

Continuing Education for Pharmacists



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Fibromyalgia: A Veritable Disease with Real Symptoms

Goal. The goal of this lesson is to discuss fibromyalgia with reference to how it is managed.

Objectives. At the conclusion of this lesson, successful participants should be able to:

1. identify the demographics and prevalence of fibromyalgia in the United States;
2. recognize the principles of fibromyalgia, including pathophysiology, clinical manifestations, and diagnosis; and
3. select from a list specific nonpharmacologic and pharmacologic management of fibromyalgia.

Long believed by some to be little more than a vague description of another, albeit unknown symptom complex, fibromyalgia is described today as a veritable disease with real symptoms! It is an idiopathic, chronic, common and complex musculoskeletal pain syndrome characterized by widespread soft tissue pain and tenderness in the absence of tissue damage. Affecting 3 to 5 percent of the population in industrialized nations, fibromyalgia is prevalent in 3.4 percent of women and 0.5 percent of men in the United

States. Rheumatologists report that it is the second most common disorder, after osteoarthritis, both in its primary form and as an accompaniment of other rheumatic disorders. The disease accounts for 5 percent of patients in general medical practice, which results in a significant burden on the nation's health system, as well as lost employment time and medical costs that are about three times higher than expenditures for people without fibromyalgia.

Pathophysiology

The pathophysiology of fibromyalgia remains elusive. A genetic predisposition is suggested since it is more prominent in females and in some families. Specific trigger factors include physical trauma (especially of the axial skeleton [cervical, thoracic and lumbar spine]), surgical interventions, infections (by *Borrelia burgdorferi*, Parvovirus, Coxsackievirus, hepatitis C and human immunodeficiency virus), and acute or chronic emotional stress.

Emerging evidence strongly supports the notion that fibromyalgia is a disorder of central pain processing. Dysregulation of the

hypothalamic-pituitary-adrenal axis and altered activity of serotonin, norepinephrine, substance P, and other neurohormones have been implicated in the transmission of painful stimuli that may contribute to heightened pain sensitivity.

This theory lends support to targeted central nervous system therapies, such as antidepressants and cognitive behavior strategies, which act through modifying the pain response. The concept of altered central pain processing helps explain why analgesics, whose activity is primarily mediated peripherally (e.g., nonsteroidal antiinflammatory drugs [NSAIDs]), are less effective unless a coexisting inflammatory disorder is also being treated. It is, therefore, essential to identify comorbid (concurrent but unrelated) disorders early and treat them appropriately. More research is needed to determine the pathophysiology of fibromyalgia, and therapies that will address the specific pain pathways involved.

Clinical Manifestations

Patients report a considerable impact on their quality of life, and their perceived disability level is influenced by their mental health

Table 1
ACR* Criteria
for Classification of
Fibromyalgia

Widespread pain for at least three months, defined as the presence of all of the following:

- Pain on the right and left sides of the body
- Pain above and below the waist (including shoulder and buttock pain)

- Pain in the axial skeleton (cervical, thoracic or lumbar spine, or anterior chest)

Pain on palpation with a 4-kg force in 11 of the following 18 sites (nine bilateral sites, for a total of 18 sites):

- Occiput: at the insertions of one or more of the following muscles: trapezius, sternocleidomastoid, splenius capitus, semispinalis capitus

- Low cervical: at the anterior aspect of the interspaces between the transverse processes of C5-C7

- Trapezius: at the midpoint of the upper border

- Supraspinatus: above the scapular spine near the medial border

- Second rib: just lateral to the second costochondral junction

- Lateral epicondyle: 2 cm distal to the lateral epicondyle

- Gluteal: at the upper outer quadrant of the buttocks at the anterior edge of the gluteus maximus muscle

- Greater trochanter: posterior to the greater trochanteric prominence

- Knee: at the medial fat pad proximal to the joint line

*American College of Rheumatology
Adapted from: Millea PJ, Holloway.
Am Fam Physician. 2000;62:1575-82, 87

condition. Effective pain relief in these patients significantly increases quality of life.

Many symptoms of fibromyalgia overlap considerably with those of other chronic illnesses, such as

chronic fatigue and irritable bowel syndromes, chronic migraine and tension headache syndromes, genitourinary afflictions, multiple chemical sensitivities and depression. Patients often complain of widespread pain, poor sleep and fatigue. They may describe low back pain radiating into the buttocks and legs, as well as pain and tightness in the neck and across the upper posterior shoulders. Pain may be described as a burning or gnawing soreness, aching or stiffness.

Headaches are present in more than half of all persons with fibromyalgia. The prevalence of migraine in these individuals suggests a common pathogenesis. The proposed etiology of migraine has been characterized by a parallel dramatic failure of serotonergic systems, along with a defect in adrenergic transmission.

Many patients with fibromyalgia have an associated sleep disorder. During sleep, sufferers are constantly interrupted by bursts of awake-like brain activity, which limits time in deep sleep. They awaken frequently during the night, have difficulty returning to sleep, and feel exhausted upon awakening. Partly due to the poor sleep, patients describe their fatigue as overwhelming exhaustion.

Irritable bowel syndrome (IBS) is often present. A functional disorder of the gastrointestinal tract, affected individuals suffer from chronic abdominal pain and disturbed bowel function, without evidence of structural or laboratory abnormalities on routine testing.

A subjective swollen feeling in the joints without objective swelling, and paresthesia (numbness or tingling in the extremities) without objective neurologic findings are two important features of fibromyalgia. Stiffness that is present in the morning upon arising typically improves as the day progresses.

Patients often experience cognitive difficulties such as memory loss and difficulty expressing themselves in normal conversation. Other manifestations include anxiety, light-headedness and

dizziness. Fibromyalgia patients also report dysmenorrhea, irritable bladder, vision irregularities, premenstrual syndrome, symptoms of Raynaud's phenomenon, restless leg syndrome and noncardiac chest pain. Symptoms are intensified by cold and humid weather, poor sleep, and physical or mental stress, and improved by warm and dry weather, moderate physical activity, adequate sleep and relaxation.

Diagnosis of Fibromyalgia

While no currently available laboratory test can confirm the diagnosis of fibromyalgia, most patients describe a history of widespread pain with physical findings and the comorbid conditions described above. It is important to confirm the diagnosis of fibromyalgia by its own characteristics rather than as a result of exclusion from other pathologies.

Although the condition of fibromyalgia dates back to early 20th century, it was not until 1990 that the American College of Rheumatology (ACR) defined specific criteria for the classification of fibromyalgia. These criteria (Table 1) require the presence of chronic (≥ 3 months), widespread musculoskeletal pain in at least 11 tender points on testing at 18 specified sites. An important consideration of the physical examination for a positive diagnosis of fibromyalgia is to systematically palpate (press) on the skin at the 18 sites, applying a moderate and consistent degree of pressure using the thumb of the dominant hand. The amount of force applied should be such that the examiner's thumbnail is blanched. The pain must occur in all four quadrants of the body and the axial skeleton. The tender points are distinct, predictable anatomical sites that are normally more sensitive to pressure than the surrounding tissue. They differ from other painful trigger points in the body in that they are not sites of tissue damage, tightness or pathology. They do not produce spontaneous pain and are usually unknown to the patient. It is known that some patients who clearly suffer

from the classic symptoms of fibromyalgia will respond affirmatively to fewer than 11 of these tender points. Men generally have a higher tenderness threshold and fewer men than women respond to a complete “set” of at least 11 positive tender points despite clearly having symptomatic disease. This may partially explain why more women than men receive the diagnosis of fibromyalgia. All this said, the ACR classification criteria for diagnosis of fibromyalgia provides a sensitivity and specificity of nearly 85 percent in differentiating fibromyalgia from other forms of chronic musculoskeletal pain.

Moreover, other symptoms of fibromyalgia including chronic fatigue, altered sleep patterns resulting in unrefreshing sleep, dizziness, emotional distress, postural hypotension and memory disturbance often fluctuate in intensity, and pain appears in different sites. Flares can be induced or worsened by situations such as emotional stress, physical exertion, concurrent illness or even seasonal changes.

Management

Obtaining relief of pain in fibromyalgia can be a challenge. Support from family, friends, and the healthcare system is often lacking. Optimal management includes nonpharmacologic and pharmacologic measures. The American Pain Society Fibromyalgia Panel recommends a multidisciplinary approach (Table 2).

It is imperative that patients have input in the management of their disease. This can reduce anxiety and depression.

Nonpharmacologic Measures

Patient Education. Although a major segment of patient education is received in the physician’s office, the effectiveness of organized programs in providing information, facilitating behavior change and improving symptoms is well documented. Providing helpful information directly or by steering patients to reliable sources of

Effectiveness	Pharmacologic	Nonpharmacologic
Strong evidence	amitriptyline cyclobenzaprine	cardiovascular exercise, cognitive behavioral therapy, patient education, multidisciplinary therapy (e.g., patient education and exercise)
Moderate evidence	Dual-reuptake inhibitors (duloxetine, venlafaxine) Fluoxetine, Pregabalin± Tramadol with or without acetaminophen	acupuncture, balneotherapy*, biofeed back, hypnotherapy, strength training
Weak evidence		chiropractic therapy, electrotherapy, manual and massage therapy, ultrasonography
No evidence	corticosteroids melatonin, NSAIDs, Opioids≠, thyroid hormone	flexibility exercise, tender (trigger) point injections

*Balneotherapy = Treatment of disease by baths.
±Pregabalin (Lyrica) is now approved by FDA for treatment of fibromyalgia
≠An exception is made for tramadol, the synthetic codeine derivative, which has moderate evidence of effectiveness in fibromyalgia.
Adapted from: Goldenberg DL, Burckhardt C, Crofford L. *JAMA*. 2004;292:2388-2395

information affords great professional opportunities for pharmacists.

Helpful information specific to fibromyalgia is available through the American College of Rheumatology (www.rheumatology.org), Arthritis Foundation (www.arthritis.org), Fibromyalgia Network (www.fmnetnews.com) and the National Fibromyalgia Association (www.fibrohope.org).

Exercise. The major goal for patients with fibromyalgia is to maintain normal function in everyday activities. An exercise program should include multiple dimensions that blend components of strength, aerobic (endurance) conditioning, flexibility and balance. To improve adherence to exercise programs, it is helpful to allow patients to choose the type of exercise (e.g., walking, bicycling, swimming, etc.) they prefer.

Cognitive Behavior Strategies. The major goal of cognitive and

behavioral strategies is to help patients understand the effect that thoughts, beliefs and expectations have on their symptoms. Patients are taught to prioritize their time to achieve a comfortable balance between work, leisure and the activities of daily living.

Pharmacologic Measures

Pharmacotherapy for fibromyalgia has been most successful with centrally-acting agents. Although the drugs are classified as antidepressants, muscle relaxants or anticonvulsants, they affect various neurochemicals (e.g., serotonin, norepinephrine, substance P) that have a broad range of activities in the brain and spinal cord, including actions on pain sensations and tolerance. Because symptoms of fibromyalgia wax and wane, effective treatment must be ongoing rather than episodic.

Antidepressants. Antidepressants have a long history in the

treatment of chronic pain syndromes. There is evidence that they alleviate pain, and improve sleep quality and overall wellbeing in approximately one-third of fibromyalgia patients. Tricyclic antidepressants (TCAs), specifically amitriptyline (Elavil, etc.), are effective in providing analgesic effect, aiding sleep, and treating concomitant mood disorders. Selective serotonin reuptake inhibitors (SSRIs) in general have poor analgesic effect; however, fluoxetine (Prozac, etc.) has been shown to have a small but significant effect on symptoms in women with fibromyalgia. A TCA, SSRI or combination of both, produces mild to moderate improvement in symptoms. One study showed that while 25 mg of amitriptyline or 20 mg of fluoxetine reduced symptom severity in fibromyalgia, the combination of the two drugs was twice as effective as either agent taken alone.

The newer serotonin-norepinephrine reuptake inhibitor duloxetine (Cymbalta) has shown promise in improving symptoms. Duloxetine 60 mg/day is effective in reducing pain and tenderness in patients with fibromyalgia regardless of whether patients have major depressive disorders. Venlafaxine (Effexor, etc.) has also been shown to be effective in alleviating pain and depressive symptoms in some small clinical trials, but this has not yet been corroborated by placebo-controlled, double-blind studies.

Chronic Opioid Analgesic Therapy (COAT). COAT may be suitable for treatment of mild to moderate pain or significant functional impairment, and for patients in whom other therapies are ineffective or contraindicated. Tramadol (Ultram, etc.), a centrally-acting, mild, narcotic analgesic, is somewhat effective in patients with mild to moderately severe pain. Combining tramadol with acetaminophen (Ultracet, etc.) has been shown to be effective without causing serious adverse effects. Other opioids have not been adequately tested in fibromyalgia; moreover, these patients seem

especially sensitive to opioid side effects (nausea, constipation, itching and mental blurring), which often rules out the long-term use of these drugs.

Other Analgesics. Acetaminophen and NSAIDs are commonly used, but have no clear evidence of effectiveness. The skeletal muscle relaxant cyclobenzaprine (Flexeril, etc.) has been shown to be effective in improving sleep and decreasing pain.

Pregabalin. At the time of preparation of this lesson, pregabalin (Lyrica) is the first and only FDA-approved drug for management of fibromyalgia. When first marketed, the drug was approved for treatment of neuropathic pain associated with postherpetic neuralgia and diabetic peripheral neuropathy, and for adjunctive treatment of partial onset seizures in adults with epilepsy.

Pregabalin, which is structurally similar to gabapentin (Neurontin, etc.), is a derivative of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). It does not bind directly to GABAA or GABAB, or benzodiazepine receptors. It does not exert gabaminergic activity or block sodium channels, is not active at opiate receptors, and does not alter cyclooxygenase enzyme activity. It is inactive at serotonin and dopamine receptors and does not inhibit dopamine, serotonin, or norepinephrine reuptake.

Lyrica binds with high affinity to the alpha2-delta site (a subunit of voltage-gated calcium channels) within the CNS. Although its mechanism of action remains unknown, there is evidence that binding to these sites may be involved in its action in fibromyalgia. *In vitro*, pregabalin reduces the calcium-dependent release of several neurotransmitters including substance P, possibly by modulation of calcium channel function. Its pharmacologic actions in fibromyalgia appear to be restricted to central neurons.

Adverse reactions range from mild to moderate in intensity with the most common ones (recorded at ≥ 5 percent and twice placebo) being

blurred vision, dizziness, dry mouth, edema, weight gain and difficulty with concentration/attention. Because pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other drugs via metabolic interactions or protein binding displacement.

The recommended dose in treating fibromyalgia is 300 to 450 mg/day given in two or three divided doses. There is no evidence that doses of 600 mg/day confer additional benefit. Lyrica is taken orally with or without food. When discontinuing therapy, doses should be tapered down gradually over a minimum of one week.

Lyrica is a Schedule V substance. In clinical trials, abrupt or rapid discontinuation has led to symptoms including headache, diarrhea, insomnia and nausea, which are suggestive of physical dependence.

Summary and Conclusions

The outlook for sufferers of fibromyalgia is better than ever before. The efforts of numerous individuals, support groups, organizations and medical professionals involved in helping people with fibromyalgia improve their quality of life are starting to pay dividends. Symptoms can fluctuate in severity, but the majority of patients do improve over time with proper treatment. With FDA approval of Lyrica, other, even more specific treatments may follow. By actively seeking the latest proven therapy, conversing with others who have fibromyalgia, reevaluating daily priorities, making appropriate lifestyle changes and working hard to maintain a hopeful attitude, the fibromyalgia sufferer can become the fibromyal.

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