



Do certain SSRIs reduce the benefits of tamoxifen in breast cancer survivors?

YES This population-based cohort study found an increased risk of death from breast cancer among women who used tamoxifen and paroxetine (Paxil) concomitantly.

Kelly CM, Juurlink DM, Gomes T, et al. Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. BMJ. 2010;340:c693.

► EXPERT COMMENTARY

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Tamoxifen is widely used by women who have receptor-positive breast cancer to lower their risk of recurrence. Tamoxifen is a prodrug converted by the hepatic cytochrome P450 enzyme system (particularly isoenzyme CYP2D6) to active metabolites, which have much higher affinity for the estrogen receptor than the parent prodrug has. Selective serotonin reuptake inhibitors (SSRIs) inhibit CYP2D6 to variable degrees, with paroxetine thought to be the most potent inhibitor.

The fact that SSRIs inhibit CYP2D6 is important because as many as one in every four women who have breast cancer experiences depression as well.¹ SSRIs are widely prescribed for these patients—not only as treatment for their depressive disorder but also because the drugs have been shown to offer some relief from hot flashes.

In this cohort study from Ontario, where health care is delivered in a centralized fashion, Kelly and colleagues assessed the survival of breast cancer survivors 66 years and older who were treated with both tamoxifen and an SSRI, or with both tamoxifen and venlafaxine

(which inhibits reuptake of both serotonin and norepinephrine).

The median age of the 2,430 eligible and evaluable women at the time of tamoxifen initiation was 74 years. These women began using tamoxifen between 1993 and 2005, with a median duration of use of 4 years. Paroxetine was the most commonly used SSRI in this study (25.9%), followed by sertraline (Zoloft, 22.3%), citalopram (Celexa, 19.2%), venlafaxine (Effexor, 15.0%), fluoxetine (Prozac, Sarafem, 10.4%), and fluvoxamine (Luvox, 7.2%).

Neither duloxetine (Cymbalta) nor escitalopram (Lexapro) were included in this analysis.

By the end of follow-up, 1,074 women (44.2%) in the cohort had died, 374 of them from breast cancer.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Do not prescribe paroxetine for women who are using tamoxifen as adjuvant hormonal therapy after treatment of breast cancer. Although this study did not address the use of tamoxifen for *chemoprophylaxis* of breast cancer, it makes sense to avoid paroxetine in this setting, as well.

Because fluoxetine is known to strongly inhibit CYP2D6, other antidepressants are more prudent choices for tamoxifen users.

In addition, switch any tamoxifen user who is taking paroxetine to an alternative antidepressant. Venlafaxine may be a sound choice in this setting, given the data indicating its efficacy as a nonhormonal treatment for vasomotor symptoms in breast cancer survivors.

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FAST TRACK

As many as one in every four women who have breast cancer experiences depression as well

When taken with tamoxifen, paroxetine increased breast cancer mortality

Concomitant use of paroxetine and tamoxifen was associated with a significantly increased risk of death from breast cancer. In addition, as the proportion of concomitant use of the drugs increased to 25%, 50%, and 75% of total tamoxifen use, the adjusted risk of death increased 24%, 54%, and 91%, respectively. Among women taking tamoxifen, concomitant use of other SSRIs or venlafaxine was not associated with an increased risk of death.

Based on their data, the investigators determined that use of paroxetine during 41% of tamoxifen treatment (the median overlap observed in this study) would result in one additional breast cancer death at 5 years for every 19.7 women treated in this fashion. If paroxetine were used for the

entire duration of tamoxifen treatment—an overlap of 100%—an additional death would occur for every 6.9 women treated.

The authors also noted that fluoxetine is a “strong inhibitor” of tamoxifen, although it was not associated with an increased risk of breast cancer death in this trial. One reason may be the small number of women who took tamoxifen and fluoxetine concomitantly in this study.

“Our results should not be viewed as evidence that fluoxetine can be safely used in combination with tamoxifen,” Kelly and coworkers write. “Similarly, we cannot exclude the possibility that insufficient sample size explains the nonsignificant mortality results with other SSRIs.”

Reference

1. Fann JR, Thomas-Rich AM, Katon WJ, et al. Major depression after breast cancer: a review of epidemiology and treatment. *Gen Hosp Psychiatry*. 2008;30(2):112-126.



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