What you can do for your fibromyalgia patient

**ABSTRACT**
Patients with fibromyalgia typically have pain “all over,” tender points, generalized weakness and fatigue, non-restorative sleep, and a plethora of other symptoms. In contrast to inflammatory and autoimmune conditions, laboratory tests and physical examination findings are usually normal. American College of Rheumatology guidelines facilitate diagnosis. Management requires a multifaceted, long-term strategy that emphasizes improving function rather than reducing pain.

**KEY POINTS**
Fibromyalgia is a clinical diagnosis, and specialized testing beyond basic laboratory tests is not indicated.

Antinuclear antibody test results can be confusing, and the test should not be ordered unless a patient has objective features suggesting systemic lupus erythematosus.

Treatment should be tailored to comorbidities such as depression, anxiety, and sleep disturbance. Options include serotonin-norepinephrine reuptake inhibitors (eg, duloxetine), selective serotonin reuptake inhibitors, low-dose tricyclic antidepressants (eg, amitriptyline), and gabapentinoids (pregabalin or gabapentin). These drugs can be used singly or in combination.

Medications that do not work should be discontinued.

“Catastrophizing” by the patient is common in fibromyalgia and can be addressed by education, cognitive behavioral therapy, and anxiolytic or antidepressant drugs.

Sustained, lifelong exercise is the treatment strategy most associated with improvement.
Rheumatology evaluation
The rheumatologist assesses the patient’s pain and reports the following:

Location and duration: Hands, wrists, elbows, shoulders, upper and lower back, sides of hips, knees, and feet; has been ongoing for 10 years, but worse in the past 3 months.

Character: The patient describes her pain as “like an ice pick being driven through my joints,” “sometimes unbearable,” and “like being hit by a truck.” She also reports numb, tingling, burning pain in her upper neck and back.

Variation with time, activity, and weather: Worse at night, causing her to wake and toss and turn all night; better with exertion, but after activity or exercise, she is exhausted for the rest of the day and sometimes for up to a week; worse with weather changes, especially during cold or humid weather.

Associated symptoms: Occasional perceived swelling of hands and feet, especially upon wakening in the morning, and 2 to 3 hours of stiffness in the morning that sometimes lasts all day.

Physical examination. Her findings are inconsistent with her symptoms. The patient exhibits limited range of motion. When asked to bend forward, rotate her neck, or flex and extend her neck and back, she does so only slightly. However, passive range of motion is normal in all joints.

When her joints are examined, she anticipates pain and withdraws her hands. But when she is distracted, examination reveals no evidence of swollen joints or synovitis. She has tenderness in 12 of 18 tender points. Her peripheral pulses are good, strength is normal, and reflexes are brisk.

Her facial rash looks more like rosacea than the butterfly rash of SLE. There is no indication of patchy hair loss. Heart and lung examinations are normal. She appears to have a good salivary pool without glossitis.

History reveals long-standing psychological issues
The patient reports a history of panic attacks and a prior diagnosis of anxiety. She is tested with the Generalized Anxiety Disorder 7-item scale (www.mdcalc.com/gad-7-general-anxiety-disorder-7) and scores 17 out of 21, indicating severe anxiety.

DISCUSSION: CHARACTERIZING PAIN
Understanding categories of pain syndromes can help us understand fibromyalgia. Pain can be categorized into 3 types that sometimes overlap:

Nociceptive or peripheral pain is related to damage of tissue by trauma or inflammation. Syndromes include osteoarthritis, rheumatoid arthritis, and SLE.

Neuropathic pain is associated with damage of peripheral or central nerves. Examples are neuropathy from herpes, diabetes, or spinal stenosis.

Centralized pain has no identifiable nerve or tissue damage and is thought to result from persistent neuronal dysregulation, overactive ascending pain pathways, and a deficiency of descending inhibitory pain pathways. There is evidence of biochemical changes in muscles, possibly related to chronic ischemia and an overactive sympathetic nervous system. Dysregulation of the sympathoadrenal system and hypothalamic-pituitary axis has also been implicated. And genetic predisposition is possible. Examples of centralized pain syndromes include fibromyalgia, irritable bowel syndrome, pelvic pain syndrome, neurogenic bladder, and interstitial cystitis.

Clues to a centralized pain syndrome
For patients with suspected fibromyalgia, distinguishing peripheral pain from centralized pain can be a challenge (Table 1). For example, SLE does not cause inflammation of the spine, so neck or back pain is not typical. Although both nociceptive and centralized pain syndromes improve with exertion, only patients with centralized pain are typically exhausted and bedbound for days after activity. Patients with centralized pain tend to describe their pain in much more dramatic language than do patients with inflammatory pain. Centralized pain tends to be intermittent; inflammatory pain tends to be constant. Patients with centralized pain often have had pain for many years without a diagnosis, but this is rare for patients with an inflammatory condition.

A patient with fibromyalgia typically has a normal physical examination, although allodynia (experiencing pain from normally nonpainful stimulation), hyperalgesia (in-
creased pain perception), and brisk reflexes may be present. Fibromyalgia may involve discoloration of the fingertips resulting from an overactive sympathetic nervous system. Laboratory results are typically normal with fibromyalgia.

Patients with either nociceptive or centralized pain report stiffness, but the cause likely differs. We typically think of stiffness as arising from swollen joints caused by inflammation, but stiffness can also be caused by abnormally tight muscles, as occurs in fibromyalgia.

### TABLE 1

Distinguishing inflammatory pain from centralized pain

<table>
<thead>
<tr>
<th>Feature</th>
<th>Inflammatory pain</th>
<th>Centralized pain</th>
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<tbody>
<tr>
<td>Location</td>
<td>Hands, wrists, cervical spine, knees, hips, ankles, feet</td>
<td>More diffuse, “all over,” tender points</td>
</tr>
<tr>
<td>Relationship to time of day</td>
<td>Nocturnal, with rest, early morning</td>
<td>Nocturnal, with rest, early morning</td>
</tr>
<tr>
<td>Relationship to exertion</td>
<td>Better with exertion</td>
<td>Better during exertion, worse after</td>
</tr>
<tr>
<td>Character of pain</td>
<td>Constant, dull, achy</td>
<td>Intermittent, stabbing, burning, “like being hit by a truck,” “unbearable”</td>
</tr>
<tr>
<td>Duration</td>
<td>Variable</td>
<td>Often many years</td>
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<tr>
<td>General associated symptoms and signs</td>
<td>Fatigue, fever, other organ signs and symptoms</td>
<td>Fatigue, weakness, headaches, irritable bowel syndrome symptoms, cognitive impairment, disturbed sleep, mood disorders, dry eyes and mouth, light sensitivity, difficulty swallowing, sensation of swollen glands in neck, urinary frequency, feeling faint after hot shower or in hot weather</td>
</tr>
<tr>
<td>Localized associated symptoms and signs</td>
<td>Stiffness ≥ 60 minutes</td>
<td>Stiffness ≥ 60 minutes</td>
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<tr>
<td></td>
<td>Objective swelling</td>
<td>Lack of objective findings</td>
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<tr>
<td></td>
<td></td>
<td>Tender points</td>
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<tr>
<td></td>
<td></td>
<td>Allodynia (pain from normally nonpainful stimuli), hyperalgesia (increased sensitivity to pain)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acrocyanosis (bluish coloring of hands and feet)</td>
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<td></td>
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<td>Brisk reflexes</td>
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<tr>
<td>Laboratory results</td>
<td>Inflammatory picture: elevated C-reactive protein and Westergren sedimentation rate, anemia, occasionally elevated platelet count, positive serologies (rheumatoid factor, anti-cyclic citrullinated peptide, extractable nuclear antigen panel)</td>
<td>Normal</td>
</tr>
</tbody>
</table>

**FIBROMYALGIA IS A CLINICAL DIAGNOSIS**

Diagnosing fibromyalgia does not require multiple laboratory and imaging tests. The key indicators are derived from the patient history and physical examination.

Diagnostic criteria for fibromyalgia published by the American College of Rheumatology have evolved over the years. The 2011 criteria, in the form of a self-reported patient questionnaire, have 2 components:

- The Widespread Pain Index measures the extent of pain in 19 areas.
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• The Symptom Severity scale assesses 3 key symptoms associated with fibromyalgia, ie, fatigue, cognitive problems, and nonrestorative sleep (scale of 0–3 for each symptom).

There are also questions about symptoms of irritable bowel syndrome, depression, and headache.

Fibromyalgia is diagnosed if a patient reports at least 7 painful areas and has a symptom severity score of at least 5. A patient may also meet the 20113 and the 2016 criteria4 if he or she has 4 painful areas and the pain is perceived in 4 of 5 areas and the Symptom Severity Scale score is 9 or higher.4 This questionnaire is not only a rapid diagnostic tool for fibromyalgia, it also helps identify and focus on specific issues—for example, having severe pain in a few localized areas, or having headache as a predominant problem.

These criteria are useful for a variety of patients, eg, a patient with hip arthritis may score high on the questionnaire, indicating that a component of centralized pain is also present. Also, people who have undergone orthopedic surgery who score high tend to require more narcotics to meet the goals of pain improvement.

The 2016 criteria,4 the most recent, maintain that pain must be generalized, ie, present in at least 4 of 5 body areas. They also emphasize that fibromyalgia is a valid diagnosis irrespective of other conditions.

CASE 1 CONTINUED:
THE PATIENT REJECTS THE DIAGNOSIS

Our patient meets the definition of fibromyalgia by each iteration of the American College of Rheumatology clinical criteria. She also has generalized anxiety disorder and a positive ANA test. She is advised to participate in a fibromyalgia educational program, start an aerobic exercise program, and consider taking an antidepressant medication with anxiolytic effects.

However, the patient rejects the diagnosis of fibromyalgia. She believes that the diagnosis of SLE has been overlooked and that her symptom severity is being discounted.

In response, the rheumatologist orders additional tests to evaluate for an autoimmune disorder: extractable nuclear antigen panel, complement C3 and C4, double-stranded DNA antibodies, and protein electrophoresis. Results are all in the normal range. The patient is still concerned that she has SLE or another autoimmune disease because of her abnormal ANA test result and remains dissatisfied with her evaluation. She states that she will complain to the clinic ombudsman.

SIGNIFICANCE OF ANA TESTING

Patients with positive test results increasingly go online to get information. The significance of ANA testing can be confusing, and it is critical to understand and be able to explain abnormal results to worried patients. Following are answers to some common questions about ANA testing:

Is ANA positivity specific for SLE or another autoimmune disease?

No. ANA is usually tested by indirect immunofluorescence assay on HEp-2 cells. The test can identify about 150 antigens targeted by antibodies, but only a small percentage are associated with an autoimmune disease, and the others do not have a known clinical association. Enzyme-linked immunosorbent assay (ELISA) ANA testing is also available but is considered less sensitive.

Abeles and Abeles5 retrospectively assessed 232 patients between 2007 and 2009 who were referred to rheumatologists for evaluation because of an elevated ANA test result. No ANA-associated rheumatic disease was found in patients who had a result of less than 1:160, and more than 90% of referrals for a positive ANA test had no evidence of ANA-associated disease. The positive predictive value was 9% for any connective tissue disease, and only 2% for SLE. The most common reason for ordering the test was widespread pain (23%). The authors concluded that ANA testing is often ordered inappropriately for patients with a low pretest probability of an ANA-associated rheumatic disease.

Screening with ANA testing generates many false-positive results and unnecessary anxiety for patients.
Clinic), about 15% of the general population test positive. By ELISA, with a cutoff of 20 ELISA units, 25% of healthy controls test positive.

It is true that ANA positivity may precede the onset of SLE.6,7 Arbuckle et al8 evaluated serum samples from the US Department of Defense Serum Repository obtained from 130 people before they received a diagnosis of SLE; in 115 (88%), at least 1 SLE-related autoantibody was present before diagnosis (up to 9.4 years earlier). However, in those who test positive for ANA, the percentage who eventually develop autoimmune disease is small.5

Is the titer of ANA significant and of diagnostic value?
The likelihood of autoimmune disease increases with increasing titer. But high titers can be seen in healthy people. Mariz et al9 examined ANA test results from 918 healthy controls and 153 patients with an autoimmune rheumatic disease. Of these, ANA was positive in 13% of healthy people and 90% of patients with an autoimmune disease. High titers were more likely in patients with an autoimmune disease, but also occurred in healthy controls.

Does the immunofluorescence pattern provide diagnostic information?
It can. There are 28 identified patterns of ANA, including nuclear, cytoplasmic, and mitotic patterns. The most common, the nuclear fine-speckled pattern, is seen in healthy controls and patients with an autoimmune disease. But other patterns are either characteristic of an autoimmune disease or, conversely, of not having an autoimmune disease (Table 2).9

Our patient has a nuclear dense fine-speckled pattern, further reducing the likelihood that she has an autoimmune disease.

### CASE 2: POORLY CONTROLLED, LONG-STANDING FIBROMYALGIA

A 43-year-old woman who has had fibromyalgia for 15 years is referred to a new primary care provider. She reports severe pain all over, low back pain, fatigue, nonrefreshing sleep, chronic migraine, constipation alternating with diarrhea, heartburn, intermittent numbness and tingling in her hands and feet, and depression. At this time, she rates her pain on a visual analog scale as 9 out of 10, and her fatigue as 8 out of 10.

Managing the pain of fibromyalgia requires a different model than that for peripheral pain

During the past 6 months, she has made 25 visits to specialists in 8 departments: spine, pain management, anesthesia, neurology, headache clinic, gastroenterology, sleep medicine, and physical therapy.

Her daily medications are duloxetine 120 mg, bupropion 300 mg, pregabalin 450 mg, cyclobenzaprine 30 mg, tramadol 200 mg, zolpidem 10 mg, nortriptyline 50 mg, acetaminophen 3,000 mg, and oxycodone 30 mg. She has also tried gabapentin and milnacipran without success. She reported previously taking different selective serotonin reuptake inhibitors and tricyclic antidepressants but cannot remember why they were stopped.

How should this complex patient be managed?

### BIOPSYCHOSOCIAL MANAGEMENT

Managing the pain of fibromyalgia requires a different model than used for peripheral pain from injury, in which the source of pain can be identified and treated with injections or oral therapy.

Neuronal dysregulation is not amenable to clinical measurement or treatment by medications at this time. But fortunately, many factors associated with fibromyalgia can be addressed: stressful life events, sleep disturbance,
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The severity of fibromyalgia increases linearly with the severity of depression. Patients who have already been treated with multiple drugs at high doses without benefit, such as our patient, should be referred to a psychiatrist. There is no additional benefit to referring this patient to a rheumatologist or spine clinic.

Addressing sleep problems
Sleep problems are not easy to manage but can often be helped. Epidemiologic studies indicate that poor sleep quality leads to chronic widespread pain in otherwise healthy people. In addition, experimental sleep deprivation leads to fatigue, cognitive difficulty, and a reduced pain threshold. In our patients with fibromyalgia, we have observed an inverse relationship between the number of hours slept and the severity of depression.

Sleep quantity and quality can be assessed by asking patients whether they have trouble sleeping, how many hours they sleep, and whether they have been diagnosed with a sleep disorder.

Patients should be counseled about sleep hygiene. Exercise can also help sleep.

Targeting maladaptive pain responses
Patients who catastrophize tend to have higher tender point counts, a hyperalgesic response, more depression and anxiety, and more self-reported disability. They are also less likely to return to work. They usually respond poorly to medications and are good candidates for cognitive behavioral therapy.

A high score on a self-reported Pain Catastrophizing Scale can help determine whether a multidisciplinary approach is advisable, although no threshold defines an abnormal score.

Educating patients about the neurobiology underlying their pain can be therapeutic. Cognitive behavioral therapy can help patients recognize their faulty thought processes and the relationship between pain and stress, and
learn better coping mechanisms. Patients who achieve the highest improvements in pain catastrophizing tend to derive the greatest benefit from cognitive behavioral therapy.

Exercise improves symptoms
Exercise improves fibromyalgia on many fronts and is associated with a host of positive effects in the brain and peripheral muscles. Exercise improves Fibromyalgia Impact Questionnaire scores, increases physical function and fitness, and reduces tender point counts, depression, and catastrophizing. There is no consensus on the best type of exercise, but both strengthening and aerobic exercises appear to be important.

I tell patients that fibromyalgia is an exercise-deprivation syndrome. Many are afraid to exercise because they associate it with pain and exhaustion afterwards. Patients should be encouraged to start with something very low-impact, such as gentle exercise in a warm-water pool. It should be emphasized that exercise is a lifelong treatment.

Drug therapy
The US Food and Drug Administration has approved 3 drugs for fibromyalgia management: 2 serotonin-norepinephrine reuptake inhibitors (duloxetine and milnacipran) and 1 gabapentinoid (pregabalin). Our patient in Case 2 is taking 2 of them without apparent benefit and has previously had no success with the third. This is not surprising. A summary of published treatment research on these drugs found that only 50% to 60% of patients tested reported more than 30% pain reduction. The studies also showed a placebo response of 30% to 40%. Depending on the study, the number needed to treat to see a benefit from these drugs is 8 to 14.

EVALUATING THE SEVERITY OF FIBROMYALGIA

Focusing on key characteristics of the patient’s history can help evaluate fibromyalgia and determine a treatment strategy (Table 3). The Fibromyalgia Impact Questionnaire is also a useful evaluation tool.

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<th>TABLE 3</th>
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<tr>
<td><strong>Evaluating fibromyalgia for management</strong></td>
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<td><strong>Domains</strong></td>
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<td>Mood</td>
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<td>Stressful life events</td>
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<tr>
<td>Maladaptive pain responses, catastrophizing</td>
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<td>Function</td>
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GAD-7 = Generalized Anxiety Disorder Assessment; MDQ = Mood Disorder Questionnaire; PHQ-9 = Patient Health Questionnaire-Depression 9
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It is important to assess the severity of fibromyalgia because patients with severe fibromyalgia are not good candidates for further referral to other specialists. They instead need chronic rehabilitation services, where they can learn to better function with a chronic pain syndrome.

In general, patients with the following features have conditions with high severity:

**Symptoms:** High burden and intensity
**Function:** Disabled, unemployed, interference with activities of daily living
**Mood:** Severe depression, bipolar disorder, axis II disorder, posttraumatic stress disorder
**Medications:** Polypharmacy, opioid drugs, multiple failed interventions
**Maladaptive attitudes:** High catastrophizing, refusal to accept diagnosis

Fibromyalgia Impact Questionnaire score: 60 or above.

The fibromyalgia of our patient in Case 2 would be categorized as severe.

■ MULTIFACETED MANAGEMENT

Patients with fibromyalgia are a heterogeneous group, and the syndrome does not lend itself to a single management strategy.\(^5^4\) Multiple guidelines have been published for managing fibromyalgia.\(^5^5\)–\(^5^7\) Thieme et al\(^5^8\) reviewed existing guidelines and the strength of their recommendations. The guidelines unanimously strongly favor exercise, and most also favor cognitive behavioral therapy. Most favor treating with amitriptyline and duloxetine; recommendations for other antidepressants vary. Nonsteroidal anti-inflammatory drugs, opioid drugs, and benzodiazepines are not recommended.

We offer a monthly 1-day clinic for patients and family members to provide education about fibromyalgia, discuss the importance of exercise, counsel on maladaptive responses, and demonstrate mindfulness techniques. We focus on function rather than pain. Interactive online-based interventions using cognitive behavioral techniques, such as *FibroGuide: A Symptom Management Program for People Living With Fibromyalgia*, developed at the University of Michigan, have proven helpful.\(^5^9\)

■ RECOMMENDATIONS

For most patients, do not focus on pain reduction, as that is ineffective. Instead, target reversible factors, eg, mood, sleep, exercise status, stressors, and maladaptive attitudes toward pain. Possible treatment combinations include:

- A serotonin and norepinephrine reuptake inhibitor (eg, duloxetine)
- A low-dose tricyclic antidepressant at bedtime (eg, amitriptyline)
- A gabapentinoid (pregabalin or gabapentin)

If a medication within a class does not work, stop it and try another rather than add on.

Treat mild to moderate fibromyalgia with multidisciplinary interventions, with or without centrally acting medications. Treat severe fibromyalgia with more intensive psychiatric or psychologic interventions, multidisciplinary care, and medications targeted at comorbidities. Provide all patients with education and advice on exercise.

Keep laboratory tests and imaging studies to a minimum: a complete blood cell count with differential, comprehensive metabolic panel, thyroid-stimulating hormone, C-reactive protein, and Westergren sedimentation rate. Do not test for ANA unless the patient has objective features suggesting SLE.

■ REFERENCES


42. Gerdie B, Ennberg M, Mannerkorpi K, et al. Increased interstitial concentrations of glutamate and pyruvate in vastus lateralis of women with fibromyalgia syndrome are normalized after exercise intervention—a case-control study. PLoS One 2016; 11(10);e0162010. doi:10.1371/journal.pone.0162010


44. Kelley GA, Kelley KS, Jones DL. Efficacy and effectiveness of exer-
FIBROMYALGIA

doi:10.1186/14651858.CD001133

doi:10.1016/j.rbr.2013.02.001

doi:10.1002/14651858.CD011336

doi:10.1002/14651858.CD010884

doi:10.1002/acr.22610

doi:10.1186/ar3002

doi:10.1016/j.jpain.2017.08.009

doi:10.1016/j.nicl.2015.08.004

doi:10.1371/journal.pone.0163037

doi:10.2217/pmt-2016-0006

pmid:26088217

pmid:23748251

doi:10.1155/2013/485272

doi:10.1136/annrheumdis-2016-209724


doi:10.1016/j.pain.2010.08.034

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