and venlafaxine were stopped because of side effects (increased anxiety/agitation and unacceptable weight gain, respectively).

S.M. had stopped taking bupropion approximately 6 months prior to her cancer diagnosis. Upon psychiatric examination, she met criteria for a major depressive syndrome and was thought to be having a recurrent episode of her depressive illness. A mood disorder—depression, secondary to tamoxifen therapy—was also considered. She had clearly responded to fluoxetine and bupropion in the past. However, both of these antidepressants are potent CYP2D6 inhibitors and posed a significant risk of interfering with the efficacy of tamoxifen therapy. Good CYP2D6 noninhibitor alternative antidepressants (venlafaxine and

mirtazapine) had been tried in this patient in the past but were not well tolerated.

The patient was started on escitalopram, a selective serotonin reuptake inhibitor similar in antidepressant action to fluoxetine, which has very mild CYP2D6 inhibitory action. The patient's depression remitted in 3 weeks with an escitalopram dosage of 20 mg/d.

Tamoxifen and metabolism

Clinical benefit in this setting requires conversion of the prodrug tamoxifen into its active metabolites—4-hydroxytamoxifen and endoxifen (4-hydroxy-N-desmethyltamoxifen)—by cytochrome P450 enzymes, the most clinically relevant of which is CYP2D6. These active metabolites bind to the estrogen receptor 100-fold more readily than tamoxifen [5], and the higher affinity for the receptor correlates with cell growth inhibition [6]. Decreased CYP2D6 activity, and therefore decreased conversion of tamoxifen to its active metabolites, may be related to allelic (genetic) phenotype variation, or exogenous competitive inhibition of CYP2D6 by medications (eg, antidepressants).

Allelic phenotype variation can be seen in 5% to 20% of the population. More that 80 different alleles of CYP2D6 have been identified, and many are associated with decreased CYP2D6 activity. These individuals would thus be poorer metabolizers of tamoxifen, and studies have shown that such genetically poor metabolizers have significantly lower serum levels of tamoxifen than good genetic metabolizers [7]. Several subsequent studies examining outcomes in tamoxifen trials for poor genetic metabolizers have been mixed, with some showing increased risk of recurrence and shorter relapse-free survival and others showing no effect or opposite effects [8,9]. Clearly, the question as to whether exogenously coadministered CYP2D6 inhibitors, such as antidepressant medications, significantly impact the clinical efficacy of tamoxifen is complicated by the fact that the population of women receiving tamoxifen are quite genetically diverse in their innate capacity to metabolize tamoxifen.

Many antidepressants are inhibitors of the CYP2D6 enzyme system, and thus have the potential to interfere with the metabolism of tamoxifen to its active metabolites (particularly endoxifen). Table 1 lists the antidepressants that are 'strong,' 'moderate,' or 'weak' inhibitors of CYP2D6, or 'noninhibitors.' A growing amount of literature has demonstrated that strong CYP2D6 inhibitor antidepressants not only reduce the serum levels of tamoxifen's active metabolite endoxifen, but may also significantly interfere with the clinical efficacy of tamoxifen. Multiple studies have demonstrated low levels of serum endoxifen in women on tamoxifen who take strong 2D6 inhibitor antidepressants such as paroxetine and fluoxetine, and intermediate levels of serum endoxifen with mild 2D6 inhibitors such as sertraline and citalopram [10–12]. The mean plasma concentration of endoxifen was more than twofold higher in women not taking a CYP2D6 inhibitor drug than in women taking a CYP2D6 inhibitor drug [7]. Thus, the question becomes whether such reductions in endoxifen caused by antidepressants that inhibit CYP2D6 translate into poorer outcomes for women with breast cancer being treated with tamoxifen.

Table 1. Antidepressants classified by potency of CYP2D6 inhibition

Strong CYP2D6 Inhibitors
Fluoxetine
Paroxetine
Sertraline
Bupropion
Moderate CYP2D6 Inhibitors
Duloxetine
Mild CYP2D6 Inhibitors
Citalopram
Escitalopram
Noninhibitors of CYP2D6
Venlafaxine
Desvenlafaxine
Mirtazapine

Tamoxifen and antidepressants

In a 2009 review of the literature on interactions between tamoxifen and antidepressants via CYP2D6 [13], the authors found consistent evidence that paroxetine and fluoxetine have large effects on the metabolism of tamoxifen and recommended that these drugs should not be used in conjunction with tamoxifen treatment in breast cancer. Indirect evidence suggests that bupropion also has considerable effects on the metabolism of tamoxifen because it is a potent CYP2D6 inhibitor. Safer choices, according to the authors, given a lack of CYP2D6 inhibition, include venlafaxine (Effexor), desvenlafaxine (Pristiq), and mirtazapine. The question remains as to whether these inhibitory effects on tamoxifen metabolism translate into poorer clinical outcomes.

Several small and large clinical trials over the past few years have examined the issue of antidepressant drug treatment effects on the efficacy of tamoxifen, in terms of risk of breast cancer recurrence and survival. The results have been primarily mixed, but the majority of studies tended to not support a negative impact of CYP2D6 inhibitor use—particularly for SSRIs with mild CYP2D6 inhibition—on breast cancer recurrence and mortality in women using tamoxifen [14–18].

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A 2008 retrospective study ($N = 368$) using data from the Danish Breast Cancer Cooperative Group [15] suggested that premenopausal and postmenopausal women with ER+ tumors who used citalopram while on tamoxifen did not have a higher rate of recurrence than women who never used citalopram while on tamoxifen. In this study, citalopram exposure was defined as the use of citalopram or its S-stereoisomer escitalopram. The data also supported the conclusion that citalopram does not directly affect risk of breast cancer recurrence in estrogen receptor–negative (ER–) and tamoxifen-naive or ER+ and tamoxifen-treated breast cancer patients.

In 2010, Lash and colleagues [16] conducted a population-based, case-controlled study in Denmark and found no increased risk of breast cancer recurrence in women on tamoxifen and concomitant citalopram or escitalopram. A recently published Dutch study, presented at the 2009 ASCO Annual Meeting [18], found no association between the CYP2D6 inhibitors paroxetine and fluoxetine and breast cancer recurrence in patients on tamoxifen. This study was based on a small sample of only 18 cancer patients and suffers from the same small sample size and power issues common to several other negative trials noted above [14,17].

By contrast, several studies have reported a higher rate of breast cancer recurrence and mortality among women receiving SSRIs, which are potent CYP2D6 inhibitors. In a 2010 Canadian population-based cohort study of 2,430 women treated with tamoxifen [19], paroxetine use was associated with increased breast cancer mortality, which increased further with more prolonged concurrent use. A U.S. population study by Aubert and colleagues [20] presented at the 2009 ASCO Annual Meeting found an increased risk of breast cancer recurrence among women concurrently taking tamoxifen and the more potent CYP2D6 inhibitor SSRIs paroxetine, fluoxetine, and sertraline. No such increase in breast cancer recurrence was found for SSRIs that are less potent inhibitors of CYP2D6, including citalopram, escitalopram, and fluvoxamine.

Although not specifically examined in many of these studies, it is important to note that several non-SSRI antidepressants, such as bupropion, are known to be strong CYP2D6 inhibitors, and antidepressants such as venlafaxine, desvenlafaxine, and mirtazapine are in fact noninhibitors of the CYP2D6 enzyme system [21]. Theoretically, noninhibitors of CYP2D6 may be safer, or at least as safe as the milder inhibitors (citalopram and escitalopram), whereas strong CYP2D6 inhibitors such as bupropion may, in fact, pose a safety problem. Interestingly, although investigators have observed a benefit with venlafaxine in the treatment of hot flashes, bupropion has not been shown to be helpful in this setting [22,23].

Summary and recommendations

A growing and evolving literature has legitimately raised concerns about the potential for antidepressant medications, particularly those that are potent CYP2D6 inhibitors, to decrease the clinical efficacy of tamoxifen when used concurrently in women with breast cancer. It has been established that tamoxifen (a prodrug) must be metabolized by the CYP2D6 enzyme system in order to be converted into its active metabolites (eg, endoxifen). Furthermore, the use of antidepressants that are potent CYP2D6 inhibitors has been demonstrated to result in lower serum levels of endoxifen. The question that remains is whether lower levels of endoxifen in women with breast cancer taking tamoxifen and antidepressants (specifically those that are potent CYP2D6 inhibitors) concurrently results in increased risk of breast cancer recurrence or increased mortality.

> An emerging consensus suggests that antidepressants that are potent inhibitors of CYP2D6 used concurrently with tamoxifen may reduce the clinical efficacy of tamoxifen.

Studies to date have reported mixed findings, but there appears to be an emerging consensus that antidepressants that are potent inhibitors of CYP2D6 (ie, fluoxetine, paroxetine, and sertraline) used concurrently with tamoxifen therapy for women with breast cancer may reduce the clinical efficacy of tamoxifen. Furthermore, evidence suggests that antidepressants that are either milder inhibitors of CYP2D6 (citalopram, escitalopram, duloxetine) or noninhibitors (venlafaxine, mirtazapine) are in fact safer choices, with less potential to decrease the clinical efficacy of tamoxifen.

In clinical practice (see case example), it is therefore reasonable to avoid potent 2D6 inhibitor antidepressants (paroxetine, fluoxetine, sertraline) for the treatment of depression or hot flashes while a woman is receiving tamoxifen therapy for breast cancer. Clinicians are advised to preferentially use antidepressants with lower CYP2D6 inhibition properties (citalopram, escitalopram, duloxetine) or CYP2D6 noninhibitor antidepressants (venlafaxine, mirtazapine). If patients are already on a potent CYP2D6 inhibitor and are unable to be crosstapered or unable to tolerate non–2D6 inhibitor options, the breast cancer treatment team, including the oncologist, surgeon, and psychiatrist, can collaboratively work to optimize a safe plan, which may include one of these drugs perhaps for a limited period of time.

One interesting question that remains concerns the utility of conducting CYP2D6 genotyping in premenopausal ER+ women with breast cancer before initiating tamoxifen therapy. Given the potential for diminished metabolism of tamoxifen

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to endoxifen as a result of both endogenous (genotypicvariability) and exogenous factors (medications), such testing could prove to be a practical approach.

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