Tamoxifen Metabolism, SSRIs, and the Cancer Patient

For patients with comorbid medical conditions, knowledge of drug metabolism is important and may in fact be critical in the oncology setting. "As physicians, we need to know everything about our patients that we can," said David Flockhart, MD, PhD, Indiana University School of Medicine, Indianapolis, IN. At the very least, it is important to know what medications they are currently taking.

A case in point is the widespread use of the anti-estrogen compound tamoxifen, which acts via estrogen receptor (ER) modulation. Tamoxifen is highly effective in the prevention of breast cancer in ER-positive women and is used both as adjuvant therapy against cancer recurrence and as a prevention measure for those who are considered to be at high risk for disease. Unfortunately, one of the more common adverse events that occur with this drug is hot flashes, a condition that is uncomfortable to the point of discouraging long-term treatment adherence. An attempt to resolve this discomfort may result in additional unforeseen risk.

To illustrate this point, Dr. Flockhart presented a case report of a 45-year-old woman with tamoxifen-related hot flashes and comorbid depression who was prescribed paroxetine. Within a week, the hot flashes resolved; the hot flashes resumed when she was taken off paroxetine. "Now, paroxetine's effect on depression takes much longer than a week, so there's something else going on here." The working hypothesis was that paroxetine had somehow interfered with the anti-estrogen activity of tamoxifen, either by preventing absorption, which seemed unlikely, or by altering the transformation of tamoxifen into its active metabolite, endoxifen. "We were lucky to have chromatograms of this woman before and after peroxetine administration," said Dr. Flockhart, and analysis of these data showed an obvious decrease in endoxifen concentrations. "We were very interested in this. There is some sort of decreased activity in this woman when she's taking paroxetine."

Cytochrome P450 enzyme activity was the most likely suspect—specifically, subtype CYP2D6, a site of metabolism for multiple commonly prescribed drugs. Prior investigations confirm that paroxetine inhibits this enzyme, but the extent and therapeutic impact of inhibition are unclear. In a small study of 12 women with tamoxifen-induced hot flashes, Dr. Flockhart, using a combination of serum concentration and genetic analysis, was able to determine that the effect of paroxetine/CYP2D6 downregulation was so pronounced, it nearly matched the lack of activity seen in women who had a mutant, non-functioning form of the enzyme [*J Natl Cancer Inst* 2003].

This observation was cause for great concern. An estimated 30% of tamoxifen-treated patients are prescribed antidepressants for depression or hot flashes. Were other SSRIs placing them at risk? One answer came from Jin et al, who investigated the plasma concentrations of endoxifen in patients who were concomitantly using one of 3 different SSRIs. Inhibition of the CYP2D6 enzyme was determined and ranked as follows: paroxetine > sertraline > venlafaxine [*J Natl Cancer Inst* 2005].

Highlights from the
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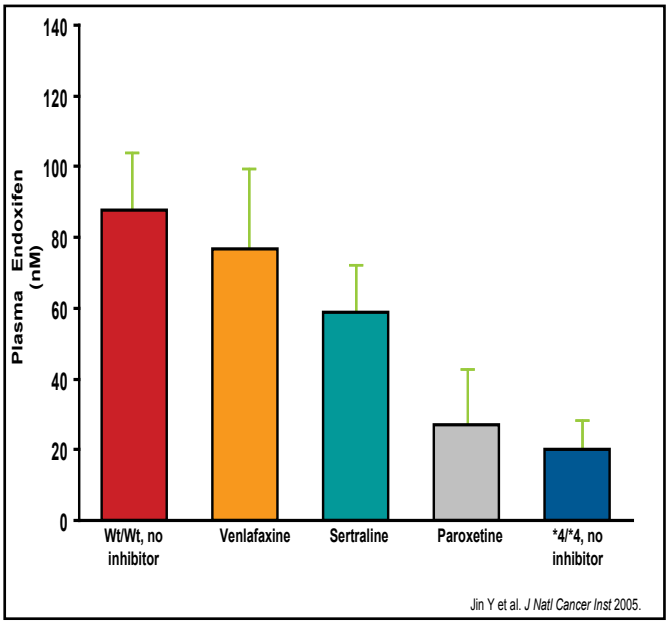
Commenting on these results, Dr. Flockhart noted that venlafaxine can be effectively used to treat tamoxifen-related hot flashes while retaining tamoxifen protection. "This can improve compliance with this very effective medication" and thereby have a direct impact on long-term survival. Other investigators have carried these observations forward, and there is now consensus that the following agents are potent inhibitors of CYP2D6 and should not be prescribed with tamoxifen: bupropion, fluoxetine, and paroxetine (Figures 1 and 2).

Figure 1. Partial List of Common CYP2D6 Inhibitors.

- **Strong (should be avoided in women taking tamoxifen)**
  - **Paroxetine (Paxil)**
  - **Fluoxetine (Prozac)**
  - **Bupropion (Wellbutrin)**
- **Moderate**
  - **Sertraline (Zoloft)**
  - **Duloxetine (Cymbalta)**
  - **Citalopram (Celexa)**
  - **Escitalopram (Lexapro)**
  - **Celecoxib**
  - **Diphenhydramine**
  - **Chlorpheniramine**
- **Weak Inhibitors**
  - **Venlafaxine (Effexor)**
  - **Desvenlalfaxine (Pristiq)**

Figure 2. Inhibition of CYP2D6 Affects Endoxifen Concentrations.



High-Tech Exposure Therapy for PTSD

Post-traumatic stress disorder (PTSD) first gained public awareness after the Vietnam War, as large numbers of returning veterans presented with depression and problems with substance abuse, which occur frequently with PTSD, and either a lack of or inappropriate emotional responses. As the Iraq War grinds into its fifth year, it's not surprising that PTSD has regained the headlines. Bringing a high-tech solution to this latest battlefield is Barbara Olasov Rothbaum, PhD, ABPP, Emory School of Medicine, Atlanta, GA.

Dr. Rothbaum first gained an understanding of the onset of PTSD. Plotting the course of PTSD after trauma exposure, Dr. Rothbaum assessed female rape victims on a weekly basis for a total of 12 weeks following their assault. Results showed that in the first week, 94% met symptomatic criteria for PTSD. "This indicates that this is the normal response to trauma," said Dr. Rothbaum. "What we wanted to figure out is when a normal response to trauma ends and when a pathopsychological response that requires diagnosis and treatment begins." While all subjects showed improvement after 4 weeks, a subset of patients stalled in their recovery. "We now see PTSD as a disorder of extinction. So, what you want to do is extinction training through exposure therapy—therapeutic exposure."

Therapeutic exposure can be imaginary, wherein the patient recalls the trauma in the present tense, or in vivo, where the site of the trauma is actually revisited; thanks to advances in technology, the trauma also can be virtually recreated. This technique, called virtual reality (VR), reasonably creates all the sensory inputs of sight, sound, vibration, and even smell of an actual traumatic setting. First used to treat Vietnam veterans, VR applications have expanded to include treatment for social disorders, fear of heights, and fear related to the events of 9/11.

VR is currently used in conjunction with relaxation techniques, education, and cognitive therapy, but Dr. Rothbaum is investigating the use of pharmacotherapy to enhance the efficacy of VR therapy. The investigative drug is D-cycloserine (DCS), an older antibiotic that has been shown to be a potential cognitive enhancer, facilitating extinction of the fear response in animal studies. Dr. Rothbaum first used DCS to help patients who had a fear of heights [*Arch Gen Psychiatry* 2004] and was eager to try it with veterans who were returning from Iraq.