Patients with fibromyalgia often resist being referred to a psychiatrist because they fear being told their pain and other somatic symptoms are “all in their heads.” Evidence is mounting that they may be literally correct—the symptoms of fibromyalgia appear to have a physiologic connection with the central nervous system. Abnormal CNS activity, including sleep patterns, response to stress, pain processing, and neurotransmitter levels, has been documented in patients with fibromyalgia.

As psychiatrists, we can reassure these patients—and their primary care physicians and rheumatologists—that we are in a position to help because we:

• have expertise in assessing mood and anxiety disorders and in managing antidepressants, the medication physicians most commonly prescribe for fibromyalgia;
• are skilled in the use of the anticonvulsant gabapentin, which is being used in fibromyalgia for its analgesic and sedative effects;
• can offer much-needed support through psychotherapy, as chronic pain and other fibromyalgia-related symptoms create great stress in these patients’ lives.

Antidepressants are showing promise as an effective treatment for pain, fatigue, and depression in patients with fibromyalgia.

Lesley M. Arnold, MD
Associate professor, department of psychiatry
Director, Women’s Health Research Program
University of Cincinnati College of Medicine

Antidepressants for fibromyalgia
Latest word on the link to depression and anxiety
## CRITERIA FOR DIAGNOSING FIBROMYALGIA

### 1. History of widespread pain
**Definition**
Pain in the right and left side of the body, pain above and below the waist, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back). In this definition, shoulder and buttock pain is considered as pain for each involved side. “Low back” pain is considered lower segment pain.

### 2. Pain in 11 of 18 tender point sites on digital palpation
**Definition**
Pain, on digital palpation, must be present in at least 11 of the following 18 tender points:

- **Occiput**: Bilateral, at the suboccipital muscle insertion
- **Low cervical**: Bilateral, at the anterior aspects of the intertransverse spaces at C5-C7
- **Trapezius**: Bilateral, at the midpoint of the upper border
- **Supraspinatus**: Bilateral, at origins, above the scapula spine near the medial border
- **Second rib**: Bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces
- **Lateral epicondyle**: Bilateral, 2 cm distal to the epicondyles
- **Gluteal**: Bilateral, in upper outer quadrants of buttocks in anterior fold of muscle
- **Greater trochanter**: Bilateral, posterior to the trochanteric prominence
- **Knee**: Bilateral, at the medial fat pad proximal to the joint line

Digital palpation should be performed with an approximate force of 4 kg.
For a tender point to be considered “positive” the patient must state that the palpation was painful.
“Tender” is not to be considered “painful”

*Source: American College of Rheumatology*¹

### LOCATION OF FIBROMYALGIA TENDER POINTS

To palpate tender point sites, pressure is applied with the thumb pad perpendicularly to each site and the force increased by 1 kg per second until 4 kg of pressure is achieved. Whitening of the thumbnail bed usually occurs when applying the 4-kg force.
fibromyalgia in studies by our group and others. The following information can help you stay current with the newest understandings of this ailment.

**Mood disorders in fibromyalgia**

A diagnosis of fibromyalgia requires the finding of widespread pain and tenderness at specific anatomic points (Table 1, Figure 1). Most patients also report fatigue, sleep disturbance, and morning stiffness (Box 1). American College of Rheumatology criteria do not require exclusionary tests such as radiographs and blood tests for the diagnosis.

Primary care physicians are increasingly making the diagnosis themselves and referring patients to rheumatologists only when conditions other than fibromyalgia are suspected. The differential diagnosis is broad, and other rheumatic and nonrheumatic disorders have similar symptoms, require different treatment, and affect fibromyalgia management (Table 2).

Patients with fibromyalgia often report symptoms of major depressive disorder, such as depressed mood, anxiety, fatigue, and insomnia. Many psychological studies of such patients have documented increased rates of depressive symptoms. Depression and anxiety symptoms are common and frequently severe, even among individuals with fibromyalgia in the general population.

Patients’ mood and anxiety disorders correlate highly with the number of medically unexplained symptoms and are associated with functional disability. The presence of psychological symptoms predicts persistent fibromyalgia symptoms, and psychological distress is strongly associated with symptom severity.

**Evidence for a CNS link**

CNS mechanisms appear to contribute to the development of clinical findings in fibromyalgia.

**Abnormal sleep**

A qualitative defect in sleep has been identified in patients with fibromyalgia. This sleep abnormality consists of inappropriate intrusion of alpha waves (normally seen during wakefulness or REM sleep) into deep sleep (usually characterized by delta waves). Some researchers believe alpha-delta sleep intrusion is associated with the chronic musculoskeletal pain and fatigue of fibromyalgia and, in turn, is mediated by an abnormality in central serotonergic neurotransmission. This sleep abnormality is not specific to fibromyalgia and can be found in other conditions, however. Debate continues regarding the role of sleep dysregulation in the pathophysiology of fibromyalgia.

**Stress response**

Stress appears to precipitate or exacerbate fibromyalgia symptoms in many patients. For example, fibromyalgia appears to be associated with victimization (adult and childhood sexual, physical, and emotional trauma), and this stress may trigger the development of fibromyalgia in some patients.

Patients with fibromyalgia appear to develop disturbances in the two major stress-response systems: the
sensitization. Patients with fibromyalgia often develop an increased response to painful stimuli (hyeralgesia) and experience pain from normally nonnoxious stimuli (allodynia).

Substance P, an important nociceptive neurotransmitter, may have a role in generating central sensitization. Elevated concentrations of substance P have been found in the cerebrospinal fluid (CSF) of individuals with fibromyalgia. Substance P also inhibits CRH release and may contribute to low CRH activity in fibromyalgia.

**Neurotransmitter defects**

A functional reduction in serotonergic activity has been demonstrated in patients with fibromyalgia. Schwarz et al found a strong negative correlation between serum concentrations of the primary serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), and substance P, pain, and insomnia. Evidence also exists of reduced concentrations of the primary norepinephrine metabolite, 3-methoxy-4-hydroxyphenethylene (MHPG), in the CSF of patients with fibromyalgia. Reduced serotonin and norepinephrine levels in descending pain-inhibitory pathways may cause the allodynia and hyperalgesia of fibromyalgia.

**Pharmacologic treatment**

Most studies of pharmacologic treatment of fibromyalgia have examined antidepressants for three reasons:

- There is evidence of the successful use of antidepressants in other chronic pain conditions.

  **Antidepressants for fibromyalgia**

  - There is evidence of the successful use of antidepressants in other chronic pain conditions.
  - These agents are effective for treating mood and anxiety disorders, which frequently occur in patients with fibromyalgia and may share a common physiologic abnormality.
  - Antidepressants might enhance the activity of neurotransmitters such as serotonin and norepinephrine in the descending inhibitory pain pathways, leading to reduced pain perception.

  **Tricyclics**

  In randomized, controlled trials, tricyclic medications (including the muscle relaxant cyclobenzaprine) appear to be moderately effective in improving fibromyalgia symptoms. Two meta-analyses of trials of tricyclic medications (amitriptyline, dothiepin, cyclobenzaprine, clomipramine, and maprotiline) have found similar results.
found the greatest effect on measures of sleep improvement, which may be due in part to tricyclics’ sedative properties. Many patients with fibromyalgia, however, cannot tolerate the sedative and other side effects associated with tricyclic agents, even though low dosages (e.g., 25 mg/d of amitriptyline) have typically been used in clinical trials.

SSRIs. Selective serotonin reuptake inhibitors, although likely to be better tolerated than tricyclics, have been examined in only five placebo-controlled trials in fibromyalgia: two with citalopram, and three with fluoxetine. One citalopram study found no significant differences in efficacy between citalopram and a placebo, but the other reported significant improvement in one measure of pain and a significant decrease in depressive symptoms compared with the placebo group. No significant differences were found between groups in the global assessment of improvement.

The initial fluoxetine trial in fibromyalgia treatment did not reveal a significant therapeutic effect over a placebo, although the study was limited by a high (57%) placebo dropout rate, small sample size (42 subjects), brief duration (3 to 6 weeks after treatment), and restriction of fluoxetine dosage to 20 mg/d. In the two other controlled trials, including one which we recently conducted, fluoxetine was superior to a placebo in reducing pain and other fibromyalgia-associated symptoms.

In our 12-week investigation (a randomized, placebo-controlled, parallel-group, flexible-dose trial), 60 subjects with fibromyalgia received fluoxetine 20 to 80 mg/d or a placebo. Those receiving fluoxetine (mean dosage 45 ± 25 mg/d) displayed significantly greater reduction in pain, fatigue, and depression compared with those receiving the placebo. The effect of fluoxetine on pain remained significant after we adjusted for change in depression.

Sertraline was evaluated in an open study of 47 fibromyalgia patients at dosages of 25 to 200 mg/d for 6 weeks. Nearly two-thirds (63%) assessed the efficacy of sertraline as good or very good in the treatment of their symptoms. Paroxetine effectively reduced fibromyalgia symptoms in a single-blind study at dosages of 20 mg/d for 3 months.

SNRIs. Venlafaxine, a dual serotonin and norepinephrine reuptake inhibitor, has shown promise in the treatment of fibromyalgia in a preliminary open trial conducted by our group. Venlafaxine at a mean dosage of 167 mg/d resulted in significant improvement in fibromyalgia symptoms and quality of life compared with baseline. Notably, lifetime comorbid depressive and anxiety disorders were common in this sample, and their presence predicted response of fibromyalgia symptoms to venlafaxine.

Gabapentin. Although no studies have been published on fibromyalgia treatment with this anticonvulsant, gabapentin has been found to exert substantial analgesic effects in controlled studies of other kinds of pain, including diabetic neuropathy, post-herpetic neuralgia, and migraines. There are also anecdotal reports of its successful use in fibromyalgia.

Nonpharmacologic treatment
Cardiovascular fitness training, regional sympathetic block, electromyographic biofeedback, hypnotherapy, and electroacupuncture have been reported to have modest efficacy for fibromyalgia symptoms in short-term, randomized controlled trials. Other studies, however, have not replicated the efficacy of these treatments.

Cognitive-behavioral therapy has shown promise in preliminary studies. Cognitive restructuring techniques that challenge negative thoughts and promote an active, positive, problem-solving approach to pain were found to be important components of fibromyalgia therapy, as were relaxation training, aerobic exercise and stretching, pacing of activities, and family education.

Recommendations
Based on our group’s experience and the limited data available, the following are recommendations for the pharmacologic treatment of fibromyalgia:

- Consider a trial of antidepressant medication for patients with a history of mood (unipolar) or anxiety disorders. First try an SSRI or an SNRI because many patients do not tolerate tricyclics. Use antidepressant therapeutic dosages and an adequate duration of treatment (at least 6 weeks).
Antidepressants for fibromyalgia

- If symptoms do not respond to an adequate trial of first-line medications, treatment with tricyclics appears warranted. Although studies have focused mostly on tertiary amine tricyclics (e.g., amitriptyline), secondary amine agents (e.g., nortriptyline) may be just as effective and better tolerated, allowing for titration to higher dosages.

- Consider combination therapy when needed. For example, in patients who experience relief of pain, fatigue, and depressed mood with fluoxetine but continue to have insomnia, gabapentin can be added at night. Begin with 100 mg/d and increase by 100 mg/d until you see improvement or intolerance. Another option is trazodone, beginning with 50 mg hs. If you add a low-dose tricyclic to an SSRI, be aware of pharmacokinetic interaction and monitor tricyclic levels.

- Gabapentin alone, although it has not been studied in controlled trials of fibromyalgia, may be an option for patients who do not respond to antidepressants. Other pain conditions treated with gabapentin have required dosages of 1,600 to 2,400 mg/d to achieve substantial analgesic effects.

Cardiovascular fitness training is a potentially important component of fibromyalgia treatment. Many patients, however, have difficulty getting started because of increased pain after exercise and disabling fatigue. Treatment with medications as recommended may provide enough relief for patients to start an exercise program. Remind patients to start slowly, increasing the frequency and intensity of exercise as their endurance improves.

Because stress and a history of psychological trauma contribute to the onset and exacerbation of symptoms in some patients, cognitive-behavioral therapy is recommended as an adjunctive treatment as appropriate.

References

Related resources
- American Fibromyalgia Syndrome Association, Inc. wwwwasafund.org

DRUG BRAND NAMES
- Amitriptyline • Elavil
- Citalopram • Celexa
- Clonipramine • Anafranil
- Cyclobenzaprine • Flexeril
- Fluoxetine • Prozac
- Gabapentin • Neurontin
- Maprotiline • Ludiomil
- Nortriptyline • Pamelor
- Paroxetine • Paxil
- Sertraline • Zoloft
- Trazodone • Desyrel
- Venlafaxine • Effexor

In patients with fibromyalgia, mood and anxiety disorders may have a physiologic connection with abnormal sleep, stress response, neurotransmitter levels, and pain processing. A trial of an SSRI or SNRI at antidepressant therapeutic dosages is worthwhile.


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