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Pregabalin for fibromyalgia: Some relief but no cure

ABSTRACT

What is the role of pregabalin (Lyrica) in the treatment of fibromyalgia? In this article the authors explore the putative pathophysiology of fibromyalgia, pregabalin's mechanism of action and evidence of efficacy, and its emerging role in treating this challenging disease.

KEY POINTS

Several lines of evidence point to functional abnormalities in the central nervous system as being responsible for fibromyalgia.

Clinical trials found pregabalin superior to placebo. Nevertheless, patients need to have reasonable expectations of its possible benefit.

In most patients with fibromyalgia, a multidisciplinary approach is used to treat pain, sleep disturbance, and fatigue, along with comorbidities such as neurally mediated hypotension and psychiatric disorders.

Research with pregabalin enhances our understanding of fibromyalgia and may point the way to future treatments.

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PREGABALIN (Lyrica) is a novel analogue of the neurotransmitter gamma aminobutyric acid (GABA) with analgesic, anticonvulsant, and anxiolytic activity. Its approval by the US Food and Drug Administration (FDA) in 2007 for the treatment of fibromyalgia made it the first drug approved for this indication. Until then, management of fibromyalgia entailed drugs to treat pain, sleep, fatigue, and psychological disorders, and a strong emphasis on exercise and physical therapy.

Those who still question the validity of fibromyalgia as a diagnosis object to drug companies "benefiting" from the sale of such drugs.[1] But many hail pregabalin as an important advance in our understanding of the pathogenesis of fibromyalgia and how to treat it. A key question remains: How will pregabalin fit into the treatment of this often-challenging disease?

FROM FIBROSITIS TO FIBROMYALGIA

Fibromyalgia is a syndrome characterized by widespread pain. Chronic muscular pain is a common problem, but fibromyalgia is distinguished from other pain disorders by additional findings, such as consistent areas of tenderness (tender points), nonrestorative sleep, severe fatigue, and frequent psychological comorbidities such as depression and anxiety.

Fibromyalgia was originally termed "fibrositis" in 1904 by Sir William Gowers, who described it as a painful condition of the fibrous tissue, which he believed was due to inflammation in the muscles.[2,3] For several decades, research was dedicated to looking for pathology in the muscle tissue, which was thought to be the major source of pain for most patients with fibromyalgia.

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In the mid-1970s, Dr. H. Moldofsky, a noted sleep researcher, reported on abnormalities of the alpha-delta component of non-rapid-eye-movement sleep in these patients. He subsequently collaborated with Dr. Hugh A. Smythe, who helped define the fibromyalgia tender points. Fibrositis was subsequently renamed fibromyalgia syndrome, since it was agreed that there was no true inflammation in muscles or fibrous tissue.

In 1990, the American College of Rheumatology published "classification criteria" for the disease.[4] The criteria include two main features:

- A history of widespread pain ("widespread" being defined as in the axial distribution, in both the left and right sides of the body, and above and below the waist), which must be present for 3 months or more, and
- Tenderness in at least 11 of 18 specified points that is elicited when a pressure of 4 kg (the amount of pressure required to blanch a thumbnail) is applied in steady increments starting at 1 kg.

Although pain is subjective and therefore difficult to assess, the classification criteria did make it easier to study the disease in a uniform way and led to an explosion of research in this field.

Pain is subjective and therefore difficult to assess

FUNCTIONAL ABNORMALITIES IN THE CENTRAL NERVOUS SYSTEM

Research to date points to the pain in fibromyalgia as being mediated by changes in the central nervous system rather than in the musculoskeletal system, as was initially thought.

In the dorsal horn of the spinal cord, nociceptive (pain-sensing) neurons from the periphery synapse with the second-order neurons that carry the pain signal to the brain. In fibromyalgia, several processes seem to amplify the signal.

Central sensitization is defined as enhanced excitability of neurons in the dorsal horn. Its features include augmented spontaneous neuronal activity, enlarged receptive field areas, and enhanced responses generated by large- and small-caliber primary afferent fibers. It can result from prolonged or strong activity in the dorsal horn neurons, and it leads to the spread of hyperactivity across multiple spinal segments.[5–7]

While much of the evidence for central sensitization in fibromyalgia is from animal studies, the phenomenon has also been studied in humans. Desmeules et al[8] found that, compared with people without fibromyalgia, those with fibromyalgia had significantly lower thresholds of pain as assessed subjectively and measured objectively using the nociceptive flexion R-III reflex, which the authors described as "a specific physiologic correlate for the objective evaluation of central nociceptive pathways."

Wind-up. Prolonged stimulation of C fibers in the dorsal horn can result in the phenomenon of wind-up, which refers to the temporal summation of second pain.

A painful stimulus evokes two pain signals. The first signal is brief and travels rapidly to the spinal cord via myelinated fibers (A fibers). The second signal, which is related to chronic pain and is described as dull, aching, or burning, travels more slowly to the dorsal horn via unmyelinated fibers (C fibers), the synapses of which use the neurotransmitter glutamate. Temporal summation is a phenomenon observed in experiments in which a series of painful stimuli are applied at regular intervals of about 2 seconds; although each stimulus is identical in intensity, subjects perceive them as increasing in intensity. The reason: during this repetitive stimulation, *N*-methyl-D-aspartate (NMDA) receptors become activated, leading to the removal of a magnesium block within the receptor. This results in an influx of calcium into the neuron and activation of protein kinase C, nitric oxide synthase, and cyclooxygenase. Ultimately, the firing rates of the nociceptive neurons are increased and the peripheral pain signal is strongly amplified.[6]

Wind-up has been shown to lead to characteristics of central sensitization related to C-fiber activity in animals.[7] Staud et al[9] studied wind-up in patients with and without fibromyalgia using series of repetitive thermal stimulation to produce temporal summation. Though wind-up was evoked in both groups, differences were observed both in the magnitude of sensory response to the first stimulus within a series and in the amount of temporal summation within a series.

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Elevated excitatory neurotransmitters. In 1994, Russell et al[10] showed that the concentration of substance P, an excitatory neurotransmitter, was three times higher in the cerebrospinal fluid of people with fibromyalgia than in normal controls.

Harris and colleagues[11] reported that glutamate, another excitatory neurotransmitter, is elevated within the brain in people with fibromyalgia. They further showed that the levels of glutamate within the insula of the brain are directly associated with the levels of both experimental pressure-evoked pain thresholds and clinical pain ratings in fibromyalgia patients.

Evidence from imaging studies. Other objective evidence of central sensitization in fibromyalgia patients comes from studies using novel imaging.

Gracely et al[12] performed functional magnetic resonance imaging (MRI) in people with and without fibromyalgia while applying pressure to their thumbs with a thumbscrew-type device. At equal levels of pressure, the people with fibromyalgia said the pressure hurt more, and specific areas of their brains lit up more on functional MRI. When the experimenters increased the pressure in the people without fibromyalgia until this group subjectively rated the pain as high as the fibromyalgia patients rated the lower level of pressure, their brains lit up to a similar degree in the same areas. These findings provide objective evidence of significantly lower pain thresholds in patients with fibromyalgia than in healthy controls, and they support the theory of central augmentation of pain sensitivity in fibromyalgia.

Staud et al[13] also used functional MRI and found greater brain activity associated with temporal summation in fibromyalgia patients compared with controls. (In this experiment, the painful stimulus consisted of heat pulses to the foot.)

Drugs other than pregabalin that modulate the dorsal horn activity of the pain pathway include opioids, tramadol (Ultram), gabapentin (Neurontin), GABA agonists such as baclofen (Lioresal), antidepressants, alpha-2 adrenergic agonists (phenylephrine), and 5-HT3 antagonists such as ondansetron (Zofran), but none has been consistently effective for fibromyalgia.[5,14]

PREGABALIN

Pregabalin is an alpha-2-delta ligand similar to GABA, but it does not act on GABA receptors. Rather, it binds with high affinity to the alpha-2-delta subunit of voltage-gated presynaptic calcium channels, resulting in reduction of calcium flow through the channels, which subsequently inhibits the release of neurotransmitters including glutamate, norepinephrine, and substance P.[15–17] Animal studies suggest that the decrease in the levels of these excitatory neurotransmitters is the mechanism of action of pregabalin, resulting in its analgesic, anticonvulsant, and anxiolytic benefit.[15] Another potential mechanism of pregabalin is enhancement of slow-wave sleep, demonstrated in one study in healthy human subjects.[18]

Besides fibromyalgia, pregabalin is also approved for the treatment of diabetic peripheral neuropathy, postherpetic neuralgia, generalized anxiety disorder, and social anxiety disorder, and as adjunctive therapy for partial-onset seizure in adults.

Pharmacokinetics

Pregabalin is quickly absorbed, primarily in the proximal colon (bioavailability > 90%), and has highly predictable and linear pharmacokinetics.[15] Food consumption does not affect its absorption or elimination but can delay its peak plasma concentration, which occurs at 1.5 hours. Its elimination half-life is approximately 6 hours.[15] Because it does not bind to plasma proteins, it freely crosses the blood-brain barrier. The drug reaches its steady-state concentration within 2 days of starting therapy.

In fibromyalgia, several processes in the dorsal horn seem to amplify the pain signal

Its clearance is not affected by the sex or race of the patient, but its total clearance may be lower in the elderly because of age-related loss of renal function. Patients on hemodialysis may require a supplemental dose after dialysis because hemodialysis removes the pregabalin.

The drug is not metabolized by the P450 system in the liver, so it interacts only minimally with drugs that do use the P450 system. However, its clearance may be decreased when it is used concomitantly with drugs that can reduce the glomerular filtration rate, such as nonsteroidal anti-inflammatory drugs, aminoglycosides, and cyclosporine.[15]

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Efficacy

The efficacy of pregabalin in fibromyalgia was evaluated in several recent trials.[19]

Crofford et al[16] assessed pregabalin's effects on pain, sleep, fatigue, and health-related quality of life. Some 529 patients with fibromyalgia were randomized in a double-blind fashion to four treatment groups: placebo, and pregabalin 150 mg/day, 300 mg/day, and 450 mg/day. The baseline mean pain scores (a 0-to-10 scale derived from daily diary ratings) were 6.9 in the placebo group, 6.9 for the pregabalin 150 mg/day group, 7.3 for the pregabalin 300 mg/day group, and 7.0 for the pregabalin 450 mg/day group.

The pain scores declined in all groups, but at 8 weeks, the mean score had declined 0.93 points more in the group receiving pregabalin 450 mg/day than in the placebo group ($P \leq .001$). The scores in the groups taking pregabalin 150 mg /day and 300 mg/day were not significantly different from those in the placebo group. Significantly more patients in the 450-mg/day group (29%, vs 13% in the placebo group) had at least 50% improvement in pain at the end of the study. Patients in both the 300-mg/day group and the 450-mg/day had statistically significant improvement in their quality of sleep, in fatigue, and on the Patient Global Impression of Change (PGIC) scale.

People with fibromyalgia have a lower pain threshold

Arnold et al[20] conducted a trial with 750 patients in which three doses of pregabalin were compared with placebo: 300 mg/day, 450 mg/day, and 600 mg/day. The primary end point was also the change in pain score from baseline (using the 0-to-10 scale derived from a daily pain diary). The mean baseline pain score was 6.7.

At 14 weeks, the mean pain score was lower than at baseline in all the groups, but it had declined 0.71 more in the pregabalin 300-mg/day group than in the placebo group, 0.98 points more in the 450-mg/day group, and 1.0 points more in the 600-mg/day group. All three pregabalin groups also showed significant improvement on the PGIC scale, and patients in the 450-mg/day and 600-mg/day groups showed statistically significant improvement in the Fibromyalgia Impact Questionnaire (FIQ) score. All three pregabalin treatment groups also had significantly better patient-reported sleep outcomes than in the placebo group, both in measures of overall sleep and quality of sleep. With the exception of a significant improvement of anxiety on 600 mg/day, there was no significant difference between the treatment and placebo groups in the secondary outcomes of depression and anxiety symptoms and fatigue.

Duan et al[21] presented a pooled analysis of this and a similarly designed double-blind, placebo-controlled trial (the results of which were not available individually) at the 71st annual meeting of the American College of Rheumatology in November 2007. The analysis included 1,493 patients with a mean baseline pain score of 6.9. Compared with the mean pain score in the placebo group, those in the pregabalin groups had declined more by the end of the study: 0.55 points more with 300 mg/day, 0.71 points more with 450 mg/day, and 0.82 points more with 600 mg/day. This pooled analysis also showed significant improvement in PGIC score with all pregabalin doses and in the FIQ score with 450 mg/day and 600 mg/day.

The FREEDOM trial[22] (Fibromyalgia Relapse Evaluation and Efficacy for Durability of Meaningful Relief) evaluated the durability of effect of pregabalin in reducing pain and symptoms associated with fibromyalgia in 1,051 patients who initially responded to the drug.

The patients received 6 weeks of open-label treatment with pregabalin and then 26 weeks of double-blind treatment (dose adjustment was allowed based on efficacy and tolerability for the first 3 weeks). The time to loss of therapeutic response was significantly longer with pregabalin than with placebo. Loss of therapeutic response was defined as worsening of pain for two consecutive visits or worsening of fibromyalgia symptoms requiring alternative therapy.

By the end of the double-blind phase, 61% of those in the placebo group had loss of therapeutic response compared with only 32% in the pregabalin group. The time to worsening of the FIQ score was also significantly longer in the pregabalin group than in the placebo group.

Adverse effects: Dizziness, sleepiness, weight gain

Dizziness and sleepiness were the most common adverse events in these studies.

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In the 8-week study by Crofford et al,[16] dizziness was dose-related, occurring in 10.7% of those receiving placebo (one patient withdrew because of dizziness), 22.7% of those receiving 150 mg/day (two patients withdrew), 31.3% of those receiving 300 mg/day (four patients withdrew), and 49.2% of those receiving 450 mg/day (five patients withdrew). Somnolence was also dose-related, occurring in 4.6% in the placebo group, 15.9% in the 150-mg/day group (two patients withdrew due to somnolence), 27.6% in the 300-mg/day group (three withdrew), and 28.0% in the 450-mg/day group (five withdrew).

The 14-week study by Arnold et al[20] also showed higher frequencies of adverse events with higher doses. The rates of dizziness were 7.6% with placebo, 27.9% with pregabalin 300 mg/day, 37.4% with 450 mg/day, and 42.0% with 600 mg/day. The rates of somnolence were 3.8% with placebo, 12.6% with 300 mg/day of pregabalin, 19.5% with 450 mg/day, and 21.8% with 600 mg/day. Dizziness and somnolence were also the most common adverse effects that led to discontinuation of pregabalin, with rates of 4% and 3%, respectively.

The open-label phase of the FREEDOM trial showed rates of 36% for dizziness and 22% for somnolence among pregabalin-treated patients.

Weight gain and peripheral edema were also common adverse effects in these studies.[22] Definitions of weight gain varied, and edema was not accompanied by evidence of cardiac or renal dysfunction.

Less common side effects seen more frequently in the treated groups included dry mouth, blurred vision, and difficulty with concentration and attention. The package insert also warns of angioedema, hypersensitivity reaction, mild asymptomatic creatine kinase elevation, decreased platelet count (without bleeding), and prolongation of the PR interval on electrocardiography.

Pregabalin is a schedule V controlled substance; in clinical studies, abrupt or rapid discontinuation of the drug led to insomnia, nausea, headache, or diarrhea in some patients, suggesting symptoms of dependence. In clinical studies involving a total of more than 5,500 patients, 4% of patients on pregabalin and 1% of patients on placebo reported euphoria as an adverse effect,[19] suggesting possible potential for abuse.

Dosing

As a result of the above studies, the recommended starting dose of pregabalin for fibromyalgia is 150 mg/day in two or three divided doses, gradually increased to 300 mg/day within 1 week based on tolerability and efficacy. The dose may be increased to a maximum of 450 mg/day. The 600-mg dose was found to have no significant additional benefit, but it did have more adverse effects and therefore is not recommended. It is important to note that in these studies multiple medications for pain and insomnia were prohibited, so data on drug interactions with pregabalin are limited.

Few achieve complete remission, but most patients feel better

Several studies of the natural history of fibromyalgia have shown that very few patients experience complete remission of the disease, even after many years. Therefore, one should try to set up realistic expectations for patients, with the goal of achieving functional improvement in activities of daily living and a return to one's predisease state.

In the longest follow-up study, 39 patients in Boston, MA, were prospectively followed for over 10 years. No patient achieved complete remission: all of them reported some fibromyalgia-related symptoms at the end of the study.[23] However, 66% of them felt a little to a lot better than when first diagnosed, 55% felt well or very well, and only 7% felt poorly.

Other studies have also shown complete remission to be rare.[24,25] A 5-year follow-up study investigating fibromyalgia patients' perceptions of their symptoms and its impact on everyday life activities demonstrated that the social consequences of fibromyalgia's symptoms are severe and constant over time.[26]

Evidence of favorable outcomes was reported in one study in which 47% of patients reported moderate to marked improvement in overall fibromyalgia status upon 3-year follow-up,[27] and in another study, in which remission was objectively identified in 24.2% of patients 2 years after diagnosis.[28]

Fibromyalgia patients scored about 1 point lower on a 0–10 pain scale with pregabalin than with placebo

OTHER THERAPIES

Although there have been many studies of pharmacologic therapies for fibromyalgia to

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date, the trials had significant limitations, such as short duration, inadequate sample size, nonstandardized measures of efficacy, question of regression to the mean, and inadequate blinding, resulting in insufficient evidence to recommend one drug over another.

Tricyclic antidepressants. Two meta-analyses and a clinical review have supported the efficacy of tricyclic antidepressants in improving symptoms in fibromyalgia patients.[29–31]

Selective serotonin reuptake inhibitors (SSRIs) have not been well studied, and the small size and methodologic shortcomings of these studies make it difficult to draw conclusions about the efficacy of SSRIs in reducing pain in fibromyalgia patients.[30,31]

Duloxetine (Cymbalta) and **milnacipran** (Savella) are serotonin and norepinephrine reuptake inhibitors.[32–34] A randomized, double-blind placebo-controlled trial evaluated duloxetine in 520 fibromyalgia patients with and without major depressive disorder. Pain scores improved significantly over 6 months in duloxetine-treated patients at doses of 60 and 120 mg/day.[33] Duloxetine became the second drug approved for the treatment of fibromyalgia in 2007, and milnacipran became the third in 2009.

Duloxetine (Cymbalta) was the second drug approved for fibromyalgia

WHAT ROLE FOR PREGABALIN?

Pregabalin may reduce pain in some patients with fibromyalgia. However, the presenting symptoms can vary significantly, and symptoms can vary even in individual patients over time. Therefore, in most patients with fibromyalgia, a multidisciplinary approach is used to treat pain, sleep disturbance, and fatigue, along with comorbidities such as neurally mediated hypotension and psychiatric disorders. Because treatment of fibromyalgia often involves multiple drugs in addition to exercise and behavioral therapies, future studies should examine combinations of drugs and the use of drugs in conjunction with nondrug treatments.

Pregabalin advances our knowledge of fibromyalgia through improving the understanding of central sensitization and how brain neurotransmitters control central pain perceptions. Drug treatment must still be part of the comprehensive management of this disease. Physician and patient education about the current understanding of the disease is paramount in setting realistic goals for treatment.[14] Future strategies to manage fibromyalgia will be based on the pathophysiology of this complex condition. ■

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ly have had shingles. I have heard that the recurrence rate is 3% to 5%, and the efficacy of the vaccine is only 50% to 65%. Though every article I have read states we *can* give the vaccine to these patients, *should* we?

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IN REPLY: We thank Dr. Shaheen for his interesting comment. He has made an important point. The data on the use of shingles vaccine in patients with a history of zoster are insufficient. The main study of shingles vaccine[1] excluded patients who had already had shingles.

The US Centers for Disease Control and Prevention says: "Persons with a reported history of zoster *can* [emphasis added] be vaccinated. Repeated zoster has been confirmed in immunocompetent persons soon after a previous episode. Although the precise risk for and severity of zoster as a function of time following an earlier episode are unknown, some studies suggest it may be comparable to the risk in persons without a history of zoster. Furthermore, no laboratory evaluations exist to test for the previous occurrence of zoster, and any reported diagnosis or history might be erroneous."[2]

Until more data are available for this patient population, current evidence and availability of shingles vaccine should be discussed with patients who report a history of shingles.

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CORRECTION

Pregabalin for fibromyalgia

(APRIL 2009)

In an article that appeared in the April issue of the *Cleveland Clinic Journal of Medicine* (Kim L, Lipton S, Deodhar A. Pregabalin for fibromyalgia: some relief but no cure. Cleve Clin J Med 2009; 76:255–261.), journal editors failed to list the participation of one of the authors in a clinical trial of pregabilin (Lyrica) that was funded by the drug's manufacturer. Dr. Atul Deodhar had disclosed his participation in the trial to an editor, and the failure to list it with the article at the time of publication was an oversight on the part of *CCJM*.