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Concerns Raised About Interaction of Some SSRIs, Cancer Drug

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Past APA President Michelle Riba, M.D., an expert in psycho-oncology, worries that depressed women may forgo treatment with medication if they believe that all antidepressants will negatively affect the efficacy of their cancer therapy.

Use of antidepressant SSRIs in some women using tamoxifen for breast cancer therapy may inhibit efficacy of the anticancer medication.

An accumulating body of evidence over three to five years is showing that a certain genetic polymorphism affecting metabolism of tamoxifen may result in diminished amounts of the active metabolite of that drug in women using certain SSRIs—especially fluoxetine and paroxetine.

A Food and Drug Administration (FDA) advisory committee reviewing the evidence in October 2006 agreed unanimously that the research to date was conclusive. Although the FDA has yet to act on that conclusion, there is an informal consensus among oncologists and psychiatrists who treat cancer patients that antidepressants affecting the metabolism of tamoxifen should be avoided.

The specific genetic variation that can adversely affect metabolism of tamoxifen when taken in conjunction with SSRIs is a polymorphism of the CYP2D6 gene, which is the enzyme primarily responsible for converting tamoxifen into its primary active metabolites, especially endoxifen.

N. Lynn Henry, M.D., Ph.D., is a lecturer in hematology/oncology at the University of Michigan Comprehensive Care Center. She told *Psychiatric News* that "at present, there aren't enough data to recommend determination of the CYP2D6 genotype in all women who are considering being treated with tamoxifen. However, whenever it is easy to avoid using SSRIs that completely or partially inhibit CYP2D6 activity in tamoxifen-treated patients, it makes sense to do so."

David Flockhart, M.D, a professor of medicine at Indiana University School of Medicine and a member of the FDA Advisory Committee that looked at the subject, agreed.

"If there is a possibility to use another antidepressant—such as venlafaxine, which is equally effective in terms of depression and hot flashes but does not run the risk of interfering with the efficacy of tamoxifen, it should be considered," he told *Psychiatric News*.

Flockhart expressed particular frustration at the FDA's lack of action on the matter, saying that many oncologists and breast cancer patients were worried about the interaction of antidepressants and anticancer agents.

Study Methodology Criticized

But the evidence has been muddied a bit by a least two studies questioning the relationship between CYP2D6 polymorphisms and tamoxifen metabolism—though Flockhart was critical of the methodology of the studies—and further research to elucidate the association is needed.

"This field is still a work in progress," Henry said." The studies have all been conducted fairly recently and primarily have been performed on retrospective sample sets as opposed to being performed prospectively."

Former APA President Michelle Riba, M.D., director of the psycho-oncology program at the University of Michigan Cancer Center, is concerned that depressed women may forgo treatment with medication if they believe that all antidepressants will negatively affect the efficacy of their cancer therapy.

"We are going to have to evaluate patients who are using tamoxifen for a number of years," Riba said in an interview. "We want them to come in and talk about what medications they are using. If there are possible pharmacogenetic issues, we may have to slowly titrate them to either a different dose or a different antidepressant or determine if there is an alternative to tamoxifen.

"But patients shouldn't automatically stop antidepressant therapy," she said. "There are side effects to that, and clinicians should not automatically tell patients to stop. We have to evaluate more carefully and consult with oncologists and sometimes with pharmacists."

Paroxetine, Fluoxetine Inhibit CYP2D6

Henry explained that in the case of CYP2D6, there are four groups of people: ultrarapid metabolizers (fast tamoxifen metabolizers), extensive metabolizers ("normal" metabolizers), intermediate metabolizers, and those who metabolize tamoxifen poorly or not at all."

The activity of CYP2D6 affects the metabolism of tamoxifen such that those who carry the poor metabolizer version of CYP2D6 produce very low levels of the active metabolite from tamoxifen, known as endoxifen. Some studies have suggested that being a poor metabolizer of tamoxifen means that breast cancer is more likely to recur, she said.

A few other studies suggest the opposite, however. "We aren't completely convinced yet that CYP2D6 metabolism data are sufficient, and CYP2D6 will never explain the entire story, which is why CYP2D6 genotype assessment isn't yet being routinely performed," Henry said.

The picture is further complicated by the fact that some SSRIs appear to inhibit the activity of CYP2D6, while the polymorphisms also directly affect the pharmacokinetics of most of the antidepressants.

"So even if a person is an extensive metabolizer, if she is taking a medication such as paroxetine, which is a potent inhibitor of CYP2D6, then her CYP2D6 enzyme is inactivated and she behaves more like a poor metabolizer," Henry said. "If a poor metabolizer takes an inhibitor of CYP2D6, there is no effect on the activity of CYP2D6, because she didn't have any activity to start with. Some of the antidepressants, such as sertraline, are only partial inhibitors of CYP2D6, so an extensive metabolizer would act more like an intermediate metabolizer and still have some CYP2D6 activity."

Other SSRIs such as venlafaxine don't seem to affect CYP2D6 activity at all, so that a patient's endoxifen level is presumably similar to what it would be if she weren't taking any antidepressant, Henry said.

Until there is a more definitive understanding, what should clinicians do with this information?

"In the situation where a woman must take an SSRI that affects CYP2D6 activity, then it is reasonable for the treating physician to discuss the situation with the patient's oncologist, because there may be other breast cancer treatment options available besides tamoxifen," Henry told *Psychiatric News*.

Among the studies suggesting an association between genetic variation and tamoxifen metabolism and/or between genetic variation and SSRI use concomitantly with tamoxifen are "The Impact of Cytochrome P54 2D6 Metabolism in Women Receiving Adjuvant Tamoxifen," posted at<www.ncbi.nlm.nih.gov/pubmed/17115111>;" Pharmacogenetics of Tamoxifen Biotransformation Is Associated With Clinical Outcomes of Efficacy and Hotflashes," posted at<http://jco.ascopubs.org/cgi/content/abstract/23/36/9312>;" Breast Cancer Treatment Outcome With Adjuvant Tamoxifen Relative to Patient CYP2D6 and CYP2C19 Genotypes," posted at<www.ncbi.nlm.nih.gov/pubmed/18024866>; and "CyP2D6 genotype, Antidepressant Use, and Tamoxifen Metabolism During Adjuvant Breast Cancer Treatment," posted at<http://jnci.oxfordjournals.org/cgi/content/full/97/1/30>.

Two studies that call into question the relationship between genetic variation of CYP2D6 and tamoxifen metabolism are "Geneotype of Metabolic Enzymes and the Benefit of Tamoxifen in Post-Menopausal Breast Cancer Patients," posted at<www.ncbi.nlm.nih.gov/pubmed/15987423>, and "Genetic Variants of CYP3A5, CYP2D6, SULT1A1, UGT2B15, and Tamoxifen Response in Postmenopausal Breast Cancer Patients," posted at<http://breast-cancer-research.com/content/9/1/R7>.▪

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