

# Beware of CYP2D6 Inhibitors in Patients Taking Tamoxifen

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Tamoxifen is a commonly used drug in the treatment of breast cancer, but growing evidence is suggesting that it may not work well in the presence of some other medications. This is an important issue, because reduced tamoxifen efficacy may lead to earlier recurrence of the cancer and reduced duration of survival.

Tamoxifen metabolism is complex, but it is known that CYP2D6 is necessary to form the 2 most important active metabolites. Thus, a patient taking a CYP2D6 inhibitor along with tamoxifen may have reduced tamoxifen efficacy. Tamoxifen also is metabolized by CYP3A4, but because CYP2D6 is the enzyme responsible for producing the active metabolites, inhibition of CYP3A4 activity does not appear to be as important as CYP2D6.

Some evidence suggests, however, that enzyme *inducers* may increase the glucuronide metabolism of the most important active metabolite, so consider the possibility that enzyme inducers such as rifampin also may reduce tamoxifen efficacy.

## What About Genetic CYP2D6 Deficiency?

This also is a potential problem and has received considerable attention. Evidence from several tamoxifen studies in breast cancer patients suggests that cancer recurrence rates are higher in patients with genetically decreased CYP2D6 activity. Although some studies failed to show this relationship,

they were flawed because they failed to account for medications that inhibit CYP2D6. At this point, we should assume that genetically determined CYP2D6 activity is an important factor in tamoxifen treatment.

## What Drugs Inhibit CYP2D6?

Many drugs are CYP2D6 inhibitors, but antidepressants are probably the most important drugs in patients receiving tamoxifen. Estimates suggest that up to nearly a third of patients on tamoxifen are also taking antidepressants. Fluoxetine (Prozac), paroxetine (Paxil), bupropion (Wellbutrin), and duloxetine (Cymbalta) can substantially inhibit CYP2D6 and may reduce tamoxifen efficacy. Other antidepressants are weaker inhibitors of CYP2D6, such as citalopram (Celexa), escitalopram (Lexapro), desvenlafaxine (Pristiq), and sertraline

(Zoloft). Although they are probably preferable to the more potent CYP2D6 inhibitors, theoretically they might inhibit tamoxifen in some patients. Venlafaxine (Effexor) seems to have little or no effect on CYP2D6. Other drugs that inhibit CYP2D6 can be found in the Table. (Note that modest inhibitors of CYP2D6 such as cimetidine and sertraline are not included in the Table.)

Some OTC antihistamines such as diphenhydramine (Benadryl) inhibit CYP2D6, so one may not be able to rely on computerized drug interaction screening systems (which may not contain OTC medications) to catch all CYP2D6 inhibitors in patients on tamoxifen.

## Recommendations

Because the potential outcome of these interactions is so serious, it is important to counsel patients on tamoxifen about CYP2D6 issues.

For patients receiving (or about to receive) tamoxifen, screen their current medications carefully for drugs that inhibit CYP2D6. The Table would be a good start, but these lists change over time with new research and new drugs on the market. Consult a current list to find CYP2D6 inhibitors.

Patients receiving tamoxifen should be advised not to start any new medications (prescription or OTC) without someone checking to make sure it is not a significant CYP2D6 inhibitor.

It would be prudent to ask patients on tamoxifen if they have discussed the CYP2D6 issue with their physician. A growing consensus suggests that every patient taking tamoxifen should have testing to determine his/her CYP2D6 genotype. This genetic testing is commercially available, and—although it is not cheap—it is apparently covered by at least some insurance plans. ■

## Table

### CYP2D6 Inhibitors

- Amiodarone (Cordarone)
- Bupropion (Wellbutrin)
- Chlorpheniramine (Chlor-Trimeton)
- Chloroquine (Aralen)
- Chlorpromazine (Thorazine)
- Cinacalcet (Sensipar)
- Diphenhydramine (Benadryl)
- Duloxetine (Cymbalta)
- Fluoxetine (Prozac)
- Halofantrine (Halfan)
- Haloperidol (Haldol)
- Imatinib (Gleevec)
- Paroxetine (Paxil)
- Perphenazine (Trilafon)
- Propafenone (Rythmol)
- Propoxyphene (Darvon)
- Quinacrine (Atabrine)
- Quinidine (Quinidex, etc)
- Quinine
- Terbinafine (Lamisil)