

# Fibromyalgia: An update for pharmacists

Mary Lynn McPherson and Judy Crespi Lofton

## Abstract

**Objective:** To review the existing literature on the presentation of fibromyalgia and its management.

**Data sources:** Searches of PubMed were conducted using one or more of the following terms: *fibromyalgia*, *prevalence*, *incidence*, *impact*, *pregabalin*, *duloxetine*, and *milnacipran*. References and related articles from relevant articles were searched to retrieve additional articles. In addition, Google was used to identify national organizations that are dedicated to fibromyalgia, and their websites were searched for additional information.

**Data extraction:** By the authors.

**Data synthesis:** Fibromyalgia is a chronic pain condition that severely affects patients. However, numerous treatments are available for treating fibromyalgia, several of which have been proven to be effective at reducing symptoms and improving patient function. These include three medications that have been approved since 2007 by FDA for treating fibromyalgia. Pharmacists can engage in several activities to support patients with fibromyalgia, including providing education, overseeing medication use, and collaborating with other members of the health care team.

**Conclusion:** Although no cure exists for fibromyalgia, several interventions have proven effective for managing this syndrome. Pharmacists can work with other members of the health care team to ensure that patient management of this syndrome is optimized.

**Keywords:** Pain (chronic), fibromyalgia, pregabalin, duloxetine, milnacipran, patient education, pharmacists.

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### Learning objectives

At the conclusion of this program, the pharmacist will be able to:

- Describe the symptoms and presentation of fibromyalgia, as well as its impact on patient quality of life.
- Evaluate the current nonpharmacologic and pharmacologic strategies for managing fibromyalgia.
- Define the role of the pharmacist in caring for patients with fibromyalgia, including identifying patients who may not be receiving appropriate care for their symptoms.

**ACPE Activity Type: Knowledge-Based**

## Understanding fibromyalgia

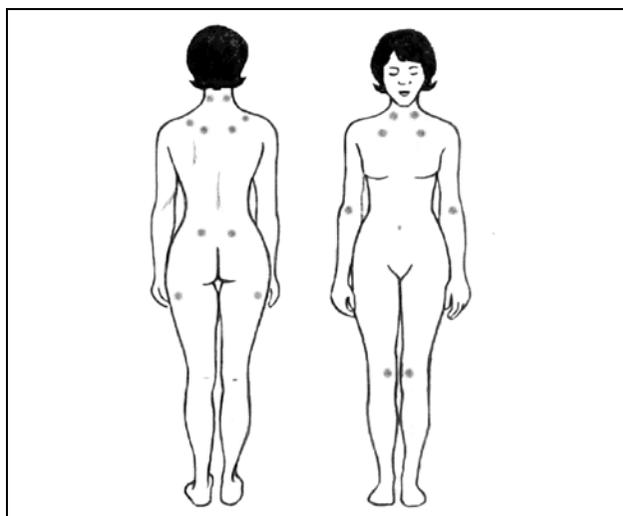
Fibromyalgia is a chronic pain syndrome that has been estimated to affect 2% to 4% of the population in the United States (~6–12 million individuals).<sup>1</sup> The prevalence of fibromyalgia in adults is generally similar around the world.<sup>2</sup> Approximately 90% of individuals affected by fibromyalgia are women.<sup>2</sup> It is most often diagnosed in patients who are 20 to 50 years of age but has also been observed in children and adolescents.<sup>3</sup>

Before 1986, fibromyalgia was referred to as fibrositis, a term that was first coined in 1904 to describe a regional pain syndrome associated with profound fatigue and sleep disturbances, and indicated that the condition was believed to be caused by inflammation of the muscles.<sup>4,5</sup> Diagnostic criteria were first proposed for “fibrositis syndrome” in 1977.<sup>6</sup> Research indicated that inflammation was not the true cause of the pain, and the term fibromyalgia, meaning muscle pain, was introduced. Additional attempts to define the condition followed.<sup>7,8</sup>

In 1990, the American College of Rheumatology (ACR) published criteria for diagnosing fibromyalgia. Currently, these criteria are the most used diagnostic guidelines for both research and clinical practice. The diagnostic criteria include

**Synopsis:** Fibromyalgia is a debilitating chronic pain syndrome that negatively affects many aspects of patients’ lives. Although this syndrome has been recognized for over a century, the term fibromyalgia was not used before 1986. Since that time, specific diagnostic criteria were established and a large body of research has investigated fibromyalgia and its treatment. Currently, three medications are approved for treating fibromyalgia, and a number of other interventions have been proven effective at reducing pain, improving function, and managing other symptoms associated with fibromyalgia. In general, patients experience the greatest improvements when multiple modalities (e.g., education, exercise, cognitive behavioral therapy [CBT], medications) are combined.

**Analysis:** *Although fibromyalgia has been carefully researched in recent years and found to be associated with specific pathophysiologic abnormalities, some health providers and others do not consider it to be a “real” diagnosis. As a result, many patients feel stigmatized and may feel that their symptoms are not taken seriously or have difficulty finding health providers who are knowledgeable about the condition. However, increasing awareness about the condition and extensive research are helping to bring treatments to patients that can improve their quality of life. Pharmacists can play important roles in ensuring that patients with fibromyalgia are receiving appropriate therapy and can make referrals to health care providers and other resources as necessary.*



**Figure 1.** Tender point location

Source: Reference 12.

a history of widespread pain and pain during palpation in at least 11 of 18 tender points (Figure 1).<sup>9</sup> When pressure is applied to these points, a person with fibromyalgia will feel pain, whereas a person without fibromyalgia would feel only “pressure.”<sup>10</sup> Patients may describe the pain associated with fibromyalgia as tender, aching, throbbing, sore, burning, and gnawing; it sometimes is accompanied by tingling, numbness, burning, or pricking.<sup>10</sup>

According to the ACR definition, “pain is considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist. In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) must be present. In this definition, shoulder and buttock pain is considered as pain for each involved side. ‘Low back’ pain is considered lower segment pain.”<sup>9</sup>

When assessing patients for fibromyalgia, recognizing that most of the general population has a few tender points is important.<sup>11</sup> The number of tender points indicates the pervasiveness of the pain and results in the diagnosis of fibromyalgia. The higher the number of tender points, the greater psychological distress and greater severity and frequency of other conditions associated with fibromyalgia.<sup>11</sup> Conversely, higher fatigue scores are associated with greater numbers of tender points.<sup>11</sup>

The ACR diagnosis does not consider whether patients with fluctuating symptoms are considered to have fibromyalgia. For some patients, the pain may begin in one region of the body, slowly spreading through the body or waxing and waning.<sup>10</sup> Some researchers have argued that the ACR definition may be most relevant for identifying clinical trial participants and that a broader set of patients may benefit from fibromyalgia treatment. The ACR criteria may also have limited specificity. For example, a patient having long-standing pain in 10 points would not meet the formal definition of fibromyalgia but

might still benefit from treatment for fibromyalgia.<sup>12</sup> Others have proposed the Symptom Intensity Scale as a measure for identifying patients with fibromyalgia.<sup>11</sup>

Research shows that people with fibromyalgia typically see multiple doctors before receiving the diagnosis.<sup>12</sup> One reason for this may be that pain and fatigue, the main symptoms of fibromyalgia, overlap with many other conditions. Therefore, doctors often have to rule out other potential causes of these symptoms before making a diagnosis of fibromyalgia.<sup>12</sup> However, recognizing that the presence of other painful conditions, such as rheumatoid arthritis, does not preclude a concomitant diagnosis of fibromyalgia is important.<sup>13</sup>

Estimations indicate that it takes 5 years on average for patients with fibromyalgia to get an accurate diagnosis.<sup>13</sup> Because of lack of awareness about the condition, some physicians may be unfamiliar with appropriate diagnostic procedures and may order numerous tests that all yield normal results. Because symptoms of fibromyalgia are subjective, some physicians may not believe patients' reports of pain, particularly when they are not supported by physical findings.<sup>12</sup> Because laboratory tests results generally are normal and no outward signs of the condition exist, patients with fibromyalgia may be told that the condition is "all in their head."<sup>10</sup>

Although fibromyalgia is recognized as a disease state with identified pathophysiologic abnormalities by the National Institutes of Health and ACR, fibromyalgia sometimes is not recognized as a "true" disorder.<sup>2</sup> Some patients continue to be told that the disorder is a symptom of depression. (The relationship between fibromyalgia and depression is complex—some overlap exists among the neurotransmitter abnormalities, symptoms, and pharmacologic treatments. However, current research indicates that they are distinct conditions.<sup>14</sup>) Others are labeled as hypochondriacs or malingerers (i.e., individuals who fabricate or exaggerate symptoms for secondary gain). Patients continue to report that physicians belittle their symptoms or react negatively when patients report symptoms of fibromyalgia.<sup>15</sup> Patients also report that even physicians who diagnose and treat fibromyalgia may have negative attitudes toward patients.<sup>15</sup>

Although the pathophysiology of fibromyalgia is not completely defined, the musculoskeletal system, neuroendocrine system, and central nervous system have been found to play important roles.<sup>4,16</sup> A genetic component to the development of fibromyalgia also appears to exist, and several candidate genes have been identified. Exposing a genetically predisposed individual to a host of environmental stressors (e.g., infection, trauma, stress) is believed to lead to the development of fibromyalgia.<sup>17,18</sup>

Abnormalities associated with fibromyalgia include an inability to sustain deep stage 4 sleep, central sensitization, impairments in descending inhibitory pain pathways, neurotransmitter abnormalities (especially serotonin, dopamine, and norepinephrine), hypothalamic–pituitary–adrenal axis dysfunction, and peripheral sensitization.<sup>19</sup>

Symptoms and comorbidities commonly associated with fibromyalgia include insomnia, fatigue, memory, and con-

centration difficulties (sometimes referred to as "fibro fog"), headaches, temporomandibular joint syndrome, irritable bowel syndrome, painful menstrual periods, numbness or tingling of the extremities, and restless legs syndrome.<sup>10,12</sup> Because of the many comorbidities, painful symptoms may be attributed to other causes, leading to misdiagnosis.<sup>1</sup>

### Impact of fibromyalgia

Fibromyalgia can result in considerable disability and loss of function that affects quality of life to an extent similar to or greater than other chronic painful conditions.<sup>1</sup> For example, one study compared patients with fibromyalgia with other patients with chronic widespread pain that did not meet the ACR diagnostic criteria for fibromyalgia and with healthy control patients.<sup>20</sup> Patients with diagnosed fibromyalgia had significantly worse function than either comparison group, including spending significantly more days in bed. Patients with fibromyalgia have significantly worse quality of life, as measured with the SF-36 (36-item short-form survey instrument), than individuals with rheumatoid arthritis, osteoarthritis, or systemic lupus erythematosus.<sup>1</sup>

#### Patient stories on fibromyalgia

Go to [www.fmaware.org/site/PageServer?pagename=community\\_PatientStories](http://www.fmaware.org/site/PageServer?pagename=community_PatientStories) for patient stories on fibromyalgia.

Fibromyalgia impairs patients' ability to work, and many patients are disabled. In one study, more than 46% of patients with fibromyalgia reported job loss as a result of their condition.<sup>21</sup> Another study found that 9% to 26% of patients were not working because of temporary or permanent disability.<sup>22</sup> Patients who are able to continue employment report that their symptoms compromise their productivity, result in frequent absences from work, and often result in a reduction of work hours.<sup>1</sup>

Patients with fibromyalgia also have higher health care costs than other individuals. In a study that compared costs associated with fibromyalgia with overall beneficiaries at one company, the total annual costs for employees with fibromyalgia claims were \$5,945 versus \$2,486 for the average beneficiary. However, only 6% of these costs were directly attributable to fibromyalgia claims. For every dollar spent on fibromyalgia-specific claims, the employer spent another \$57 to \$143 on additional direct and indirect costs.<sup>23</sup>

In another study, a claims database of privately insured individuals was used to compare employees with fibromyalgia with employees with osteoarthritis and control patients. Total costs for employees with fibromyalgia were similar to those for osteoarthritis and significantly higher than those for control patients.<sup>20</sup>

Research shows that indirect costs for fibromyalgia patients can meet or exceed those of other similar chronic pain conditions. One study compared commercially insured patients with fibromyalgia with patients with rheumatoid ar-

thritis. Patients with fibromyalgia had similar annual health care expenditures as those with rheumatoid arthritis and an increased number of absences and short-term disability days. Patients with fibromyalgia had more emergency department, physician, and physical therapy visits than rheumatoid arthritis patients.<sup>24</sup>

Fibromyalgia also interferes with patients' lives outside of work. In one study, 93% reported that fibromyalgia interferes with managing their household.<sup>1</sup> Many patients are unable to fully participate in their family lives and have to forgo social obligations.

Many tools are available for assessing the impact of fibromyalgia on patients and can be used to measure the impact of treatments on patients' symptoms and function (see **TOOLS FOR ASSESSING FIBROMYALGIA**). These tools are often used in addition to numerical rating scales to gain a broader view of the impact of fibromyalgia.

#### Tools for assessing fibromyalgia

- **Fibromyalgia Impact Questionnaire (FIQ):** The FIQ was first developed in 1991 and is widely used to assess problems associated with fibromyalgia, including pain, fatigue, and functional impairment, as well as anxiety and depression.
- **Patient Global Impression of Change (PGIC):** A patient-rated instrument that measures changes in overall health status and allows assessment of pain, other symptoms, functioning, and adverse events.
- **Brief Pain Inventory:** Assesses intensity of pain and the degree to which pain interferes with function and provides questions about pain relief, pain quality, and the patient's perception of the cause of pain.

### Treatment of fibromyalgia

Because no known cure for fibromyalgia exists, treatment is focused on managing symptoms. Goals in treating fibromyalgia include reducing pain, improving function, and increasing restorative sleep. A number of nonpharmacologic and pharmacologic treatments are used to achieve these goals, often in combination. Multidisciplinary treatment that combines modalities and treatments (sometimes called multicomponent therapy) appears to be significantly more beneficial at reducing fibromyalgia symptoms than any single modality.<sup>25,26</sup>

Evidence based-guidelines for treating fibromyalgia have been developed by the American Pain Society (APS) and the European League Against Rheumatism (EULAR).<sup>27,28</sup> However, they were developed before FDA approved any medications for treating fibromyalgia and substantial heterogeneity exists between the recommendations. Furthermore, the studies evaluated during the development of these guidelines were not directly comparable as a result of variations in study design and had short durations, limiting their generalizability and applicability to clinical practice.<sup>29</sup>

#### Nonpharmacologic options

For nonpharmacologic therapy, the APS guidelines cited gave the strongest level of recommendation (A) to patient educa-

tion, cognitive behavioral therapy (CBT), aerobic exercise, and multidisciplinary therapy and moderate level of recommendation (B) to strength training, acupuncture, hypnotherapy, biofeedback, and balneotherapy.<sup>27</sup> The EULAR guidelines gave a moderate recommendation (B) for balneotherapy (bathing, especially in warm water), weaker recommendations (C) for individually tailored exercise and other therapies (relaxation, rehabilitation, physiotherapy, and psychological support), and a low level of recommendation (D) for CBT.<sup>28</sup>

Educational programs for patients with fibromyalgia are designed to increase patient understanding of the relationships between the pathophysiology of fibromyalgia with behaviors (e.g., sleep) and symptoms.<sup>30</sup> Educating patients about the pathophysiology of fibromyalgia and stressing that the symptoms are not psychogenic (i.e., "all in your mind") can help to reduce the stigma associated with fibromyalgia.<sup>30</sup> Education alone has been shown to improve subjective reports of fibromyalgia symptoms compared with waitlisted control patients; however, the greatest improvements are generally seen when education is combined with other interventions.<sup>30</sup>

CBT trains patients to associate maladaptive thoughts and behaviors (irrational thoughts that lead to negative emotions and behaviors that inhibit the ability to adjust to situations) with increased pain and decreased function. For example, patients with fibromyalgia who catastrophize (view minor mishaps and setbacks as catastrophes) have been found to have increased pain, decreased functioning, and greater affective distress.<sup>30</sup> In cognitive therapy, patients are taught to reframe their thinking and look for positive aspects of a situation. Behavioral techniques for patients with fibromyalgia include working to start exercise therapy with a graded program, teaching patients to pace themselves, sleep hygiene, and the use of relaxation techniques.<sup>30</sup> Together, such interventions are referred to as CBT. Explaining the importance of mind-body interactions to patients is important before referring patients for CBT, in order to reduce patient perceptions that health providers believe the syndrome is purely psychological.<sup>30</sup>

Available evidence indicates that CBT is effective for patients with fibromyalgia; however, recognizing that CBT provided can vary greatly among providers and research studies is important. For example, some CBT providers focus on cognitive strategies, some focus on behavioral strategies, and some combine the two. In addition, individual factors, such as good pain-coping strategies at the beginning of treatment, can affect the outcome. Nevertheless, CBT has been noted to decrease stress and improve mood, pain-coping strategies, and problem solving in patients with fibromyalgia.<sup>30</sup>

Positive results have been reported for the use of various relaxation techniques, including progressive muscle relaxation, guided imagery, meditation, and biofeedback. However, data to support the use of these techniques are limited, and more randomized controlled trials are needed to confirm current findings.<sup>30</sup>

Substantial evidence supports the use of exercise in treating fibromyalgia. A Cochrane review reported that "gold level

**Table 1.** Good sleep hygiene

Recommendation for patients	Details
Keep regular sleep habits.	Patients should attempt to go to bed at the same time and get up at the same time every day.
Avoid stimulants, including caffeine, and alcohol in the late afternoon and evening.	If consumed close to bedtime, the caffeine and some medications can interfere with sleep. Although alcohol can make patients sleepy, it also can disturb sleep.
Exercise regularly but not close to bedtime.	Regular daytime exercise can improve nighttime sleep. However, because it can be stimulating, patients should avoid exercising within 3 hours of bedtime.
Avoid daytime naps.	Sleeping in the afternoon can interfere with nighttime sleep. If patients absolutely need to nap, they should set an alarm so that they get up after 1 hour.
Reserve the bed for sleeping.	Watching the news, reading a suspense novel, or working in bed can make it hard to sleep.
Create a restful environment.	Patients should keep their bedrooms dark, quiet, and cool.
Avoid liquids and spicy meals before bed.	Large meals at bedtime can cause heartburn. Liquids can lead to nighttime awakening to use the bathroom.
Wind down before bed.	Patients should be advised to engage in relaxing activities, such as listening to soft music or taking a warm bath, which may also soothe aching muscles.

Source: Reference 12.

evidence” exists for supervised aerobic exercise training having beneficial effects on physical capacity and symptoms of fibromyalgia. This review found that strength training may also have benefits on some fibromyalgia symptoms.<sup>31</sup>

Although pain and fatigue may make exercise and daily activities difficult, fibromyalgia patients need to be as physically active as possible. Research has repeatedly shown that regular exercise is one of the most effective treatments for fibromyalgia. However, because of the pain and fatigue, many patients with fibromyalgia are very sedentary and have become deconditioned and overweight.<sup>32</sup> People who have too much pain or fatigue to do vigorous exercise should begin with walking or other gentle exercise and build their endurance and intensity slowly.<sup>12</sup> These patients may need more support from their health care team to maintain an exercise regimen, particularly if they overexert themselves, resulting in worsening pain, when they first attempt an exercise program. Patients should be advised to start slowly, expect some muscle soreness and fatigue, and use support to persevere with their exercise regimen in order to experience benefits.

Patients with fibromyalgia often report sleep disturbances, which can contribute to the fatigue associated with fibromyalgia. Patients with fibromyalgia should be encouraged to practice good sleep hygiene to help support restful and restorative sleep (Table 1).

Balneotherapy has been investigated as a therapy for fibromyalgia and has been found to substantially reduce symptoms of fibromyalgia, including the number of tender points, reported pain, and depressive symptoms.<sup>33</sup> A review of the use of balneotherapy for treating various musculoskeletal conditions, including fibromyalgia, also reported positive effects associ-

ated with the treatment.<sup>34</sup> Another study reported that the use of pool-based exercise was more effective than balneotherapy without exercise at improving fibromyalgia symptoms.<sup>35</sup>

**Complementary and alternative medicine**

Complementary and alternative medicine (CAM) is commonly used to treat fibromyalgia. The majority of patients with fibromyalgia will visit at least one CAM provider (e.g., chiropractors, massage therapists, acupuncturists), and the use of CAM has been found to be 2.5 times higher compared with control patients without fibromyalgia.<sup>36</sup>

The evidence supporting chiropractic treatment of fibromyalgia is mixed. Two reviews of chiropractic treatment for fibromyalgia were published in 2009. One review found that limited evidence exists to support the use of chiropractic treatment of fibromyalgia, while the other reported that insufficient evidence exists to draw conclusions about its efficacy.<sup>37,38</sup>

Researchers have investigated the use of other CAM therapies for treating fibromyalgia, including massage, qigong, tai chi, acupuncture, and yoga.<sup>30,39</sup> Limited data have reported some positive findings; other data are mixed. More research is needed to better quantify the effects of such approaches.<sup>30,39</sup>

Numerous dietary supplements are marketed for treating fibromyalgia symptoms. Although positive evidence for using some supplements (vitamin D and S-adenosyl methionine) is limited, little scientific evidence exists to support the use of the majority of supplements.<sup>12</sup> Some supplements were found to have positive results in early trials, but these results were not replicated by more methodologically rigorous trials.<sup>30</sup> Furthermore, FDA has limited oversight of dietary supplements, and information about appropriate dosages, risks of adverse

events, or risks for drug–drug and drug–disease interactions is often lacking.<sup>12</sup>

#### **Beware of misinformation**

Search for *fibromyalgia natural cure* on the Internet and investigate some of the websites that are returned. What do you think about these websites' proposed treatments for fibromyalgia and the evidence used as the basis to support their claims? What might patients think of these websites, particularly if their symptoms have been dismissed by conventional health providers?

#### **Pharmacologic options**

Before 2007, a number of different medications had been investigated and used off label to treat fibromyalgia. Both the APS and EULAR guidelines provided recommendations for pharmacologic therapy, based on the evidence available at the time the guidelines were developed.

The APS guidelines cite strong evidence supporting the use of tricyclic antidepressants and moderate evidence for serotonin and norepinephrine reuptake inhibitors (SNRIs), fluoxetine, tramadol, and pregabalin (Lyrica—Pfizer).<sup>27</sup> The EULAR guidelines recommend tramadol (grade A); antidepressants (grade A); tropisetron, pramipexole (Mirapex—Boehringer Ingelheim), and pregabalin (grade A); and analgesics (i.e., acetaminophen and weak opioids; grade D).<sup>28</sup> However, these guidelines were developed before any medications had been approved for treating fibromyalgia, limiting their use for guiding current practice.<sup>29</sup>

Before any medications were approved by FDA for treating fibromyalgia, the tricyclic antidepressants were generally used as first-line agents, particularly amitriptyline.<sup>19</sup> However, their use was limited because of adverse events. Selective serotonin reuptake inhibitors (SSRIs) have also been tried in patients with fibromyalgia, and although they generally were associated with fewer adverse events, their efficacy was reduced.<sup>19</sup> SSRIs that have the greatest effect on serotonin and least effect on norepinephrine were found to have the least efficacy for treating fibromyalgia symptoms, suggesting that SNRIs might be more effective.<sup>40,41</sup>

From 2007 to 2009, three medications were approved for treating fibromyalgia: pregabalin, duloxetine (Cymbalta—Lilly), and milnacipran (Savella—Forest). Pregabalin is an alpha-2 delta ligand that was approved for treating fibromyalgia in 2007. Duloxetine and milnacipran are SNRIs; duloxetine was approved for treating fibromyalgia in 2008 and milnacipran in 2009. These medications are currently the only approved pharmacologic treatments available; additional therapies remain under investigation.

**Pregabalin.** Pregabalin was studied in three randomized, double-blind, short-term (≤14 weeks) trials of patients with fibromyalgia. Compared with placebo, pregabalin produced significant reductions in mean pain scores, improvements in sleep, improvements in PGIC and FIQ scores, and improvements in patients' impressions of their global improvement.<sup>42,43</sup> Pregabalin reduced pain regardless of whether patients had comorbid anxiety or depressive symptoms.<sup>25</sup>

Longer-term studies, including a 6-month trial and a

1-year trial, found that patients who had initially improved during short-term treatment had sustained improvement with continued pregabalin therapy.<sup>25,44</sup>

The most common adverse reactions associated with pregabalin are dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and thinking abnormalities (primarily difficulty with concentration and attention).<sup>45</sup> Pregabalin may also cause angioedema, which can result in life-threatening respiratory compromise. In addition, antiepileptic drugs, including pregabalin, may increase the risk of suicidal thoughts and behavior. Patients receiving pregabalin should be given a medication guide.<sup>45</sup> Pregabalin is a Schedule V controlled substance. Rapid discontinuation may result in withdrawal symptoms (insomnia, nausea, headache, and diarrhea).<sup>45</sup>

The recommended dosage of pregabalin for treating fibromyalgia is 300 to 450 mg/day given in divided doses. Dosing should be initiated at 75 mg twice daily and increased to 150 mg twice daily within 1 week if tolerated. Patients who do not experience sufficient benefit at this dosage may be increased to 225 mg twice daily. Pregabalin is eliminated primarily by renal excretion; dosage should be adjusted for patients with reduced renal function.<sup>45</sup>

**Duloxetine.** In a randomized, double-blind, placebo-controlled trial, patients treated with duloxetine had significant improvements in FIQ scores, reductions in Brief Pain Inventory average pain severity score, number of tender points, and several quality-of-life measures. Women experienced a greater treatment response than men. These improvements in fibromyalgia symptoms and pain severity were seen regardless of the baseline status of major depressive disorder and were independent of the effect on mood or anxiety.<sup>46</sup>

Duloxetine was also studied in women with primary fibromyalgia with or without comorbid major depressive disorder for 12 weeks in a randomized, double-blind, placebo-controlled trial. Compared with placebo, patients treated with duloxetine experienced significantly greater improvements on the Brief Pain Inventory average pain severity score, as well as the FIQ, Clinical Global Impression severity scale, Patient Global Impression of Improvement, and several quality-of-life measures.<sup>47</sup> The effect of duloxetine on pain was independent of effects on mood and independent of the presence of comorbid major depressive disorder.<sup>47</sup> The effects of duloxetine on reducing pain were found to be maintained during a 52-week randomized double-blind trial comparing 60 and 120 mg dosages of duloxetine.<sup>48</sup>

The most common adverse events associated with duloxetine include nausea, dry mouth, constipation, somnolence, hyperhidrosis (excessive sweating), and decreased appetite. Other warnings and precautions include hepatotoxicity, orthostatic hypotension, serotonin syndrome or neuroleptic malignant syndrome, abnormal bleeding, hypomania, seizures, urinary retention, hyponatremia, and alterations in blood pressure and blood glucose levels. As with all antidepressants, duloxetine may increase the risk of suicide and therefore has a Risk Evaluation and Mitigation Strategy (REMS) program that includes a medication guide.<sup>49</sup> Duloxetine is a moderate inhibitor of cyto-

chrome P450 (CYP)2D6; potent inhibitors of CYP2D6 may increase duloxetine concentrations. In addition, potent inhibitors of CYP1A2 should be avoided.<sup>49</sup> Use of duloxetine is contraindicated in patients taking monoamine oxidase inhibitors and in patients with uncontrolled narrow-angle glaucoma.

The recommended dose of duloxetine for treating fibromyalgia is 60 mg/day; however, some patients may benefit from starting at 30 mg/day. A gradual dose reduction is recommended if duloxetine is discontinued to prevent withdrawal symptoms.

**Milnacipran.** Milnacipran was studied in a double-blind placebo-controlled trial for 12 weeks. Patients treated with milnacipran were significantly more likely to report overall improvement and reduction in pain.<sup>50</sup> In a 15-week trial, patients receiving milnacipran were reported to have significant improvement in fibromyalgia pain within 1 week of treatment and to have significant improvements in PGIC, physical function, and fatigue compared with placebo.<sup>52</sup> In a longer, 27-week, randomized, double-blind, multicenter study, milnacipran was significantly more likely than placebo to significantly reduce pain, cognition, and fatigue.<sup>51</sup>

As seen in the trials of duloxetine, improvements in patients taking milnacipran were independent of effects on mood. Furthermore, most fibromyalgia trials have excluded patients with major depressive disorder. Thus, the efficacy of SNRIs in treating fibromyalgia appears to be independent of their antidepressant effects.<sup>52</sup>

The most common adverse events occurring with milnacipran are nausea, headache, constipation, dizziness, insomnia, hot flush, hyperhidrosis, vomiting, palpitations, increased heart rate, dry mouth, and hypertension. Other warnings and precautions include serotonin syndrome or neuroleptic malignant syndrome, (a potentially fatal condition that may be caused by certain medications; symptoms include high fever, sweating, unstable blood pressure, confusion, and stiffness), elevated blood pressure and heart rate, seizures, hepatotoxicity, and abnormal bleeding. Male patients with a history of obstructive uropathies may experience higher rates of genitourinary adverse events. As with all antidepressants, milnacipran may increase the risk of suicide and has a REMS program that includes a medication guide.<sup>53</sup>

Use of milnacipran is contraindicated in patients taking monoamine oxidase inhibitors. Milnacipran is unlikely to be involved in clinically important pharmacokinetic drug interactions. However, pharmacodynamic interactions with other medications can occur.<sup>53</sup>

The recommended dosage of milnacipran is 100 mg/day administered in two divided doses. Dosing should be initiated at 12.5 mg (once daily on the first day) and increased over a 1-week period to 100 mg/day. The dosage may be increased to 200 mg/day based on individual patient responses.<sup>53</sup>

### Pharmacist's role in managing fibromyalgia

Pharmacists can assist patients with fibromyalgia in many ways. They can educate patients about nonpharmacologic and pharmacologic options of which patients may not be aware.

For patients who are using medications to manage their symptoms, pharmacists can educate patients about the benefits of the medications and about safe and appropriate use. Several medications that are used in treating fibromyalgia must be titrated when therapy is initiated. When dispensing a prescription for one of these medications, pharmacists should engage in a conversation to ensure that patients understand the titration schedule. Likewise, several medications should be tapered upon discontinuation to avoid withdrawal symptoms; patients may need education to ensure these medications are tapered appropriately.

Pharmacists can work with patients to help them establish realistic expectations for treatment with medications, as well as other interventions used in managing fibromyalgia. In addition, pharmacists can educate patients about adverse events associated with treatment, the expected course of the adverse events, and management strategies. For example, when discussing exercise, pharmacists should stress the importance of gradually increasing the amount of physical activity to avoid exacerbating fibromyalgia symptoms and to expect some delayed-onset muscle soreness.

All three medications that are FDA approved for treating fibromyalgia are covered by REMS programs that include the distribution of a Medication Guide. Pharmacists should ensure that patients receive a copy of the Medication Guide with each prescription and answer any patient questions about the information in the Medication Guides.

Pharmacists can participate in ongoing follow-up to monitor patients' responses to both pharmacologic and nonpharmacologic interventions. The assessment should consider both the impact on symptoms of fibromyalgia and on the patient's function. If patients do not achieve a satisfactory treatment response or experience intolerable adverse events, pharmacists can collaborate with other members of the health care team to determine whether a trial of another medication would be appropriate. Because emerging evidence indicates fibromyalgia has many possible root causes, lack of treatment response to one medication does not affect whether another medication will be effective.<sup>52</sup>

When assessing pain in patients with fibromyalgia, it is important to consider that other painful conditions may be present and reports of pain should not necessarily be attributed to fibromyalgia. Each pain complaint should be investigated individually, particularly when new pain complaints are reported. For example, a patient with fibromyalgia could also develop migraine headaches, which should be treated in addition to the fibromyalgia treatments.

Pharmacists can assess and triage patients who present to the pharmacy with a history of symptoms that are associated with fibromyalgia. Although fibromyalgia is a relatively common condition, it was not widely recognized until recently and not all primary care providers are familiar with its presentation and diagnostic criteria. In other cases, patients may have had their symptoms dismissed by other health providers. If patients present to the pharmacy with complaints of symptoms that are consistent with fibromyalgia, the pharmacist can refer them to

other health providers with experience treating fibromyalgia.

Other patients with diagnosed fibromyalgia may have attempted trials with medications in the past and discontinued treatment because of lack of efficacy and/or adverse events. Pharmacists may wish to inform such patients that new treatment options are available and explore with the patient and other members of the health care team whether a trial with a newer agent is warranted. Furthermore, because many patients benefit from a combination of treatment approaches, pharmacists should work with the patient and other members of the health care team to determine whether additional interventions are needed and make referrals as necessary. However, evidence to support combining multiple medications is lacking.

Many patients with fibromyalgia may attempt trials with various dietary supplements to manage their fibromyalgia symptoms. To ensure that pharmacy records are thorough, pharmacists should question patients about their use of dietary supplements and ensure that their use is noted in the patient's record and is also included on any medication list that the patient shares with other health providers. If patients are using dietary supplements or are considering using them, pharmacists can research available evidence about the dietary supplements in question to assess for possible interactions and provide the patient with scientific information to support them in making an informed choice about whether and how to use them. However, because data about many dietary supplements are limited, pharmacists should advise caution and recommend that patients keep track of the supplement's impact on their symptoms, as well as any adverse events that they experience.

Because of the devastating impact fibromyalgia can have on patients' lives, many patients benefit from participation in support groups. Pharmacists can help connect patients with both national patient organizations and local support groups (Table 2).

## Conclusion

Fibromyalgia is a chronic pain condition that has been recognized for more than a century. However, diagnostic criteria were not established until 1990. Fibromyalgia is characterized by chronic widespread pain, fatigue, and sleep disturbances and may be associated with several other troublesome symptoms. The impact of fibromyalgia on patient function can be severe, with many patients unable to work or perform routine household maintenance.

During the previous few decades, substantial research has investigated the causes of fibromyalgia and its treatment. Although the exact etiology of fibromyalgia remains uncertain, current evidence indicates that environmental triggers in patients with a genetic susceptibility lead to the development of fibromyalgia and that several neurologic and endocrine changes are present in patients with fibromyalgia. However, because most common laboratory findings are normal and because no physical signs of the disorder are present, some health providers and researchers do not consider fibromyalgia to be a "real" condition and therefore dismiss

**Table 2.** National organizations and online resources that provide fibromyalgia information and support

Organization/online resource	Website
Advocates for Fibromyalgia Funding, Treatment, Education, and Research	<a href="http://www.affer.org">www.affer.org</a>
Arthritis Foundation	<a href="http://www.arthritis.org">www.arthritis.org</a>
Chronic Fatigue Syndrome and Fibromyalgia Self-Help	<a href="http://www.cfidsselfhelp.org">www.cfidsselfhelp.org</a>
Fibromyalgia Network	<a href="http://www.fmnetnews.com">www.fmnetnews.com</a>
KnowFibro	<a href="http://www.knowfibro.com">www.knowfibro.com</a>
National Fibromyalgia Association	<a href="http://www.fmaware.org">www.fmaware.org</a>
National Fibromyalgia Partnership, Inc.	<a href="http://www.fmpartnership.org">www.fmpartnership.org</a>

patients' symptoms.

A multimodal approach to managing fibromyalgia appears to be more effective than any single intervention alone. Non-pharmacologic treatment can include education, exercise, CBT, relaxation strategies, and balneotherapy, as well as other interventions that have less proven effectiveness. Numerous agents have been investigated for treating fibromyalgia; however, only pregabalin, duloxetine, and milnacipran have received FDA approval for this indication.

Pharmacists can play many important roles in managing patients with fibromyalgia, including assessing responses to therapy, identifying patients who may require additional therapy, and educating patients about fibromyalgia, fibromyalgia management, and fibromyalgia medications. Pharmacists can also help patients identify other health providers that are familiar with the diagnosis and management of fibromyalgia and help them locate local and national resources that provide support.

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## Assessment Questions

**Instructions:** The assessment test for this activity must be taken online; please see “CPE processing” below for further instructions. There is only one correct answer to each question. This CPE will be available at [www.pharmacist.com](http://www.pharmacist.com) no later than January 31, 2010.

1. **Which of the following statements about the prevalence of fibromyalgia is true?**
  - a. The prevalence of fibromyalgia is highest during adolescence.
  - b. The prevalence of fibromyalgia is higher in the United States than the rest of the world.
  - c. Approximately 90% of patients are women.
  - d. Approximately 80% of patients are women.
2. **Which of the following is a requirement for diagnosing fibromyalgia pain, according to criteria from the American College of Rheumatology?**
  - a. Pain must occur only on one side of the body.
  - b. Patients must have axial skeletal pain.
  - c. Patients must have at least eight tender points.
  - d. Pain must be accompanied by tingling, numbness, burning, or prickling.
3. **Which of the following statements about tender points associated with fibromyalgia is true?**
  - a. Tender points are painful even without touching.
  - b. Tender points are never present in patients without fibromyalgia.
  - c. Higher numbers of tender points are associated with more severe symptoms.
  - d. The number of tender points that a patient has is usually static.
4. **Which of the following statements about the development of fibromyalgia is true?**
  - a. The development of fibromyalgia is usually precipitated by psychological distress.
  - b. Both genetic and environmental factors appear to contribute to the development of fibromyalgia.
  - c. Fibromyalgia is associated with hypothyroidism.
  - d. Fibromyalgia appears to be an autoimmune disorder.
5. **Fibromyalgia has been found to impair patient function and quality of life to an extent similar to, or worse than, which of the following conditions?**
  - a. Rheumatoid arthritis
  - b. Seasonal allergic rhinitis
  - c. Alzheimer's disease
  - d. Posttraumatic stress disorder
6. **Which of the following patient assessment tools does not evaluate patient function?**
  - a. Fibromyalgia Impact Questionnaire
  - b. Patient Global Impression of Change
  - c. Brief Pain Inventory
  - d. Numerical rating scales
7. **Which nonpharmacologic therapy received the same level of recommendation from both the American Pain Society (APS) and European League Against Rheumatism (EULAR) guidelines for treating fibromyalgia?**
  - a. Exercise
  - b. Balneotherapy
  - c. Cognitive behavioral therapy (CBT)
  - d. Patient education
8. **Which of the following statements about patient education about fibromyalgia is true?**
  - a. Education is only effective when it is combined with other interventions.
  - b. Education teaches patients that fibromyalgia symptoms are simply an overreaction to ordinary stimuli and trains patients to ignore their symptoms.
  - c. Appropriate education can reduce the stigma associated with fibromyalgia.
  - d. Patients should receive a trial of educational interventions before attempting other therapies for fibromyalgia.
9. **The use of CBT to treat fibromyalgia has been shown to**
  - a. Decrease stress and improve mood and coping strategies.
  - b. Improve patient function and quality of life.
  - c. Increase the number of disabled patients who return to work.
  - d. Reduce pain scores and fatigue.
10. **Which of the following nonpharmacologic interventions has been shown in clinical trials to be most effective for reducing symptoms of fibromyalgia?**
  - a. Supervised aerobic exercise
  - b. Progressive muscle relaxation
  - c. Biofeedback
  - d. CBT
11. **Which of the following statements about the use of complementary and alternative medication (CAM) is true?**
  - a. Several dietary supplements have been proven to be effective at reducing pain and improving function in patients with fibromyalgia.
  - b. Patients with fibromyalgia are 2.5 times more likely than control patients to visit CAM providers.
  - c. Currently, no evidence supports using chiropractic therapy for fibromyalgia.
  - d. Patients with fibromyalgia are less likely than patients with other chronic pain conditions to visit CAM providers.

**12. Which of the following medications were given a “grade A” recommendation by the EULAR guidelines but not mentioned by the APS guidelines?**

- Tropisetron and pramipexole
- Acetaminophen and weak opioids
- Tropisetron, pramipexole, and pregabalin
- Tramadol, acetaminophen, and weak opioids

**13. Which of the following statements about the use of antidepressants for treating fibromyalgia is true?**

- They appear to be most effective in patients who have comorbid depression or mood disorders.
- Their efficacy appears to be mostly a result of their effects on serotonin.
- The use of tricyclic antidepressants for treating fibromyalgia is limited by their adverse events.
- They should be used as adjunctive therapy to other medications used in treating fibromyalgia.

**14. Which of the following statements about pregabalin, duloxetine, and milnacipran is true?**

- Improvements in symptoms seen in short-term trials have been sustained during long-term follow-up trials.
- None of these medications require a medication guide.
- These agents are able to improve pain and fatigue, but no effects on patient function or quality of life have been reported.
- Men have been found to have a greater response to therapy than women.

**15. Which of the following medications is a controlled substance?**

- Amitriptyline
- Pregabalin
- Duloxetine
- Milnacipran

**16. Which medication(s) should not be coadministered with potent inhibitors of cytochrome P450 1A2?**

- Pregabalin and duloxetine
- Duloxetine
- Pregabalin and milnacipran
- Milnacipran

**17. Which medication(s) are contraindicated in patients taking monoamine oxidase inhibitors?**

- Pregabalin
- Duloxetine
- Milnacipran
- Duloxetine and milnacipran

**18. Patients who have difficulty sleeping should**

- Take naps whenever they feel tired.
- Work or read in bed to help them get comfortable before falling asleep.
- Finish exercising at least 3 hours before bedtime.
- Have a large meal before bedtime.

**19. Which of the following statements about ongoing assessment and monitoring in patients with fibromyalgia is true?**

- If new pain complaints are reported, they can usually be considered part of the fibromyalgia syndrome and do not require additional investigation.
- Patients who fail to respond to one medication are unlikely to respond to others.
- If patients fail to respond to medications approved for treating fibromyalgia, they should be discontinued without tapering.
- Monitoring should evaluate the impact of treatment on patient function, as well as fibromyalgia symptoms.

**20. Patients who are interested in using dietary supplements for treating fibromyalgia should be educated that**

- They should include all dietary supplements on medication lists that they share with other health providers.
- No dietary supplements are known to interact with medications used in treating fibromyalgia; therefore, experimenting with various products is safe.
- Dietary supplements that are advertised as “natural” are generally considered safe.
- A large body of evidence supports the use of several dietary supplements in treating fibromyalgia.

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