Small Benefit of SNRIs for Fibromyalgia Pain

Pauline Anderson

Feb 28, 2013

Compared with placebo, the selective serotonin and noradrenaline reuptake inhibitors (SNRIs) duloxetine (*Cymbalta*) and milnacipran (*Savella*) are slightly more likely to reduce pain in patients with fibromyalgia syndrome (FMS), according to a new Cochrane meta-analysis. However, they're not substantially superior in terms of reducing fatigue and sleep problems or in improving quality of life, and they appear to cause more adverse effects.

If patients do get pain relief from one of the SNRIs, it's likely to be only slight, and it's not clear how long that relief might last, said study author Brian T. Walitt, MD, associate professor, medicine, Georgetown University, Washington, DC.

Dr. Walitt stressed that fibromyalgia encompasses more than just pain. "And considering that these drugs don't really do much for any other aspect of a patient's life, the value of these medications seems small at best."

Both patients and doctors lean too heavily on drugs to find answers to the troubling symptoms associated with fibromyalgia, Dr. Walitt said. "The medical model relies on these drugs to do the heavy lifting for the treatment of fibromyalgia and studies such as this one suggest that this is a failed strategy."

But other suggested modes of therapy — cognitive-behavioral therapy (CBT) and exercise — have not been proven to be effective in fibromyalgia, said Dr. Walitt.

The review was published online January 31 in *The Cochrane Library*.

Small Incremental Effect

The analysis included 10 studies (all sponsored by pharmaceutical companies) with 6038 patients. Five studies investigated milnacipran against placebo, and 5 investigated duloxetine against placebo, for up to 6 months.

Most of the patients were aged 47 to 51 years and most were women — not surprising, since 80% of the estimated 5 million Americans with fibromyalgia are women.

The study found that duloxetine and milnacipran had a small incremental effect compared with placebo in reducing pain (standardized mean difference [SMD], -0.23; 95% confidence interval [CI], -0.29 to -0.18; 6.1% relative improvement). There were 192 per 1000 patients in the placebo groups reporting at least a 50% pain reduction compared with 280 per 1000 of those receiving an SNRI (risk ratio, 1.49; 95% CI, 1.35 - 1.64).

"The data says that for every 11 people with fibromyalgia that you treat with 1 of these drugs, 1 of them will have a good outcome in terms of a worthwhile pain relief," said Dr. Walitt. "About the same number need to be treated to have a serious adverse event."

Duloxetine was superior to milnacipran in reducing pain.

The authors noted that although these drugs led to a moderately important pain reduction, placebo also reduced pain, albeit minimally. Placebo response rates tend to be elevated in trials assessing subjective symptoms, such as depression and anxiety, as well as fibromyalgia, said Dr. Walitt.

The study found that the effect of the SNRIs in reducing fatigue (SMD, -0.14; 95% CI, -0.19 to -0.08; 2.5% relative improvement) and quality of life (SMD, -0.20; 95% CI, -0.25 to -0.14; 4.6% relative improvement) were not substantial compared with placebo. And the drugs were not superior to placebo in reducing sleep problems (SMD, -0.07; 95% CI, -0.16 to 0.03; 2.5% relative improvement).

The dropout rate due to adverse events was significantly higher for duloxetine and milnacipran than for placebo (196 per 1000 vs 107 per 1000). Nausea, dry mouth, constipation, headache, dizziness, and insomnia were the most frequently reported symptoms leading to stopping medication.

The recommended doses are 60 mg/d for duloxetine and 100 mg/d for milnacipran. The authors noted that higher doses are not more efficacious and are associated with more adverse events.

Both drugs have been approved for treatment of FMS in the United States, but not in Europe. A third drug — pregabalin (*Lyrica*) — has also been approved by the Food and Drug Administration for the treatment of fibromyalgia.

Dr. Walitt criticized advertisements depicting seemingly healthy women whose fibromyalgia disappeared after taking an SNRI. This study might help physicians discuss more realistic expectations with their patients, he said.

Multimodal Approach

Current guidelines recommend using a combination of pharmacologic therapy with aerobic exercise and psychological therapies, such CBT, to treat fibromyalgia, but this "multimodal" approach has not been proven to be particularly effective in treating fibromyalgia symptoms, said Dr. Walitt. Because there is such a lack of proven therapies, and because CBT and exercise are time-consuming and not well compensated, the treatment approach will always favor drugs, said Dr. Walitt.

Research shows that fibromyalgia symptoms change in small amounts over time but few people get substantially better, no matter what they do, said Walitt. "These problems don't go away. The truth is that nothing really works."

Patients who seem to fare the best are those who "take stock of their lives, sort of accept that they have this issue, and make adjustments to their life and way of being," said Dr. Walitt.

The applicability of the evidence from the meta-analysis is strongly limited because the studies were performed in research centers rather than in routine clinical care.

> These problems don't go away. The truth is that nothing really works.
> Dr. Brian T. Walitt

As well, the exclusion criteria were strict (eg, participants were not allowed to take some defined concomitant medications for their FMS symptoms), and most participants were middle-aged women.

Future clinical trials should focus on a better understanding of the neuroanatomy behind fibromyalgia and the biology driving the "persistent and bothersome" experiences faced by patients with the disease, said Dr. Walitt.

He believes that research will eventually prove some of the current thinking about the disorder to be wrong. For example, the theory of central sensitization — that patients with fibromyalgia have a lower threshold for pain because of increased brain sensitivity to pain signals — "may not be as true as is believed."

Analysis "'Much Needed"

Asked for her views on the analysis, Ann Vincent, MD, medical director, Fibromyalgia Clinic, Mayo Clinic, Rochester, Minnesota, said that it was "much needed and well-done" and that it "highlights the small analgesic benefit of SNRIs" for patients with fibromyalgia.

"The results can guide pharmacological therapy for pain in this null population," said Dr. Vincent. "The small benefit of SNRIs on pain needs to be balanced with their adverse effects in patients with fibromyalgia, who frequently have multiple medication sensitivities."

Dr. Vincent added that she did not find the results surprising because she regularly observes these outcomes in her clinical practice.

She agreed with the authors that a physician should engage a patient in a frank discussion about the potential benefits and harms of both of these drugs.

Matching the right patients to the right medication "is always the challenge," commented Dr. Vincent.

Dr. Walitt received a consulting fee from Jazz Pharmaceuticals and was a site investigator for a milnacipran trial. For conflict of interest information on other authors, see original paper. Dr. Vincent has disclosed no relevant financial relationships.

Cochrane Library. 2013, Issue 1. Abstract

Latest in Neurology & Neurosurgery

AAN Releases New Sports Concussion Guidelines

What's Hot at AAN 2013?

Mixed Messages on New Bleeding Data With Dabigatran

Value of MRI Assessment in Sciatica Questioned

AAN Takes a Position on 'Neuroenhancement' in Children