Dual Drug Improves Symptoms of Fibromyalgia

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CHICAGO — Milnacipran, the first in a new class of dual norepinephrine and serotonin reuptake inhibitors, significantly improved the multiple core symptoms of fibromyalgia regardless of severity of baseline depressive symptoms in a double-blind 888-patient clinical trial.

The tripartite composite study end point required concurrent 30% or greater improvement in pain scores in a daily diary, plus patient self-assessment as "much improved" or "very much improved" in global disease state, along with significantly improved physical functioning.

All three elements of the end point were achieved at 3 months by 33% of milnacipran-treated patients, regardless of whether assigned to 100 mg/day or 200 mg/day. This was significantly better than the 17% placebo response, Peter Werner, Ph.D., reported at the annual American Psychiatric Association's Institute on Psychiatric Services.

Improvements in pain scores became significant after just 1 week of treatment with milnacipran, added Dr. Werner of the Forest Research Institute, Jersey City, N.J.

The trial's sponsors, Forest Laboratories and Cypress Bioscience, have filed for Food and Drug Administration marketing approval for milnacipran with an indication for fibromyalgia. A decision is expected imminently, Dr. Werner said in an interview. "I'm reasonably optimistic. The efficacy data are good; the safety is good."

In 2007, pregabalin (Lyrica) became the first drug to receive an indication for fibromyalgia. It was joined last June by duloxetine (Cymbalta).

The original end point in the milnacipran trial had to be changed while the study was underway to conform to revised FDA guidelines for consideration of proposed fibromyalgia therapies. The physical function component of the revised composite end point required at least a 6-point improvement over baseline on the Short Form–36 Physical Component Summary Score.

Milnacipran is approved in Europe and Asia under the trade name Ixel for treatment of depression. One purpose of the current study was to demonstrate that the drug's benefit in fibromyalgia patients does not stem only from its antidepressant action.

To accomplish this, participants were stratified based on their baseline Beck Depression Inventory scores. Among those with a baseline BDI of 0-9, indicating no or minimal depressive symptoms, the proportion who rated themselves as globally much or very much improved after 3 months of treatment was 49% with milnacipran at 200 mg/day, 61% with milnacipran at 100 mg/day, and 33% with placebo.

Among the largest patient subgroup—those with mild to moderate depressive symptoms at baseline as defined by a BDI of 10-18—the proportion rating themselves as globally much or very much improved was 61% with milnacipran at 200 mg/day, 52% with the same drug at 100 mg/day, and 42% with placebo.

And in those with moderate to severe depression as indicated by a BDI greater than 18, the improvement rates were 52%, 43%, and 38%, respectively. That's a smaller difference in response rate between patients on milnacipran at 100 mg/day and placebo than seen in less severely depressed or nondepressed patients, suggesting that those with more severe depressive symptoms may require a higher dose of milnacipran to experience significant improvement in their fibromyalgia.

Most side effects were mild to moderate. The most common were nausea, reported by 40% on milnacipran at 200 mg/day, 33% on 100 mg/day, and 21% on placebo, followed by headache, which affected 18%, 16%, and 12%, respectively. Constipation was reported by 14% on milnacipran at 200 mg/day, 18% on 100 mg/day, and 3% on placebo.

Hypertension occurred in 4% of patients on milnacipran at 200 mg/day, 5% of those on 100 mg/day, and 2% of those on placebo. An increase in heart rate was noted in 7% on high-dose milnacipran and in 5% on low-dose milnacipran, compared with 2% of controls.

Study discontinuation because of adverse events occurred in 19.6% of patients assigned to milnacipran at 100 mg/day, 27.2% of those on 200 mg/day, and 10.8% of those on placebo. ■