Risk of Recurrent Breast Cancer With SSRI/Tamoxifen Interaction

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The risk of breast cancer recurrence related to some SSRI antidepressants interacting with and reducing the effectiveness of tamoxifen was quantified in 2 epidemiological studies published in February.

The drug interaction was described in a review in the December Journal of Clinical Psychiatry, which noted that prescribing of antidepressants for women being treated for breast cancer is common (20% to 30%), for either depression or the hot flashes accompanying anti-estrogen treatments. The interaction occurs with inhibition of the cytochrome P-450 2D6 (CYP2D6) enzyme, which interferes with the metabolic conversion of tamoxifen to its most active metabolite, 4-hydroxytamoxifen. “Consequently,” the reviewers warn, “CYP2D6 inhibitors may increase their risk of relapse of breast cancer and death.”

In one population-based cohort study of 2430 women in Toronto treated with tamoxifen and a single SSRI in the period between 1993 and 2005, the risk of death from breast cancer after completing tamoxifen treatment during a mean 2.38-year follow-up was analyzed as a function of the proportion of the tamoxifen treatment during which an SSRI was taken. The antidepressants prescribed concurrently with tamoxifen that were analyzed in this sample were paroxetine, fluoxetine, sertraline, citalopram, fluvoxamine, and venlafaxine. Only paroxetine, an irreversible inhibitor of CYP2D6, was associated with increased risk in this study. The researchers determined 24%, 54%, and 91% increases in the risk of death from breast cancer for, respectively, 25%, 50%, and 75% absolute increases in the proportion of time of concurrent prescribing.

“We estimate that use of paroxetine for 41% of tamoxifen treatment (the median overlap in our sample) would result in one additional breast cancer death within 5 years of cessation of tamoxifen for every 19.7 . . . patients so treated,” the researchers indicated.

Although fluoxetine and its metabolites are also strong inhibitors of CYP2D6, there was no association of heightened risk with increased use of fluoxetine in this study. The researchers suggest that this may have been due to the relatively small number of women receiving fluoxetine in their sample. “Our results should not be viewed as evidence that fluoxetine can be safely used in combination with tamoxifen,” they caution.
Second study offers “alternative view” of interaction
Antidepressants that have been recommended for concurrent use with tamoxifen include citalopram and venlafaxine, because they exert relatively little activity on CYP2D6. A second epidemiological study published in February sought evidence to support the recommendation for the SSRI citalopram in a large Danish population treated with tamoxifen between 1994 and 2001, with up to a 10-year follow-up. The researchers found no increased risk of cancer recurrence with concurrent use of citalopram, as they had anticipated, but also reported a lack of association with other SSRIs. The lack of associated risk for even the antidepressants with potent CYP2D6 inhibition appears at odds with the in vivo evidence for the interaction. The researchers offer possible explanations, including the limitations of the population study in which there are various tamoxifen treatment durations, varied sample sizes with each antidepressant, and no verification of medication intake. An additional possible reason for the disparity between in vivo and epidemiological evidence, according to the researchers, is that the SSRI reduction of the plasma concentration of the tamoxifen active metabolites may not be sufficient to reduce its effectiveness. With some biomarkers unable to distinguish between the effectiveness of tamoxifen in 1 or 20 mg/d dosages, the researchers indicate, “the 3-fold reduction in the concentration of tamoxifen’s secondary metabolites associated with receipt of the SSRI paroxetine may have little consequence.” Although suggesting an “alternative view of the limited potential for CYP2D6 inhibition to interact with tamoxifen,” they stop short of advocating for concurrent use of the SSRIs that are strong CYP2D6 inhibitors and conclude only that citalopram would have “little effect, if any, on the risk of breast cancer recurrence.”

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