



Practical Psychopharmacology

Breast Cancer and Antidepressant Use

Chittaranjan Andrade, MD

In this column, Dr Andrade offers practical knowledge, ideas, and tips in psychopharmacology to JCP readers in psychiatric and general medical settings.

- Tamoxifen, an antiestrogen drug, is used for many indications related to breast cancer. Antidepressants are also often used in breast cancer patients, for states such as depression, anxiety, and hot flashes associated with chemical menopause.
- Tamoxifen is a prodrug. Some antidepressants (eg, paroxetine, fluoxetine, bupropion, duloxetine) inhibit CYP2D6, the enzyme that converts tamoxifen into endoxifen, its most important active metabolite. This could compromise tamoxifen's efficacy.
- Clinicians should avoid CYP2D6 inhibitors in patients receiving tamoxifen in favor of drugs with low or no CYP2D6 inhibitor activity (eg, mirtazapine, escitalopram, fluvoxamine, reboxetine, citalopram, sertraline, venlafaxine, desvenlafaxine).



Department of Psychopharmacology,
National Institute of Mental Health
and Neurosciences, Bangalore, India
(candrade@psychiatrist.com).

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Clinical Problem

Ms P, a 38-year-old woman, is receiving tamoxifen for breast cancer. She has clinically significant anxiety and depression. She also suffers from tamoxifen-related hot flashes. Paroxetine is an effective treatment for anxiety,¹ depression,² and menopausal hot flashes,³ including those related to tamoxifen.⁴ What are the concerns regarding the use of paroxetine (or other antidepressants) in patients receiving tamoxifen?

For Starters, What Is Tamoxifen?

Tamoxifen is a drug with many indications in the context of breast cancer. It is used for the prevention of breast cancer in women at high risk of developing the disease. It is used to treat early as well as advanced or metastatic estrogen receptor-positive breast cancer in both premenopausal and postmenopausal women. It is used to reduce cancer risk in the contralateral breast. It is also used for male breast cancer.^{5,6}

How Does Tamoxifen Act?

Tamoxifen acts through estrogen receptor antagonism in hormone receptor-positive breast cancer cells.⁵ Tamoxifen is a prodrug. That is, it has little activity of its own on the target cells, and its efficacy arises from metabolites (chiefly endoxifen, but also 4-hydroxytamoxifen) that have markedly greater affinity for the target cells.^{4,7,8} There are several cytochrome P450 (CYP) enzymes that activate tamoxifen, including CYP2D6, 3A, 2B6, and 2C19.⁴

CYP2D6 and Tamoxifen

Much research has examined variations in CYP2D6 activity and treatment outcomes with tamoxifen⁹; variations in the other enzymes involved in tamoxifen metabolism do not appear to result in meaningful differences in the efficacy of treatment.⁴ The CYP2D6 research data show that persons who are 2D6 poor metabolizers have lower levels of endoxifen; some (but not all) studies show that such patients do less well with tamoxifen therapy.^{4,7,10,11}



Implications for Ms P

Who Is Receiving Tamoxifen for Breast Cancer

Although paroxetine is effective for anxiety, depression, and the hot flashes of menopause,¹⁻³ it should not be advised for Ms P and other breast cancer patients receiving tamoxifen. This is because paroxetine is a strong CYP2D6 inhibitor¹²; it would therefore reduce the activation of tamoxifen, thereby potentially compromising treatment outcomes.

What Is the Evidence?

Most of the literature on the subject is observational and has focused on CYP2D6 genetic variations in tamoxifen-treated women.⁹ Specifically, what have outcomes been in women who received antidepressants that varied in their potential to inhibit CYP2D6?

Kelly et al¹³ examined whether treatment with a selective serotonin reuptake inhibitor (SSRI) increased mortality risk in women receiving tamoxifen for breast cancer. The sample comprised a population-based cohort of 2,430 women 66 years and older who were treated with an SSRI during the period of tamoxifen therapy. The antidepressants used included paroxetine (26%), sertraline (22%), citalopram (19%), venlafaxine (15%), fluoxetine (10%), and fluvoxamine (7%). Overall, 30% of patients also received at least 1 non-SSRI antidepressant in a distribution that was similar across the SSRI groups.

During a mean of 2.4 years of follow-up, 374 women (15.4%) died of breast cancer. In analyses that adjusted for age, duration of tamoxifen treatment, and other potential confounders, Kelly et al¹³ found that an absolute increase of 25%, 50%, or 75% in the proportion of time on tamoxifen that overlapped with paroxetine treatment was associated with an increase of 24%, 54%, or 91%, respectively, in the risk of death from breast cancer. No significant risk was identified for the other SSRIs.

Kelly et al¹³ estimated that the use of paroxetine for 41% of the duration of tamoxifen treatment (the median period of overlap in the study) would significantly increase the risk of breast cancer death within 5 years of cessation of tamoxifen; the number needed to harm (NNH) was 20 (95% CI, 13–46). With a 100% overlap between paroxetine and tamoxifen therapy, the NNH was estimated to be 7.

Other Antidepressants That Are Also Best Avoided

Antidepressants such as fluoxetine, bupropion, and duloxetine also moderately to potently inhibit CYP2D6^{14,15}; therefore, it may be desirable to avoid their use as well in breast cancer patients receiving tamoxifen.

Antidepressants That May Be Safe

CYP2D6 inhibition with fluvoxamine, sertraline, venlafaxine, and desvenlafaxine is unlikely to be clinically significant,^{16,17} so these drugs would therefore be safer than paroxetine, fluoxetine, bupropion, and duloxetine in tamoxifen-treated patients. Mirtazapine, citalopram, escitalopram, and reboxetine are other examples of drugs that could be safer because of their low propensity to inhibit CYP enzymes.¹⁸

Additional Notes

Hertz et al⁹ observed that over 20 published studies examined the association between CYP2D6 variations and tamoxifen treatment outcomes; the results of these studies were strikingly inconsistent. Hertz et al⁹ suggested that a number of variables interplay to influence treatment results, including hormone receptor classification, menopausal status, tamoxifen combination therapy, adherence to tamoxifen, genotyping comprehensiveness, and CYP2D6 inhibitor coadministration.

Take-Home Message

Tamoxifen is a prodrug that needs to be activated by CYP2D6 for efficacy in the prevention or treatment of estrogen receptor–positive breast cancer. Therefore, antidepressants that inhibit CYP2D6 should not be prescribed to patients receiving tamoxifen. Prominent examples of such antidepressants include paroxetine, fluoxetine, bupropion, and duloxetine.

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