

# A New Option for the Treatment of Fibromyalgia

By Michael Lemon, PharmD

**F**ibromyalgia syndrome is a complex, chronic condition causing widespread musculoskeletal pain that is persistent but usually varying in intensity. Patients might also experience fatigue, sleep disturbances, headaches, anxiety, cognitive difficulties, paresthesias and multiple tender points.<sup>1</sup> Fibromyalgia most commonly affects women and is thought to affect about three to six million people in the United States.<sup>2</sup> The pathophysiology of fibromyalgia is unknown, but it may involve dysregulation of neurotransmitters and central pain sensitization.<sup>1,3</sup> Many pharmacologic and nonpharmacologic therapies have been used in the treatment of fibromyalgia with varying degrees of success.

The current treatment of fibromyalgia is targeted to provide pain relief, improve sleep and improve physical functioning. The best treatment regimen for a patient with fibromyalgia usually involves both pharmacologic and nonpharmacologic interventions. Nonpharmacologic interventions with the strongest evidence for efficacy include exercise and cognitive behavioral therapies.<sup>4</sup> Pharmacological options that have been tried include antidepressants, muscle relaxants, tramadol, anticonvulsants, corticosteroids, melatonin, nonsteroidal anti-inflammatory agents, opioids and thyroid hormone. A key feature of medications with strong efficacy in the treatment of fibromyalgia is the ability to affect neurotransmitters such as serotonin, norepinephrine and substance P.<sup>4</sup> The tricyclic antidepressant (TCA) amitriptyline in doses of 25 to 50 mg at bedtime has demonstrated efficacy in the treatment of fibromyalgia in the areas of pain relief and improvement in sleep.<sup>4</sup> Cyclobenzaprine, which is structurally similar to the TCAs, in doses of 10 to 40 mg has also been shown to improve sleep and decrease pain.<sup>4</sup> Both of these agents are considered first-line therapy in the treatment of fibromyalgia.<sup>4</sup> The selective serotonin and norepinephrine reuptake inhibitors (SNRI) duloxetine and venlafaxine have also demonstrated modest efficacy in the treatment of fibromyalgia and may be considered second-line agents.<sup>4</sup> Tramadol, which is a weak, centrally acting mu agonist that also inhibits the reuptake of serotonin and norepinephrine,

has also demonstrated moderate evidence of efficacy in the treatment of fibromyalgia.<sup>4</sup> Finally, the anticonvulsant gabapentin was found safe and effective for the treatment of fibromyalgia in doses of 1,800 to 2,400 mg daily in one randomized trial.<sup>5</sup> However, none of these medications have Food and Drug Administration (FDA) approval for the treatment of fibromyalgia, and currently, no evidence of efficacy in the treatment of fibromyalgia is available for corticosteroids, melatonin, nonsteroidal anti-inflammatory drugs, opioids and thyroid hormone.<sup>1</sup> In June 2007, pregabalin (Lyrica) received FDA approval for the treatment of fibromyalgia, making it the first medication approved for the treatment of fibromyalgia.<sup>6</sup>

The exact mechanism of action of pregabalin in the treatment of fibromyalgia is not known. In the central nervous system, pregabalin binds to the alpha2-delta subunit of voltage-gated calcium channels.<sup>7</sup> As a result of this binding, levels of glutamate, norepinephrine and substance P are reduced, which may result in the analgesic and anxiolytic properties of pregabalin. The most common adverse events with pregabalin include dizziness, somnolence, dry mouth, edema, blurred vision, weight gain and difficulty concentrating. Pregabalin is excreted unchanged in the urine and no drug interactions have been reported. Warnings and precautions include a risk of angioedema, peripheral edema, and impairment of the ability to drive as a result of somnolence and dizziness. Patients should be cautioned regarding abrupt discontinuation because withdrawal symptoms of insomnia, nausea, headache and diarrhea have occurred. It is recommended to taper the medication over a minimum of one week. Pregabalin is a schedule V controlled substance due to reports of "good drug effect," "high," and "liking" in a small study of recreational users of sedative hypnotic drugs when comparing pregabalin to 30 mg of diazepam. The usual dose of pregabalin for the treatment of fibromyalgia is 300 to 450 mg per day in two divided doses, given without regard to food. Dosing begins with 75 mg twice a day and may be increased within one week to 150 mg twice a day. Doses above 450 mg per day were associated with increased side

effects and less tolerability.

Currently, efficacy trials used to approve pregabalin in the treatment of fibromyalgia have not been published. In the first trial, pregabalin doses of 300, 450 and 600 mg per day were studied in a randomized, double-blind, placebo-controlled trial lasting 14 weeks.<sup>7</sup> The study demonstrated improvements in the patient global response, which was 47.6 percent in the placebo and 68.1 percent in the 300 mg, 77.8 percent in the 450 mg and 66.1 percent in the 600 mg dosages. An increase in adverse reactions was noted in the 600 mg group. The second study was a six-month withdrawal study with a primary endpoint of time to loss of therapeutic response. In this study, patients were titrated over six weeks to pregabalin dosages of 300, 450 or 600 mg daily. Following the six-week phase, patients were randomized to the active treatment or placebo. The study demonstrated that 53 percent of the patients in the pregabalin group versus 33 percent of the placebo group remained on their study drug and maintained a therapeutic response to Week 26 of the study.

The only currently published study was an eight-week randomized, double-blind, placebo-controlled trial comparing placebo to pregabalin in doses of 150, 300 and 450 mg/day.<sup>8</sup> Only the 450 mg/day dose produced statistically significant pain relief through Week 7 of the trial compared to placebo. However, at Week 8, the statistically significant difference was not apparent in pain relief. Significant improvements in sleep quality, fatigue and global measures of change were demonstrated in the 300 and 450 mg/day doses. The authors speculated that the decrease in effectiveness seen at Week 8 may have been caused by a reduced statistical power at a time point later in the study, comparison to a placebo group where many patients responded to placebo, symptom fluctuation and possibly a loss of analgesic effect based on the duration of the study.

Although pregabalin has FDA approval for the treatment of

fibromyalgia, it may not be the first-line agent used in many patients. Reasons include the potential for waning efficacy over time and its cost compared to amitriptyline and cyclobenzaprine. Based on the evidence, amitriptyline and cyclobenzaprine may still be used first line. If those agents fail, then other agents with moderate to strong evidence of efficacy, including pregabalin, could be considered. The true place in therapy for pregabalin is likely to evolve with updated fibromyalgia treatment guidelines and clinical experience.

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