

## REVIEW ARTICLE

## Use of Antidepressants in Patients with Breast Cancer Taking Tamoxifen

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Tamoxifen, a selective estrogen modulator has been used for more than three decades to treat all stages of estrogen receptor (ER)-positive breast cancer and to prevent the disease. Tamoxifen is a pro-drug that requires metabolic activation to 4-hydroxytamoxifen and 4-hydroxy-N-desmethyltamoxifen (endoxifen) to elicit its pharmacological activity. Endoxifen has identical properties and potency with 4-hydroxytamoxifen, but is present in concentrations up to 10-fold higher than 4-hydroxytamoxifen. The cytochrome P450 2D6 (CYP2D6) enzyme plays a key role in converting tamoxifen into its active metabolites with significantly greater affinity for the ER and greater ability to inhibit cell proliferation. Genetic variants in the CYP2D6 gene may result in CYP2D6 enzymes with reduced or null activity, thereby decreasing the anti-cancer effect. In addition to genetic inactivation of CYP2D6, inhibitors of CYP2D6, including some antidepres-

sants to treat hot flashes or depression in patients with breast cancer, may also alter enzyme activity and negatively affect the outcomes of patients receiving adjuvant tamoxifen. This article reviews and discusses the following issues: tamoxifen metabolism, antiproliferative effects of tamoxifen and its metabolites, CYP2D6 genetic polymorphisms, treatment for hot flashes and depression in breast cancer, and the pharmacological interactions between tamoxifen and antidepressants via CYP2D6. Although routine CYP2D6 testing is not recommended yet, coadministration of potent or intermediate CYP2D6 inhibitors in women taking tamoxifen should be avoided.

**Key Words:** Antidepressants, Breast neoplasms, Cytochrome P450 2D6, Tamoxifen

## INTRODUCTION

Breast cancer is the most common malignancy in women, and more than 1.5 million women are expected to be newly diagnosed with the disease. (1) The occurrence of the disease in Korean women is rapidly increasing due to a westernized lifestyle and early diagnosis. (2)

The majority of the patients with breast cancer have tumors that express the estrogen receptor (ER) and/or progesterone receptor (PR) on the cell surfaces. Also, endocrine therapy, which reduces the estrogen level is

effective for patients with hormone receptor-positive tumors. The standard endocrine treatment for premenopausal women with ER-positive breast cancer is tamoxifen for 5 yr. In contrast, both tamoxifen and aromatase inhibitors (AIs) are acceptable treatment options for postmenopausal women. (3) But the use of AIs has been prohibited in premenopausal patients with breast cancer, as it can activate ovarian functions and cause polycystic ovarian diseases. (4,5) Therefore, tamoxifen administration is generally recommended as the principal treatment for premenopausal hormone receptor-positive patients with breast cancer or for patients in which AI use is inappropriate.

Tamoxifen was approved by the US Food and Drug Administration (FDA) in 1977 for use as an adjuvant in the treatment of postmenopausal women with ER-positive breast cancer or ductal carcinoma *in situ* and is currently

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used in all stages of breast cancer.(6–8) As tamoxifen has been widely used for the last 30 yr, it contributed to reduce 50% of breast cancer recurrence and to decrease the annual breast cancer death rate by one third. The clinical effects of tamoxifen with respect to efficacy and toxicity vary widely among individuals. For example, 30–40% of patients with ER-positive advanced breast cancer do not respond to tamoxifen, and all tumors that do respond eventually become resistant to tamoxifen treatment.(9) Genetic variability in the enzymes related to tamoxifen metabolism is responsible for the failure of some breast cancer treatment.

In Western countries, most patients with breast cancer are diagnosed after menopause, whereas 60% of the patients are premenopausal women, and the mean age of onset is 47.1 yr in Korea. The peak prevalence occurs in the 50's, and the incidence progressively decreases after menopause. Such a trend has been maintained despite the increasing occurrence of breast cancer and a westernized lifestyle.(10) Depression is the most common psychiatric problems in patients with cancer. Its occurrence risk becomes higher when the onset age of breast cancer is low, so younger patients suffer more from psychiatric distress causing negative effects on their quality of life.(11) Because relatively younger populations are diagnosed with breast cancer compared to Western countries, the prevalence of depression is high. The symptoms of depression in patients with breast cancer not only have negative effects on the patient's adaptation and quality of life, but also lower survival rate. Once the symptoms of depression and anxiety are severe, the patients' quality of life may be lowered, resulting in negative effects on the progression and outcome of the disease.(12–14) Therefore, treatment of depression is an important issue in patients with breast cancer. But, as the treatment responses to antidepressants differ by gender and menopausal state,(15) different responses should be expected when treating female patients with breast cancer than general patients with depression, and a drug interaction must be considered if patients undergo chemotherapy or antiestrogen therapy.

Although antidepressants are mainly used to relieve

depression in patients with cancer, they are also commonly prescribed as adjuvant therapy to treat neuropathic pain and to relieve menopausal vasomotor symptoms such as hot flashes. The antiestrogen treatment can induce or aggravate depression or anxiety, and commonly causes hot flashes, indicating that a discussion between the physicians treating breast cancer and the psychiatrist may be required. Additionally the use of antidepressants may act negatively on tamoxifen, from a pharmacokinetic aspect, and influences the recurrence and survival rate of patients with breast cancer.

The present study aimed to review the use and effect of antidepressants in patients with breast cancer, tamoxifen metabolism, the effect of the cytochrome P450(CYP)2D6 polymorphism on tamoxifen function, and potential drug interactions between tamoxifen and antidepressants.

## USE OF ANTIDEPRESSANTS IN PATIENTS WITH BREAST CANCER

### Treatment of depression

Many women experience distress following a diagnosis of breast cancer, and some patients experience clinically significant depression.(16) The prevalence of depression in patients with breast cancer is estimated to be in the range of 10–20%, depending on the method of assessment. Rates appear higher in the first yr following diagnosis, especially in young women or in those treated with chemotherapy.(17)

Antidepressants are the most frequently prescribed medications in the world, and one-third of patients visiting medical offices in the United States are taking an antidepressant. Among the patients with breast cancer taking tamoxifen, 20–30% are also taking antidepressants.(18) Currently, various classes of antidepressants are prescribed for the treatment of depression. Newer antidepressants, including selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), are the most commonly prescribed. Although, tricyclic antidepressants (TCAs) have been used effectively to treat neuropathic pain in patients with cancer, their use for treating depression as a primary strategy has been

largely limited. TCAs have a low therapeutic index, take longer to elucidate the clinical effects compared to the newer antidepressants, and an overdose is can be highly fatal. The use of monoamine oxidase inhibitors extremely difficult in patients with cancer, as they can cause a hypertensive crisis by taking sympathetic medications concurrently or by eating foods containing tyramine. Furthermore, coadministration with meperidine can cause hypertension, high fever, convulsions, and even death. Therefore, the newer antidepressants such as the SSRIs or SNRIs are currently used as the first choice medication in the treatment of depression or for menopausal symptoms in patients with cancer.

So far, few clinical studies have been conducted on the treatment of depression in patients with breast cancer. Four double-blinded randomized controlled studies were conducted only for patients with breast cancer; three paroxetine studies and one mianserin study. Pezzella et al. (19) compared the effects and tolerability of paroxetine (20–40 mg/day) and amitriptyline (75–150 mg) in 179 patients with breast cancer and depression. After 8 weeks of treatment, the depressive symptoms improved in 43.7% of the paroxetine group and 37.9% of the amitriptyline group. Although both medications were effective for treating depression, the anticholinergic side effects occurred at rates of 11.4% in the paroxetine group and 19.1% in the amitriptyline group. In the other double-blinded study, the administration of paroxetine to 94 patients with breast cancer receiving chemotherapy was effective in improving depression symptoms compared to the placebo. (20) But, in a double-blind, placebo-controlled study comparing paroxetine (n=13), desipramine (n=11), or placebo (n=11) for 6 weeks, no significant treatment effect was found among the three groups. (21) The small number of women in this study most likely contributed to the lack of a statistical significance observed during the 6 weeks of treatment. In a study evaluating the effect of mianserin including 55 patients with breast cancer without metastasis, mianserin significantly improved depressive symptoms compared to the placebo group, and the treated group had a better dropout rate and side-effect frequency result than the placebo group. (22) Several double-blinded

studies and open tests on the efficacy of antidepressants for patients with cancer including breast cancer have been conducted, but the results have been equivocal. In the largest 8-weeks trial, 549 patients including those with breast cancer, pulmonary cancer, blood cancer, gynecologic cancer, and gastrointestinal cancer were randomly assigned to receive either 20 mg of paroxetine daily or a placebo. In that study, Morrow et al. (23) reported the effectiveness of paroxetine for alleviating depressive symptoms compared to the placebo group, but no difference was found in reducing fatigue between the groups.

In conclusion, pharmacologic studies on the effects of antidepressants in patients with cancer and depression are limited due to the difficult current situation in conducting controlled pharmacologic trials, and, moreover, double-blinded studies of antidepressants in patients with breast cancer are limited. Additionally, most of the studies had limited numbers of test subjects, a short follow-up period, and the data were assessed by different tools. Despite these limitations, the use of antidepressants in patients with cancer is effective and similar to patients with various other physical illnesses.

### Treatment of hot flashes

Approximately 75% of menopausal women develop signs of hot flashes. Typically, hot flashes begin with an abrupt flash in the chest, neck, and facial area, which tends to expand into other parts of the body, and is accompanied by skin rashes, perspiration, palpitation, anxiety, and insomnia. In particular, hot flashes accompanied by the abrupt menopause after an ovariectomy, chemotherapy, or radiation therapy in patients with cancer are more frequent and intense compared to natural menopause. (24) Although the hot flash mechanism has not been clearly elucidated, dysfunction of the body temperature control mechanism in the hypothalamus due to a reduction in estrogen is considered to be the cause of the symptoms. (25) Changes in body temperature are recognized in the thermoregulatory center located in the medial preoptic area of the hypothalamus, which controls physiological responses that conserve or dissipate heat, such as skin vasodilation or vasoconstriction. The threshold between sweating

and shivering (inter-threshold zone) is wide in premenopausal women, but narrow in menopausal women. An increase in body temperature precedes most hot flashes. Because menopause is associated with a decline in estrogen concentrations, and women with low amounts of circulating estrogens are more likely to have symptoms, estrogen deprivation has been thought to be the most likely triggering event for hot flashes due to activation of the heat loss mechanism by a small body temperature elevation.(26)

Although tamoxifen is generally well tolerated, up to 80% of women who take tamoxifen complain of hot flashes and up to 45% of women grade the hot flashes as severe enough to cause a decrease in quality of life and therapy noncompliance.(27,28) To improve hot flash symptoms in healthy women, hormonal therapy such as estrogen has been used as the most common and effective treatment. Approximately 80–90% of patients administered with hormonal medications report the desired effects.(29)

Exogenous estrogens are not commonly recommended for treating hot flashes in women with breast cancer, as they can cause recurrence and metastasis of breast cancer.(30) Because of such a limitation, other therapies have been sought. Antidepressants including SSRIs and SNRIs, clonidine and gabapentin are effective as nonhormonal therapies for hot flashes.(31)

As estradiol ( $E_2$ ) works in the thermoregulatory center through serotonin,(32) antidepressants that act on the serotonin system have been tested as nonhormonal therapy for hot flashes. Among the several serotonin receptors, direct activation of the 5-HT<sub>2a</sub> receptor induces hyperthermia, and stimulation of the 5-HT<sub>1a</sub> receptor results in hypothermia. So, a balance between the 5-HT<sub>1a</sub> and 5-HT<sub>2a</sub> receptors might be important for optimizing thermoregulation.(33) Because the development of flushing is related to a body temperature increase through an overload of the serotonin receptors in the hypothalamus, it has been suggested that SSRIs or SNRIs improve flushing.(34) In general, several studies have shown that these medications reduce hot flash frequency by about 60%, compared with a decrease of 25–35% with a placebo.(31, 34–37)

Among these antidepressants, paroxetine and venlafaxine are more effective for improving the frequency of hot flashes in patients with breast cancer, and fluoxetine(38) and setraline(39) are also effective for managing symptoms. Stearns et al.(34,40) reported the effect of paroxetine on reducing hot flash frequency and severity compared with a placebo in menopausal women and patients with breast cancer, respectively. In a good-quality trial that enrolled menopausal women, the paroxetine controlled release groups (12.5 or 25 mg/day) experienced fewer daily hot flashes than the placebo group (3.2–3.3 vs. 1.8,  $p=0.01$ ) and reduced hot flash composite scores (frequency  $\times$  severity, 62–65% vs. 38%,  $p=0.03$ ).(34) In a fair-quality trial that included predominantly women with breast cancer using tamoxifen, the paroxetine groups (10 or 20 mg/day) also showed fewer daily hot flash episodes compared with placebo (50–51% vs. 16%,  $p<0.001$ ) as well as a reduction of composite score (54% vs. 19%,  $p<0.001$ ) compared to a placebo group.(40)

Venlafaxine also showed excellent effects in several studies for treating flushing including randomized controlled trials. Loprinzi et al.(35) conducted a randomized double-blind, placebo-controlled study to assess the efficacy of venlafaxine in 221 patients with breast cancer, 69% of whom were taking tamoxifen. The subjects were assigned to a placebo or one of three venlafaxine groups (37.5, 70, or 150 mg daily) to compare the improvement of flushing after 4 weeks of treatment. The results showed that the reduction in hot flash frequency was 19, 30, 46, and 58% and the decrease in composite scores was 27, 37, 61 and 61%, respectively. Although, all of the venlafaxine groups showed a significant improvement compared to the placebo group, 70 mg venlafaxine was the most effective dose considering side effects. In another study evaluating the efficacy and tolerability of long-term treatment with venlafaxine for reducing vasomotor symptoms in patients with breast cancer, the use of the low dose venlafaxine (37.5 mg/day) was associated with minimal side effects and produced a good improvement in hot flashes.(41) Loibl et al.(42) compared the efficacy of clonidine (0.075 mg twice/day) and venlafaxine (37.5 mg twice/day) in a double-blinded, randomized study. The investigators demonstrated

that venlafaxine is significantly more effective in reducing the frequency of hot flashes in patients with breast cancer than clonidine.

In conclusion, as both SSRIs and SNRIs have been suggested as effective in reducing the vasomotor symptoms of healthy menopausal women and female patients with breast cancer, regardless of whether they were receiving endocrine treatment or not, (31,34–36) these medications could be considered first line treatments to improve menopausal symptoms in patients with breast cancer or women in which hormonal therapy is not appropriate. Therefore, SSRIs and SNRIs could be prescribed to treat hot flashes in patients with breast cancer, but it would be safest to select a drug having a low possibility of drug interactions if patients are taking tamoxifen.

### TAMOXIFEN METABOLISM AND ITS EFFECTS ON BREAST CANCER

Tamoxifen has both estrogenic and antiestrogenic activity, depending on the target organ. These differential effects lead to clinical benefits as well as to side effects and, rarely, severe toxicity. (9) Tamoxifen is antiestrogenic in the breast as well as in the brain, resulting in decreased breast cancer development and recurrence, but leading to hot flashes. In contrast, tamoxifen is estrogenic in the bone, liver, and uterus, resulting in improvements in bone density and lipid profile, but also potentially increasing the risk of both thromboembolic disease and uterine cancer. (9,28)

The ER-dependent growth inhibitory effect of antiestrogens is mediated by activation of antiproliferative transforming growth factor beta (TGF $\beta$ ) signal transduction pathways. (43) TGF $\beta$  is a strong inhibitor of breast cancer cell growth and induces cell cycle arrest in the early G1 phase. (44) Although it is not clearly understood how tamoxifen causes depression or aggravates the illness, anti-manic effects of tamoxifen in bipolar disorder were reported recently. (45)

The mechanisms and effects of tamoxifen have been the subject of much scrutiny but remain obscure. Attempts to link a clinical response to tamoxifen therapy with

plasma tamoxifen concentrations revealed no statistically significant differences in outcomes between women who received 20 mg of tamoxifen daily and those who received 40 mg of tamoxifen daily, even though women in the 40 mg tamoxifen group had higher plasma tamoxifen concentrations than those in the 20 mg tamoxifen group. (46) These results have been widely cited as evidence that plasma tamoxifen concentration is not a predictor of clinical outcome. (47)

Tamoxifen undergoes extensive hepatic oxidation by the cytochrome (CYP) P450 enzymes to several primary and secondary metabolites with variable potencies toward the ER. Major primary metabolites include N-desmethyltamoxifen, 4-hydroxytamoxifen, tamoxifen-N-oxide,  $\alpha$ -hydroxytamoxifen, and N-didesmethyltamoxifen. N-desmethyltamoxifen, resulting from the CYP3A4/5-mediated catalysis of tamoxifen, is the major primary quantitative metabolite of tamoxifen and accounts for approximately 92% of primary tamoxifen oxidation. N-desmethyltamoxifen has weak antiestrogenic effects similar to tamoxifen. (48) Using N-desmethyltamoxifen as an intermediary substrate, it is biotransformed to  $\alpha$ -hydroxy-N-desmethyltamoxifen and N-didesmethyltamoxifen by CYP3A5 as well as 4-hydroxy-N-desmethyltamoxifen (endoxifen) by CYP2D6.

Jordan et al. (49,50) demonstrated that hepatic metabolism of tamoxifen results in a statistically significant increase in its efficacy and they also showed, for the first time, that 4-hydroxytamoxifen, one of the human tamoxifen metabolites is approximately 100 times more potent than tamoxifen as an estrogen antagonist. 4-hydroxytamoxifen possesses a much higher affinity for ERs and is 30- to 100-fold more potent than tamoxifen in suppressing estrogen-dependent cell proliferation. (51,52) For this reason, 4-hydroxytamoxifen has been considered as the major active metabolite of tamoxifen and is frequently used to characterize tamoxifen activity. In women receiving tamoxifen at a dose of 20 mg/day, plasma steady state concentrations of tamoxifen and N-desmethyltamoxifen are 362.5 and 654.9 nM, respectively, whereas the steady-state concentrations of 4-hydroxytamoxifen are extremely low (9 nM). (53) However, new data suggest

that endoxifen has identical properties and potency as 4-hydroxytamoxifen, but is present at higher blood concentrations than 4-hydroxytamoxifen, (54) Recent studies have confirmed that endoxifen has equivalent potency to 4-hydroxytamoxifen in ER- $\alpha$  and ER- $\beta$  binding, (54) in suppression of ER-dependent breast cancer proliferation, (54,55) and in global ER-responsive gene expression. (56) Because of such results, it is currently accepted that the major pharmacological effects of tamoxifen are most largely affected by the blood concentration of endoxifen.

Antiestrogen treatment of hormone responsive breast cancer cells and breast cancer tissue results in enhanced secretion of active TGF $\beta$ 1; induction of TGF $\beta$ 2-, and TGF $\beta$  type II receptor (T $\beta$ RII)-expression; and subsequent activation of downstream TGF $\beta$  signal transduction pathways. Blocking of TGF $\beta$  signal transduction leads to antiestrogen resistance. (43) Buck et al. (57) investigated the breast cancer cell growth suppression effects of the six major metabolites including tamoxifen on the TGF $\beta$  signaling pathway and reported that only endoxifen and 4-hydroxytamoxifen had significant antiproliferative activity and were able to induce TGF $\beta$ 2 and T $\beta$ RII. The authors suggested that TGF $\beta$ 2 and T $\beta$ RII are biological indicators of tamoxifen treatment response in evaluating the tamoxifen treatment effect in breast cancer.

The pharmacological action of tamoxifen is due to its conversion to active metabolites. Because there is strong evidence that tamoxifen is converted to antiestrogenic metabolites, which are more potent than tamoxifen itself, altered patterns of tamoxifen metabolism might contribute to interindividual variability in effects despite the same dosage. For this reason, pharmacogenetic and drug interactions relating to CYP2D6 activity may affect endoxifen concentrations and possibly tamoxifen-associated long-term outcomes.

## CYP2D6 POLYMORPHISMS

Multiple CYP isoenzymes including CYP3A, CYP2D6, CYP2C9, CYP2C19, CYP2B6, and CYP1A2 are involved in tamoxifen metabolism. A comprehensive kinetic charac-

terization of tamoxifen metabolism demonstrated that CYP3A is the major CYP isoform responsible for the formation of N-desmethyltamoxifen, whereas the generation of endoxifen and 4-hydroxytamoxifen appear to be catalyzed predominantly by CYP2D6. As the major metabolites that determine the effects of tamoxifen are transformed by CYP2D6, the difference in the treatment response could exist based on CYP2D6 enzyme activity.

More than 100 CYP2D6 allelic variations have been identified, (58) and might explain, in part, the observed interpatient variability in the concentrations of tamoxifen and its metabolites. The frequency of the single nucleotide polymorphism in CYP2D6 varies according to race and ethnicity. (59) Individuals can be divided into poor, intermediate, extensive, and ultra-rapid metabolizers based on the CYP2D6 genotype. An accepted classification of CYP2D6 activity designates persons homozygous for alleles that produce enzymes with normal activity (such as wild-type CYP2D6\*1) as extensive metabolizers (EM). Persons carrying multiple copies of CYP2D6 alleles associated with high enzyme activity are termed ultra-rapid metabolizers (UM), and individuals with one or two variant alleles with reduced or null activity are designated intermediate (IM) and poor metabolizers (PM). While 60% of European individuals are homozygous for the active, most common allele (CYP2D6\*1), approximately 7% are homozygous for an inactive, variant allele (CYP2D6\*4). (60) Approximately 24% of African and African-American populations have the CYP2D6\*17 variant allele with reduced enzyme activity, (61) and the most common allele in Asians (with an allele frequency >50%) is CYP2D6\*10, which produces an enzyme with reduced activity (Table 1). (62)

It has been hypothesized that women have the CYP2D6 enzyme with reduced activity, and that because this results in presumably low endoxifen concentrations, these women might have poor long-term treatment outcomes. The North Central Cancer Treatment Group conducted a study investigating the relationship between CYP2D6 genotypes and treatment outcomes of tamoxifen with ER-positive postmenopausal patients with breast cancer who were randomly assigned to receive 5 yr of tamoxifen. (63,64) The investigators reported that the patients with the

**Table 1.** Major CYP2D6 alleles, effect on enzyme metabolism, and allele frequencies in selected populations

Major variant alleles	Consequence (enzyme activity)	Allele frequencies (%)		
		Caucasians	Asians	Black Africans
CYP2D6*2xn	Increased enzyme activity	1-5	0-2	2
CYP2D6*4	Inactive enzyme	12-21	1	2
CYP2D6*5	No enzyme	27	6	4
CYP2D6*10	Decreased activity	1-2	51	6
CYP2D6*17	Decreased activity	0	0	20-35
CYP2D6*41	Decreased activity	8-10	0-2	11-14

CYP2D6 \*4/\*4 variant allele, absent of enzyme activity, had a significantly short relapse-free time and disease-free survival compared to individuals with CYP2D6\*4/wt or with the wt/wt genotype.<sup>(63)</sup> However, no difference was found for the frequency of hot flashes by genotype. A follow-up study by the same investigators reported that not only the CYP2D6 variant allele, but also the concomitant prescription of CYP2D6 inhibitors was an independent predictor of poorer outcome in the same population.<sup>(64)</sup> Schroth et al.<sup>(65)</sup> assessed the predictive value of genetic variants of CYP2D6, CYP2C19, CYP2B6, CYP2C9, and CYP3A5 for tamoxifen treatment outcome in 486 patients with breast cancer (206, tamoxifen treatment group; 280, non-tamoxifen treatment group, mean follow-up investigation period of 71 months) and reported significantly more breast cancer recurrences, shorter relapse-free periods and worse event-free survival rates among patients carrying the \*4, \*5, \*10, and \*41 CYP2D6 alleles, compared with carriers of two functional alleles. A follow-up large-scale study conducted over 6.3 yr showed a significantly higher relapse risk in the IM and PM than in the EM, and the relapse time in the PM was shorter than in the EM.<sup>(66)</sup>

Several retrospective studies have reported an inverse association between the CYP2D6 genotype and breast cancer outcomes. Nowell et al.<sup>(67)</sup> reported better overall survival in tamoxifen-treated patients with breast cancer and the CYP2D6\*4 genotype. A Swedish study showed a 62% reduction of recurrence risk in women with at least one CYP2D6\*4 allele who were treated with tamoxifen.<sup>(68)</sup> In other retrospective large-scale studies performed by the same investigators, patients homozygous for CYP2D6\*4 showed a better prognosis compared with those who were

homozygous or heterozygous for CYP2D6\*1 among patients with ER-positive menopausal breast cancer.<sup>(69)</sup>

Some limitations exist when directly comparing these contradictory reports through a meta-analysis. First, most of the studies were conducted retrospectively and differences in genotype analysis methods, in tamoxifen administration dose and administration period, and in the presence of comparison groups exist. In 2006, the FDA Endocrinologic and Metabolic Drugs Advisory Committee discussed routine CYP2D6 genotyping for patients prescribed tamoxifen, but no agreement was made.<sup>(70)</sup> Until now, no consistent established guideline exists as to whether the CYP2D6 genotype test must be conducted before using tamoxifen. Therefore, follow-up studies must be conducted to support the necessity of CYP2D6 genotype testing in patients with breast cancer.

### COADMINISTRATION OF ANTIDEPRESSANTS AND TAMOXIFEN

Approximately 25% of all clinically used medications are metabolized by CYP2D6, including antiarrhythmic agents (propafenone, flecainide), beta-blockers (timolol, metoprolol, alprenolol), antidepressants (tricyclic antidepressants, fluoxetine, paroxetine, bupropion), anti-psychotics, and opioids such as codeine, and dextrometophan. Therefore, CYP2D6 genotype status may influence the activity of many commonly used medications. For example, PM may experience decreased analgesic effect due to difficulty in converting codeine to morphine and increased adverse effects from  $\beta$ -blockers. In contrast, UM could experience excessive effects. Use of CYP2D6 inhibitors in patients who are being treated with tamox-

ifen, even if they have the homozygous active genotype, could potentially affect breast cancer outcomes, in a manner similar to PM. Inhibition of tamoxifen conversion to endoxifen may decrease the efficacy of tamoxifen therapy and increase the risk of breast cancer development or recurrence. Medications that inhibit CYP2D6 may turn EM into PM.

Women with breast cancer have high rates of depression and are likely to be prescribed antidepressants; therefore, clarifying drug interactions between drugs to treat breast cancer and depression should become breast cancer research priorities. Several SSRIs and SNRIs are potent, moderate, or mild inhibitors of CYP2D6 (Table 2). Antidepressants such as paroxetine, fluoxetine, and bupropion strongly inhibit CYP2D6 enzyme activity, and sertraline, duloxetine, and diphehydramine are graded as moderate inhibitors. Consequently most antidepressants act as CYP2D6 inhibitors and may increase the risk of breast cancer relapse or death.(71) Although consistent study results are not available, most experts agree that caution should be exercised when prescribing tamoxifen with a CYP2D6 inhibitor and consideration should be given to the use of an alternate antidepressant.

In an experiment conducted by the Consortium on Breast Cancer Pharmacogenomics, coadministration of paroxetine to women with wild-type CYP2D6 and on chronic tamoxifen therapy was associated with a 56% reduction in plasma concentrations of endoxifen.(72) At the follow-

up prospective study by the same investigators, women with homozygous or heterozygous for the variant CYP2D6 allele had a decreased endoxifen concentration, and, moreover, the coadministration of tamoxifen and CYP2D6 inhibitors caused a reduction of endoxifen concentration in proportion to the potency of CYP2D6 inhibition.(53) Borges et al.(73) conducted a prospective trial in 158 patients with breast cancer who were taking tamoxifen to evaluate the effect of the CYP2D6 genotype and concomitant medications on endoxifen plasma concentrations. They found that the CYP2D6 genotypes are highly associated with endoxifen plasma concentrations and account for their variability. While no significant differences in mean plasma concentrations of tamoxifen, N-desmethyltamoxifen, or 4-hydroxytamoxifen were observed between users and non-users of concomitant CYP2D6 inhibitors, the mean endoxifen plasma concentration was significantly lower in patients taking CYP2D6 inhibitors compared to that in patients who did not. When the authors divided the CYP2D6 inhibitors into potent (paroxetine, fluoxetine) and weak (sertraline and citalopram), they found low serum concentrations of endoxifen in those concomitantly treated with potent inhibitors of CYP2D6, and intermediate levels of endoxifen in those concomitantly treated with weak inhibitors. Concomitant use of venlafaxine, which is considered the least potent inhibitor, showed no significant effect. The authors observed that the mean plasma endoxifen concentration was signifi-

**Table 2.** Proposed risk of decreased metabolism of tamoxifen by antidepressants inhibiting the CYP2D6 enzyme

Antidepressants inhibit CYP2D6	Degree of decreased tamoxifen metabolism		Use in women taking tamoxifen
	<i>In vivo</i>	<i>In vitro</i>	
Strong inhibitors			Avoid
Fluoxetine	Severe	Severe	Avoid
Paroxetine	Severe	Severe	Avoid
Bupropion	Lack	Severe	Avoid
Moderate inhibitors			Consider use based on risk-benefit assessment
Duloxetine	Lack	Moderate	Consider use based on risk-benefit assessment
Fluvoxamine	Lack	Moderate	Consider use based on risk-benefit assessment
Sertraline	Moderate	Moderate	Consider use based on risk-benefit assessment
Weak or non inhibitors			
Mirtazapine	Lack	Minimal or no	Secondary option
Citalopram	Mild	Mild	Secondary option
Escitalopram	Lack	Mild	Secondary option
Venlafaxine	Little or no	Little or no	Use preferentially safest choice

cantly lower in CYP2D6 EM patients who were taking potent CYP2D6 inhibitors compared to that in patients who were not. Thus, CYP2D6 genotype and concomitant potent CYP2D6 inhibitors are highly associated with plasma endoxifen concentrations and may substantially impact outcomes during tamoxifen treatment by phenocopying effects, i.e., converting an EM into a PM phenotype.

The influence of a concomitant CYP2D6 inhibitor on tamoxifen-associated outcome has also been investigated. Goetz et al. (64) demonstrated that women with decreased CYP2D6 metabolism had increased rates of breast cancer recurrence and decreased relapse-free survival time. The authors concluded that CYP2D6 inhibitors should probably be avoided in patients being treated with tamoxifen. Ahern et al. (74) investigated the association between concurrent use of tamoxifen and CYP2D6 inhibiting medications and breast cancer recurrence among Danish women diagnosed with early-stage, ER-positive breast cancer. They computed the breast cancer recurrence odds ratio (OR) and 95% confidence intervals for 15 medications including antidepressants and reported that the pooled recurrence OR was null, and that recurrence ORs for individual drugs ranged from 0.3 to 3.4. The investigators suggested a null association between drug-compromised CYP2D6 activity and breast cancer recurrence among tamoxifen-treated women. However that study had some limitations such as a small number of women associated with each drug.

When reviewing the evidence from clinical and non-clinical studies regarding the effects of antidepressants on the CYP2D6 enzyme, there are consistent results that paroxetine, (21, 53, 71) fluoxetine, (21, 53, 71) and bupropion (75, 76) have a large effect on tamoxifen metabolism and should not be used in women taking tamoxifen. Currently, it is difficult to evaluate the clinical results of antidepressants with mild and moderate inhibiting potency; a retrospective study showed no association with breast cancer recurrence and the use of citalopram. (77) However, when prescribing these antidepressants, it should be considered a secondary option in which the risk of not treating depression needs to be weighed against

the possibility of some reduction in the metabolism of tamoxifen. It is suggested that venlafaxine has little or no effect on the metabolism of tamoxifen and may be considered the safest choice of antidepressants. Moreover, desvenlafaxine, the active metabolite of venlafaxine, does not inhibit the activity of CYP2D6 even at twice the recommended therapeutic dose. (78–80) A clinical trial investigating tamoxifen levels in women with breast cancer and in women at high risk for breast cancer who are receiving tamoxifen together with venlafaxine, citalopram, escitalopram, sertraline, or gabapentin is currently ongoing and may help us develop guidelines about the risks associated with these medications when prescribed concomitantly with tamoxifen. (81)

## CONCLUSION

Tamoxifen has been used to treat and prevent breast cancer for more than 30 yr. Tamoxifen itself is a relatively weak selective estrogen receptor modulator and is considered a classical pro-drug, requiring metabolic activation to elicit pharmacological activity. CYP2D6 appears to be the rate-limiting enzyme converting the pharmacologically inactive metabolites (tamoxifen and N-desmethyl-tamoxifen) into endoxifen. Both genetic and environmental (drug-induced) factors that alter CYP2D6 enzyme activity affect tamoxifen treatment outcomes. In patients with breast cancer, antidepressants are commonly used to treat symptoms of depression and anxiety or to alleviate menopausal symptom such as hot flashes. The use of antidepressants in patients with cancer is effective and safe, but most SSRIs or SNRIs are CYP2D6 inhibitors. Therefore, coadministration of potent or intermediate CYP2D6 inhibitors in women taking tamoxifen should be avoided.

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