Treatment in Psychiatry begins with a hypothetical case illustrating a problem in current clinical practice. The authors review current data on prevalence, diagnosis, pathophysiology, and treatment. The article concludes with the authors' treatment recommendations for cases like the one presented.

Drug Interactions and Pharmacogenomics in the Treatment of Breast Cancer and Depression

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"Ms. B" is a 45-year-old married premenopausal woman who was diagnosed with major depressive disorder 10 years ago and then successfully treated for 12 months with fluoxetine (20 mg/day) without significant side effects. She remained free of depressive symptoms for the next 8–9 years. One year ago, she was diagnosed with estrogen receptor-positive invasive breast cancer and underwent treatment with surgery, followed by chemotherapy, and then radiation therapy. Ms. B. has been treated with tamoxifen (a selective estrogen receptor modulator) for the past 6 months to reduce the likelihood of breast cancer recurrence. She has tolerated tamoxifen relatively well, except for moderately bothersome hot flashes, for which she has received no pharmacotherapy. Recently, however, she developed recurrent depressive symptoms and sought treatment from her psychiatrist. What pharmacologic agents are effective against both depression and hot flashes in women with breast cancer? Would any of these agents compromise the efficacy of tamoxifen or increase its toxicity through a drug-drug interaction?

Depression in Breast Cancer

Many women experience distress following the diagnosis of breast cancer, and a subset of these women experience clinically significant depression (1). The estimated point prevalence of major depressive disorder in all women is in the range of 3.5%–7% (2). In comparison, the rate of depression in women with breast cancer is estimated to be in the range of 10%–25%, depending on the method of assessment (3). Rates appear higher in the first year following diagnosis, especially in younger women and in women treated with chemotherapy (3).

Studies evaluating the association between depression and treatment with tamoxifen have yielded mixed results. In some trials, a subset of patients have discontinued tamoxifen therapy because of depressive symptoms, whereas in other studies, conducted primarily in the breast cancer prevention setting, no increased risk of depression was observed during treatment with tamoxifen (4, 5).

Endocrine Therapy for Breast Cancer

Approximately 180,000 women are diagnosed with invasive breast cancer in the United States each year (6). The majority of these patients will have tumors that express estrogen receptor and/or progesterone receptor on the cell surfaces. Women with hormone receptor-positive tumors obtain substantial benefit from treatment with tamoxifen or agents that decrease circulating levels of estrogen, such as aromatase inhibitors (7). At present, the standard of care for treatment of premenopausal women with estrogen receptor-positive invasive breast cancer is tamoxifen therapy, whereas for postmenopausal women, both tamoxifen and aromatase inhibitors are acceptable treatment options. Analyses of thousands of women treated with 5 years of tamoxifen versus no endocrine therapy for invasive breast cancer demonstrate a 31% decrease in annual breast cancer death rate with tamoxifen (7).

An additional 60,000 women are diagnosed with noninvasive breast cancer each year (6), and many will be offered tamoxifen to reduce the risk of an in-breast recurrence or a new primary tumor. Moreover, well-validated population-based models have been developed to estimate an unaffected woman's risk of developing breast cancer. Women at risk for breast cancer may be recommended for therapy with tamoxifen or raloxifene (8). Several prospective randomized controlled trials have demonstrated that tamoxifen decreases the risk of a new primary breast cancer in high-risk women by 40%–50% (8). Thus, a substantial number of women with an increased risk for breast cancer are treated annually with antiestrogen therapy.

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Tamoxifen has both antiestrogenic and estrogenic activity, depending on the target organ. These differential effects lead to clinical benefit as well as to potentially bothersome side effects and rare but severe toxicity (9). Tamoxifen is antiestrogenic in the breast, resulting in decreased breast cancer development and recurrence, as well as in the brain, leading to hot flashes. Conversely, 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 (8, 9). As noted above, it is unclear whether tamoxifen causes or exacerbates depression, but this agent was recently demonstrated to have antimanic properties in patients with bipolar disorder (10).

Treatments for Concurrent Hot Flashes and Depression

Antiestrogen therapy for patients with breast cancer, which may induce or exacerbate depression and anxiety and which frequently causes hot flashes, has led to an intersection between clinical oncology and clinical psychiatry. Prospective randomized clinical trials have demonstrated that selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) effectively decrease vasomotor symptoms in healthy menopausal women and women with breast cancer, on or off endocrine therapy (11–16). In general, these studies have shown that most of these medications decrease hot flash frequency by about 60%, compared with a decrease of 25%–35% with placebo (11, 12, 16). These observations have primarily been made with venlafaxine, paroxetine (continuous release formulation), and citalopram (11, 12, 15, 16). In addition to these antidepressants, the anticonvulsant gabapentin has been shown to decrease hot flashes to a similar degree (16, 17). Modest improvements in hot flashes have also been reported for other SSRIs and SNRIs, including fluoxetine and sertraline (18, 19).

Tamoxifen Metabolism

Tamoxifen itself is a relatively weak selective estrogen receptor modulator and is considered to be a classical prodrug—it is converted to metabolites that are notably more potent than the parent drug itself. It is primarily metabolized in the liver by the cytochrome P450 system to a number of active metabolites, including 4-hydroxytamoxifen (4-OH tamoxifen) and 4-hydroxy-N-desmethyltamoxifen, designated endoxifen (20). Endoxifen and 4-OH tamoxifen are equipotent, and both are approximately 100 times more active as antiestrogens than the parent compound, tamoxifen (21). However, endoxifen is present in concentrations 5–10 times higher than 4-OH tamoxifen in most women taking tamoxifen.

Tamoxifen is converted to endoxifen principally by a noninducible P450 enzyme that is coded for by the most polymorphic, and most studied, gene in the cytochrome P450 system: CYP2D6. More than 80 different major alleles of the CYP2D6 gene have been identified, many of which confer decreased or absent CYP2D6 activity, and patients can be divided into poor, intermediate, extensive, and ultrarapid metabolizers on the basis of their genotype. While 60% of individuals of European descent are homozygous for the active, most common allele (*1), approximately 7% are homozygous for an inactive, variant allele (*4). Other alleles, including *5, *10, and *41, also confer absent CYP2D6 activity. In one study, breast cancer patients treated with tamoxifen who were homozygous for a poor metabolizer genotype (*4/*4) had significantly lower serum concentrations of endoxifen than those with the active (*1/*1) genotype (22).

"Use of CYP2D6 inhibitors in patients who are being treated with tamoxifen … could potentially affect breast cancer outcomes."

These results have led to retrospective studies evaluating the effect of CYP2D6 genotype on breast cancer outcomes. In one study, estrogen receptor-positive breast cancer patients homozygous for the poor metabolizer genotype who were treated with tamoxifen monotherapy were more likely to experience a recurrence of breast cancer than those patients who carried an allele coding for active enzyme (adjusted hazard ratio=1.86, p=0.089) (23). These findings were consistent with the hypothesis that homozygous *4/*4 patients did not activate tamoxifen to endoxifen and therefore received less or no benefit from the drug. Results from subsequent studies have been mixed; some confirmed this finding (24–26), while others did not (Table 1) (27, 28). In fact, two of these studies suggested just the opposite effect: CYP2D6 *4/*4 patients actually had better outcomes with tamoxifen monotherapy (27, 28). Nevertheless, although further studies are required, these investigations suggest an important role for CYP2D6 activity in tamoxifen metabolism.

Coadministration of Tamoxifen and an SSRI or SNRI

In addition to genetic inactivation of CYP2D6, CYP2D6 activity can be decreased by medications that inhibit the enzyme (22, 29, 30). Therefore, use of CYP2D6 inhibitors in patients who are being treated with tamoxifen, even if they have the homozygous active genotype, could potentially affect breast cancer outcomes, in a manner similar to the poor metabolizer genotype. Inhibition of tamoxifen conversion to endoxifen may decrease the efficacy of tamoxifen therapy and increase the risk of breast cancer development or recurrence. Several SSRIs and SNRIs are potent, moderate, or mild inhibitors of CYP2D6 (Table 2).

Indeed, women with wild-type CYP2D6 genotype treated with tamoxifen have been shown to have statistically significant decreases in endoxifen concentration following initiation of concomitant paroxetine therapy (20).

TABLE 1. Summary of Associations Between CYP2D6 Genotype and Breast Cancer Outcome

Study	N	Treatment Setting	Took 2D6 Inhibitors Into Account?	Comparison[a]	Hazard Ratio	p
Goetz et al. (23)	223	Adjuvant	No	*4/*4 vs. wt/*4 and wt/wt	Disease-free survival: 1.86	0.089
Goetz et al. (31)	190	Adjuvant	Yes	Decreased vs. increased	Relapse-free survival: 1.74	0.034
Lim et al. (25)	202	Metastatic	No	*10/*10 vs. others	Time to progression: 5 months vs. 21.8 months	0.0032
Nowell et al. (26)	162	Adjuvant	No	wt/*4 and *4/*4 vs. wt/wt	Progression-free survival: 0.67	0.19
Schroth et al. (24)	206	Adjuvant	No	Nonfunctional allele carriers (*4, *5, *10, *41) vs. wt	Event-free survival: 1.89	0.02
Wegman et al. (28)	110	Adjuvant	No	wt/*4 and *4/*4 vs. wt/wt	Relapse-free survival: 0.33	0.14

[a] wt=wild-type. *4, *5, *10, and *41 are nonfunctional CYP2D6 alleles.

TABLE 2. Effect of SSRIs or SNRIs and Gabapentin on CYP2D6 Activity and on Hot Flashes

CYP2D6 Activity and Agent[a]	Efficacy Compared With Placebo for Hot Flashes	References
Strong CYP2D6 inhibitors		
Fluoxetine	50% vs. 36%, p=0.02	18, 30
Paroxetine	62% vs. 37%, p=0.007	12, 20, 30
Moderate CYP2D6 inhibitors		
Duloxetine	Not assessed in placebo-controlled trial	33
Weak CYP2D6 inhibitors or noninhibitors		
Citalopram	49% vs. 23%, p=0.0021	15, 30
Escitalopram	Not assessed in placebo-controlled trial	34
Fluvoxamine	Not assessed in placebo-controlled trial	35
Gabapentin	46% vs. 15%, p=0.007	17
Sertraline	36% vs. 27%, p=0.03	19, 30
Venlafaxine	60% vs. 27%, p<0.0001	11, 22, 29

[a] Information about the CYP2D6 activity of these agents is from www.drug-interactions.com.

An observational study of women treated with tamoxifen demonstrated low serum concentrations of endoxifen in those concomitantly treated with strong inhibitors of CYP2D6, such as paroxetine and fluoxetine, and intermediate levels of endoxifen in those concomitantly treated with weak inhibitors, such as sertraline and citalopram (29). It is noteworthy that venlafaxine, which does not inhibit CYP2D6, had little effect on endoxifen concentration. Similarly, it would be expected that other SSRIs and SNRIs that have not been shown to inhibit CYP2D6 activity, such as fluvoxamine and escitalopram, would have little effect on endoxifen concentration, although this hypothesis has not yet been formally studied.

The influence of concomitant medications in addition to CYP2D6 genotype on breast cancer outcome has also been investigated in one of the retrospective patient cohorts mentioned earlier (31). Information about concomitant treatment with CYP2D6 inhibitors was extracted from medical records and combined with genotype information to classify patients on the basis of metabolizer status. Those women with decreased CYP2D6 metabolism had increased rates of breast cancer recurrence and decreased relapse-free survival time. Since it was a retrospective analysis of a previously conducted study, endoxifen concentrations were not available. Nonetheless, the authors concluded that based on these data, CYP2D6 inhibitors should probably be avoided in patients being treated with tamoxifen.

Although these studies are small relative to major studies of breast cancer outcome, the data suggest that SSRIs and SNRIs with no or minimal effect on CYP2D6 activity, such as citalopram and venlafaxine, are unlikely to interfere with the formation of endoxifen. Similarly, the anticonvulsant gabapentin is not known to affect CYP2D6 activity or the formation of endoxifen. Other SSRIs that inhibit CYP2D6 may prevent endoxifen formation and adversely affect tamoxifen activity. However, since SSRIs and SNRIs have been demonstrated to decrease hot flashes in otherwise healthy postmenopausal women who are not taking tamoxifen, and since citalopram, venlafaxine, and gabapentin are as effective in reducing hot flashes as strong CYP2D6 inhibitors in women taking tamoxifen, the mechanism by which these antidepressants reduce hot flashes is likely not due to blockade of endoxifen production. Taken together, these data suggest that concomitant use of potent CYP2D6 inhibitors (Table 2) should be avoided in women taking tamoxifen, unless the patient is committed to one of these drugs as an effective antidepressant where other medications have been ineffective, or a patient requiring antidepressant therapy cannot tolerate alternative agents. Antidepressant therapy with escitalopram or fluvoxamine could also be considered in patients being treated with tamoxifen, but the effect of these medications on hot flashes has not yet been assessed.

Summary and Recommendations

The retrospective data regarding CYP2D6 genotype and breast cancer outcomes in patients receiving treatment with tamoxifen were presented to the U.S. Food and Drug Administration (FDA) at an advisory committee meeting in October 2006. At that time, some members of the panel recommended routine CYP2D6 genotyping for patients

being treated with tamoxifen. However, others were more conservative given the mixed results described above (Table 1) and recommended that genotyping be considered as an option in these patients. At this time, the FDA has not recommended changing the package insert for tamoxifen to describe metabolism by CYP2D6 or to recommend CYP2D6 genotyping of patients prior to initiation of therapy, and genotyping for CYP2D6 is not routinely performed in the clinical management of breast cancer patients. Further studies of the impact of CYP2D6 genotype on breast cancer outcomes are under way, so additional information should be available in the near future to help guide treatment decision making for individual patients (32).

At present, however, since the data suggest that CYP2D6 activity may adversely affect tamoxifen metabolism, which in turn may influence breast cancer outcomes, it is reasonable to avoid known CYP2D6 inhibitors in women taking tamoxifen, assuming that alternative treatment options (such as citalopram, gabapentin, and venlafaxine) will be tolerable. Some women are stable on therapy with an SSRI or SNRI that inhibits CYP2D6 or are unable to tolerate the medications that do not inhibit CYP2D6. In these situations, the patient's psychiatrist should discuss therapy options with the treating oncologist, since there may be alternative endocrine therapy options available for management of the patient's breast cancer. For example, ovarian suppression can be used for treatment of premenopausal women, and aromatase inhibitor therapy can be an excellent option for postmenopausal women.

In the vignette, Ms. B was interested in taking a single medication that could treat both her depressive symptoms and her hot flashes, and she had heard that some antidepressants were able to manage both. Because she had previously tolerated fluoxetine well, she requested this medication. Her psychiatrist had heard about the possible drug-drug interactions between tamoxifen and some SSRIs, however, and therefore encouraged Ms. B to consider trying a different antidepressant to avoid any potential decrease in tamoxifen efficacy. The psychiatrist initiated therapy with extended-release venlafaxine, and Ms. B is currently taking 75 mg daily. Ms. B has tolerated this antidepressant well, her depressive symptoms have improved, and her hot flashes are now mild and infrequent.

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