Tamoxifen Relieves Symptoms of Mania in Bipolar Disorder Trial

BY JANE SALODOF MACNEIL
Southwest Bureau

PARIS — Tamoxifen, a drug that is widely used in the treatment of breast cancer, significantly reduced the manic symptoms of bipolar disorder in a randomized, placebo-controlled trial presented in a breaking news session at the annual congress of the European College of Neuropsychopharmacology.

Dr. Aysegul Yildiz-Yesiloglu reported that 14 of 29 acutely ill patients had at least a 50% reduction in their scores on standard measures of mania with tamoxifen treatment. Only 1 of 21 patients improved on placebo during the 3-week trial. Depressive symptoms were not affected.

Although tamoxifen use in breast cancer is based on its antiestrogen effects, the investigators were drawn to the drug's activity as a protein kinase C (PKC) inhibitor, according to Dr. Yildiz-Yesiloglu, of Dokuz Eylul University in Izmir, Turkey, where the study was conducted.

She said the researchers hypothesized that inhibiting the PKC pathway could be important in bipolar disorder because lithium and valproate interfere with PKC signaling. For reasons not well understood, both mood stabilizers can reduce mania despite being structurally different.

Tamoxifen was chosen for the trial because it is the only direct PKC inhibitor approved for use in humans. It had been well tolerated in a pilot study that reported amelioration of manic symptoms in five of seven bipolar patients in the neuropsychiatric research unit at the Detroit Medical Center (Arch. Gen. Psychiatry 2000;57:95-7).

Dr. Yildiz-Yesiloglu, currently at Harvard Medical School in Boston, and her colleagues randomized 67 manic patients in the double-blind study. All had provided written consent together with at least one first-degree relative.

Researchers focused on tamoxifen because of its activity as a protein kinase C inhibitor.

DR. YILDIZ-YESILOGLU

Six patients in the tamoxifen group and 11 patients in the placebo group dropped out because of severity of symptoms. This left 29 patients randomized to tamoxifen and 21 to placebo who completed the trial. To counteract any potential bias, Dr. Yildiz-Yesiloglu said the researchers performed secondary linear mixed-model analyses, incorporating all patients and all observations up to the point a person who dropped out left the study.

Patients started on 20 mg of tamoxifen twice daily, and the dose was increased up to 40 mg twice daily. The only psychotropic agent they could use during the study was lorazepam as a rescue medication for anxiety. The number of tablets used declined significantly over the course of the study in patients treated with tamoxifen but not in those in the placebo group.

Mania scores began dropping within 2 weeks of the start of tamoxifen treatment on both the Young Mania Rating Scale and the Positive and Negative Syndrome Scale. The improvements observed over 3 weeks with both scales were highly significant statistically, compared with placebo.

Scores on the Hamilton Rating Scale for Depression showed no improvement with tamoxifen or placebo and no difference between the two groups.

Most adverse events were minor and did not include the hormonal effects common in breast cancer patients taking tamoxifen as an adjunct therapy. "For long-term use, there are some side effects that we would expect, but for 21 days' use we would expect only some flushing on the face and maybe some small acne reaction," Dr. Yildiz-Yesiloglu said in an interview after her presentation.

The Stanley Medical Research Institute in Chevy Chase, Md., financed the study, which received no drug company funding. Dr. Yildiz-Yesiloglu said that the outcome supports further investigation of the PKC pathway as a target for drugs treating bipolar disorder. ■

Quetiapine Okayed For Treatment of Bipolar Depression

BY ELIZABETH MECHCATIE
Senior Writer

Quetiapine has been approved for the treatment of major depressive episodes associated with bipolar disorder.

The approval for this indication was made by the Food and Drug Administration based on two 8-week double-blind, placebo-controlled studies of more than 1,000 outpatients.

Quetiapine (Seroquel), an atypical antipsychotic marketed by AstraZeneca, was first approved for treating schizophrenia in 1997 and is now also approved for treating acute manic episodes associated with bipolar I disorder (as either monotherapy or adjunct therapy to lithium or divalproex).

The most recent approval cited the two BOLDER (BipOLar DEpRession) studies of 1,045 outpatients with bipolar I or II disorder, including those with or without a rapid cycling course. Investigators found that patients on 300 mg or 600 mg quetiapine once a day showed improvements in depressive symptoms starting the first week of treatment through 8 weeks that were "superior" to improvements seen among placebo-treated patients, in terms of the reduction in scores on the Montgomery-Asberg Depression Rating Scale, according to the revised package label.

Patients on the 600 mg dosage showed no additional benefit, so the recommended dosage is 300 mg once a day.

In addition, those on 300 mg showed significantly greater improvements in overall quality of life and satisfaction, related to various areas of functioning.

Dry mouth, sedation, somnolence, dizziness, and constipation were the most common adverse events in the bipolar depression studies, according to AstraZeneca. ■

Treat Anxiety in Patients With Depressive, Bipolar Disorders

BY JANE SALODOF MACNEIL
Southwest Bureau

SANTA FE, N.M. — Anxiety disorders are a common comorbidity that lead to worse outcomes for patients with major depressive and bipolar disorders, speakers warned at a psychiatric symposium sponsored by the University of Arizona.

Dr. A. John Rush reported that more than half, 53%, of 2,876 depressed patients in the first phase of the STAR*D trial had anxious depression (Am. J. Psychiatry 2006;163:28-40).

Anxious patients were significantly less likely to achieve remission on their first medication for depression (odds ratio 0.77), according to Dr. Rush, principal investigator of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial.

Each of the comorbid anxiety disorders was associated with a lower remission rate. Posttraumatic stress disorder (PTSD) had the most negative effect (OR 0.6). Only social phobia did not have a significant impact, though it also reduced the odds of remission (OR 0.87).

"A person coming in with anxiety disorder takes longer and is less likely to remit," said Dr. Rush, a distinguished professor in mental health at the University of Texas Southwestern Medical Center in Dallas.

About half of bipolar depression patients also had an anxiety disorder, according to an analysis of the first 500 patients in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trial, another large multicenter study supported by the National Institute of Mental Health. Lifetime prevalence was 51%, and 31% had a current anxiety disorder when they entered the study.

Bipolar patients with comorbid anxiety were significantly more likely to have a history of suicide attempts, said Dr. Gary Sachs, principal investigator of STEP-BD and director of the Bipolar Clinic and Research Program at Massachusetts General Hospital in Boston.

The rate of suicide attempts was 52% in patients with lifetime anxiety disorder, compared with 22% in patients who did not have a history of anxiety disorder. The highest rate, 65%, was in patients with a history of posttraumatic stress disorder (Am. J. Psychiatry 2004;161:2222-9).

Bipolar patients with lifetime anxiety disorders also had an earlier age of bipolar onset, 15.6 years vs. 19.4 years in patients who did not have a history of anxiety disorder, Dr. Sachs said at the meeting, which also was sponsored by the University of Texas Southwestern Medical Center at Dallas and the University of New Mexico.

Length of recovery was shorter as well in patients with a history of anxiety disorder. Their longest mean period of euthymia was 183 days, compared with 254 days for patients without lifetime anxiety.

Dr. Murray B. Stein called for greater efforts to treat comorbid anxiety in patients with mood disorders. About 50%-60% of people with mood disorders also have an anxiety disorder, according to Dr. Stein, director of the Anxiety and Traumatic Stress Disorders Program at the University of California, San Diego. Conversely, he estimated that 80%-90% of people with general anxiety disorder will also have major depression at some point, and most had the anxiety disorder first.

Though anxiety is an early-onset disorder, he noted that it is rarely studied in children. In one of the few studies that did so, he said, nearly two-thirds of children with social anxiety disorder responded to a selective serotonin reuptake inhibitor (SSRI), and nearly as many went into remission.

Most antidepressants relieve symptoms in adult patients with anxiety disorders, Dr. Stein said, possibly because they treat both syndromes. "You get some benefit, but you don't get a really robust response," he said of SSRIs used in PTSD. Though SSRIs have been shown to be better than placebo for general anxiety disorder, he said the benefit likewise was not robust.

As benzodiazepines are effective for anxiety disorders, he suggested they might also treat depression. "We were taught it is important to separate anxiety and depression because benzodiazepines could make people worse. I don't think there are any data that benzodiazepines make people worse."

Other classes of medication, including anticonvulsants, are sometimes used for resistant anxiety disorders, but Dr. Stein said more information is needed about their safety and effectiveness.

Cognitive-behavioral therapy should be considered as an adjunct or an alternative to medication for anxiety disorders, he added. "The best cognitive-behavioral therapy is as good as the best medication we can provide." ■