Clinical Crossroads

Fibromyalgia
A Clinical Review

Daniel J. Clauw, MD

IMPORTANCE Fibromyalgia is present in as much as 2% to 8% of the population, is characterized by widespread pain, and is often accompanied by fatigue, memory problems, and sleep disturbances.

OBJECTIVE To review the epidemiology, pathophysiology, diagnosis, and treatment of fibromyalgia.

EVIDENCE REVIEW The medical literature on fibromyalgia was reviewed from 1955 to March 2014 via MEDLINE and the Cochrane Central Registry of Controlled Trials, with an emphasis on meta-analyses and contemporary evidence-based treatment guidelines. Treatment recommendations are based on the most recent evidence-based guidelines from the Canadian Pain Society and graded from 1 to 5 based on the level of available evidence.

FINDINGS Numerous treatments are available for managing fibromyalgia that are supported by high-quality evidence. These include nonpharmacological therapies (education, exercise, cognitive behavioral therapy) and pharmacological therapies (tricyclics, serotonin norepinephrine reuptake inhibitors, and gabapentinoids).

CONCLUSIONS AND RELEVANCE Fibromyalgia and other "centralized" pain states are much better understood now than ever before. Fibromyalgia may be considered as a discrete diagnosis or as a constellation of symptoms characterized by central nervous system pain amplification with concomitant fatigue, memory problems, and sleep and mood disturbances. Effective treatment for fibromyalgia is now possible.

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Dr Tess Ms P is a 64-year-old woman who has ongoing diffuse muscle pain and fatigue. She developed chronic back pain in 1991, followed by chronic ankle pain after a motor vehicle collision. In 2009, she developed a deep ache in her lower extremities and back that worsened over several months. Her pain is aggravated by touch or pressure and relieved by rest and topical heat. The pain has limited her ability to exercise. She was diagnosed as having fibromyalgia and given numerous medications (gabapentin, venlafaxine, pregabalin, and hydrocodone/acetaminophen), most of which resulted in significant adverse effects. She currently undergoes treatment with acupuncture therapy along with pregabalin, hydrocodone/acetaminophen, and cyclobenzaprine.

Over the past several years, she has experienced loss of energy, weight gain, occasional headaches, insomnia, and occasional depressed mood. Pain and fatigue limit her physical activity to not more than a few contiguous hours. She does not have paresthesias.

Ms P has hypertension, Graves disease with hypothyroidism, degenerative disk disease, migraines, hyperlipidemia, fibroadenomatous breast disease, eczema, gastroesophageal reflux disease, and carpal tunnel syndrome. She takes amlodipine, cyclobenzaprine, hydrochlorothiazide, hydrocodone-acetaminophen, levothyroxine, moexipril, pantoprazole, pravastatin, pregabalin, aspirin, and multivitamins. She is a former nurse who no longer works because of her physical limitations.

During the physical examination, Ms P was found to be afebrile and had normal vital signs. She did not have alopecia, oral ulcers, or exudates. There were no skin lesions or rashes and her nails were normal. There were many areas of tenderness with palpation, including her upper and lower back, near lateral epicondyle, upper chest, and trochanteric prominences. Her joint examination results were normal, as was the remainder of her physical examination.

Her complete blood count, chemistries, and liver function tests yielded normal results. Antinuclear antibody, anticytoplasmic antibody, serum protein electrophoresis, urine protein electrophoresis, and Lyme serology test results were all unremarkable. Her erythrocyte sedimentation rate was 33 mm/h.

Ms P now asks if there is a treatment regimen that will allow her to be more functional while avoiding adverse effects.

Ms P: Her View

Most people do not understand fibromyalgia. They don't really get it; they see you, they look at you, and you look fine. So they do not understand. The fibromyalgia pain feels like a deep muscle strain or pain. For me, it has been mostly a dull, deep pain and ache throughout my body. I never know what my day is going to be like. I have to wake up in the morning and see what hurts and how I can medicate it and how I can function for the day. During the day, I feel I have an expiration date on me. It's like I have a weight around my neck, back, or waist and I start to go down after a while. I still can feel okay mentally but my body just quits on me and I have to lie down.

The medication is affecting my activities of daily living. I usually take it at night so that I can function in the morning but I can never just jump up to go and do anything the way I used to. I have to have a grace period for getting up, seeing what hurts ... see if I need to take additional medication. It's kind of like I'm walking through a fog. The acupuncture has helped alleviate the pain. I did not expect it to be as helpful as other medications, but with it I can take less medication overall.

At first, the hardest part was getting a diagnosis. It had to be either A, B, C, D, or E, and it was not. Since my doctor diagnosed me, the frustrating part has been finding medications or treatments that will help me to get back to as much of a normal life as I can. Is there a better plan for me?

Fibromyalgia

Search Methods

Dr Clauw The medical literature on fibromyalgia was searched from 1955 to March 2014 using MEDLINE and the Cochrane Central Registry of Controlled Trials. The search terms used were *fibrositis* and *fibromyalgia*. The limits used were "clinical trial" or "review."

The best-quality evidence (eg, meta-analyses, systematic reviews) received the greatest emphasis. Treatments recommendations in this review are generally derived from the Canadian Pain Society guidelines,[1] which are the most recent guidelines to have considered North American randomized clinical trials of drugs for this condition. Recommendations were graded from 1 to 5 based on the evidence quality.[2]

Epidemiology and Pathophysiology of Fibromyalgia

After osteoarthritis, fibromyalgia is the second most common "rheumatic" disorder. Depending on the diagnostic criteria used, the prevalence is from 2% to 8% of the population.[3-5] The diagnostic criteria for fibromyalgia were originally published in 1990 and emphasized chronic widespread pain with a number of tender points.[6] Using this definition, almost all patients with fibromyalgia were women because they have many more tender points than do men. Newer diagnostic criteria are entirely symptom based and do not require counts of the number of tender points.[7] With the newer diagnostic criteria, the disease has a female:male ratio of 2:1, similar to other chronic pain conditions.[5] Fibromyalgia can develop at any age, including in childhood. The prevalence is similar in different countries, cultures, and ethnic groups; there is no evidence that fibromyalgia has a higher prevalence in industrialized countries and cultures.[4]

Patients developing fibromyalgia commonly have lifelong histories of chronic pain throughout their body. Any regional or widespread chronic musculoskeletal pain occurs in about 30% of the population.[4] Ms P's "pain-prone phenotype," manifested by having many discrete episodes of chronic pain in her lifetime, is an important part of her medical history. Patients with fibromyalgia are likely to have a history of headaches, dysmenorrhea, temporomandibular joint disorder, chronic fatigue, irritable bowel syndrome and other functional gastrointestinal disorders, interstitial cystitis/painful bladder syndrome, endometriosis, and other regional pain syndromes (especially back and neck pain).[8,9] What might appear to one health care practitioner as a new episode of acute or subacute pain can in fact be simply another region of the body associated with pain.[10]

Fibromyalgia can be thought of as a centralized pain state. Centralized pain is a lifelong disorder beginning in adolescence or young adulthood manifested by pain experienced in different body regions at different times.[11-13] "Centralized" refers to central nervous system origins of or amplification of pain. This term does not imply that peripheral nociceptive input (ie, damage or inflammation of body regions) is not contributing to these individuals' pain but rather that they feel more pain than would normally be expected based on the degree of nociceptive input. Understanding centralized pain is important for surgeons and proceduralists because patients with these disorders may request interventions to eliminate pain (eg, hysterectomy, back surgery).[14] Not surprisingly, this pain-prone phenotype, best exemplified by a patient with fibromyalgia, predicts failure to respond to opioids or operations performed to reduce pain.[15]

Family members of patients with fibromyalgia may also have a history of chronic pain. Compared with relatives of individuals without fibromyalgia, first-degree relatives of patients with fibromyalgia are more likely (odds ratio, 8.5; 95% CI, 2.8-26; $P<.001$) to have fibromyalgia and other chronic pain states.[16] Genetic factors may explain the strong familial predisposition to fibromyalgia and many chronic pain conditions.[13,17] Genes associated with increased or decreased frequency of chronic pain states or pain sensitivity regulate the breakdown or binding of pain sensitivity–modulating neurotransmitters and others of inflammatory pathways. Pain sensitivity is polygenic, and differential pain sensitivity between individuals may result from imbalances or altered activity of various neurotransmitters, explaining why centrally acting analgesics either help many cooccurring symptoms (pain, sleep, mood, fatigue) or do not help at all in a given individual. Twin studies suggest that approximately 50% of the risk of developing fibromyalgia and related conditions such as irritable bowel syndrome and headache is genetic and 50% is environmental.[18]

Environmental factors most likely to trigger fibromyalgia include stressors involving acute pain that would normally last for a few weeks. Fibromyalgia or similar illnesses, such as chronic fatigue syndrome, can be triggered by certain types of infections[19] (eg, Epstein-Barr virus, Lyme disease, Q fever, viral hepatitis), trauma[20] (motor vehicle collisions), or deployment to war.[21] Psychological stress may also trigger fibromyalgia.

Fibromyalgia may also occur with other chronic pain conditions like osteoarthritis, rheumatoid arthritis, and lupus. Approximately 10% to 30% of patients with these rheumatic disorders also meet criteria for fibromyalgia.[22] Previously termed secondary fibromyalgia, this phenomenon is better viewed as centralized pain because this presentation is common and might occur in a subset of

any chronic pain cohort. The term *centralization* implies that peripheral nociceptive input might be responsible for some of a patient's pain but central nervous system factors likely amplify the pain. An individual's "set point" or "volume control" for pain is set by a variety of factors, including the levels of neurotransmitters that facilitate pain transmission (turn up the gain or volume control) and those that reduce pain transmission. These central factors may also result in fatigue, memory problems, and sleep and mood disturbances, probably because the same neurotransmitters that control pain and sensory sensitivity also control sleep, mood, memory, and alertness.[22]

The observation that fibromyalgia patients had diffuse tenderness led to functional, chemical, and structural brain neuroimaging studies. These studies showed a biological basis for fibromyalgia pain and related pain amplification syndromes.[23] Fibromyalgia patients experience pain for what patients without fibromyalgia perceive as touch. Functional magnetic resonance imaging studies of the brain response to these stimuli show brain activation patterns in pain processing areas in fibromyalgia patients when given a mild pressure or heat stimulus.[24,25]

Psychological, behavioral, and social issues contribute to the pathogenesis of fibromyalgia and complicate its treatment. Individuals with fibromyalgia more likely have psychiatric disorders, including depression, anxiety, obsessive-compulsive disorder, and posttraumatic stress disorder. This may result from common triggers for these psychiatric conditions and fibromyalgia like early-life stress or trauma. Neurotransmitters mediating pain transmission may also affect mood, memory, fatigue, and sleep. Potentially modifiable risk factors for developing fibromyalgia include poor sleep, obesity, physical inactivity, and poor job or life satisfaction. Cognitive factors such as catastrophizing (a way of thinking about pain such that it will have very negative consequences) or fearing that movement will worsen pain are poor prognostic factors for fibromyalgia and other chronic pain states. The psychological components of fibromyalgia or other pain conditions are treatable by cognitive behavioral therapy, which can be very effective but, unfortunately, is rarely used in clinical practice. Many patients seen in routine clinical practice who have fibromyalgia or fibromyalgia-like syndromes may respond well to simple interventions such as stress reduction, improved sleep patterns, and increased activity and exercise. These interventions should always be emphasized and may suffice, precluding the need for drug therapy.

Diagnosis of Fibromyalgia

The 1990 American College of Rheumatology criteria for fibromyalgia were research classification criteria and were never intended to be used as strict diagnostic criteria for use in clinical practice.[6] These criteria require that individuals have widespread pain (pain in the axial skeleton, above and below the waist, and on both sides of the body) as well as tenderness in 11 or more of 18 possible "tender points." Many individuals who clearly have fibromyalgia do not have pain throughout their entire body or may not have at least 11 tender points. Moreover, the symptoms of pain and tenderness are common and it is impossible to know where to draw the line between an individual with isolated symptoms and someone with a pain-inducing illness.[26]

The alternative 2011 fibromyalgia survey criteria were intended for use in epidemiological studies and represent an alternative method to assess fibromyalgia.[7,27,28] These criteria include a patient self-report survey that is administered on a single piece of paper (**Figure**). Patients fill out a symptom survey asking about the locations of pain as well as the presence and severity of fatigue, sleep disturbances, memory difficulties, headaches, irritable bowel, and mood problems. Practitioners may prefer this approach of assessment for fibromyalgia because it does not require performing a tender-point examination. These criteria identify most of the same individuals who meet the 1990 criteria but identifies many more male patients (who rarely meet the 1990 criteria because of inadequate numbers of tender points).[7,28] The new criteria have the advantage of conceptualizing the core symptoms of fibromyalgia as a continuum of pain centralization or "fibromyalgia-ness."[29]

In clinical practice, fibromyalgia should be suspected in patients having multifocal pain not fully explained by injury or inflammation. In most cases, musculoskeletal pain is the most prominent feature. Because pain pathways throughout the body are amplified, pain can occur anywhere. Consequently, chronic headaches, sore throats, visceral pain, and sensory hyperresponsiveness are very common in individuals with fibromyalgia and were seen in Ms P.

Pain is a defining feature of fibromyalgia. Features of the pain distinguishing fibromyalgia from other disorders are important to consider when evaluating patients (**Box 1**). These same features are also useful when considering other centralized pain syndromes. Ms P had nearly all of the characteristics summarized in Box 1.

Usually, the physical examination is unremarkable in patients with fibromyalgia. Nevertheless, most patients have diffuse tenderness. This can be ascertained by performing a tender-point count as was done for Ms P. Patients with fibromyalgia are more sensitive to the inflation of a blood pressure cuff.[31] The overall pain threshold also can be assessed by performing a rapid examination of the hands and arms by applying firm pressure over several interphalangeal joints of each hand and over the adjacent phalanges, then caudally to include firm palpation of the muscles of the forearm. Diffuse tenderness from a low central pain threshold is present if the patient has tenderness in many of these areas or only in the forearm muscles. When tenderness is present only over the interphalangeal joints and not the other regions (especially if there is any swelling over these joints), a diagnosis of a systemic autoimmune disorder should be considered.

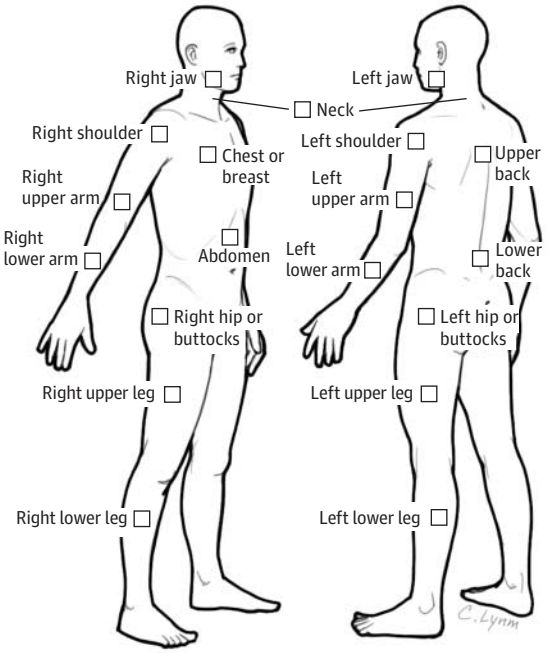
Apart from sorting through the differential diagnosis, laboratory testing is not useful for establishing a diagnosis of fibromyalgia. Basic laboratory evaluation may include complete blood count, routine serum chemistries, thyrotropin, vitamin D, erythrocyte sedimentation rate, and C-reactive protein. Serologic studies such as antinuclear antibody and rheumatoid factor assays are generally avoided unless symptoms or signs (eg, swollen joints) suggest an autoimmune disorder.

Once other pain disorders are excluded and any peripheral sources of pain are treated, an important and perhaps controversial step is asserting the diagnosis of fibromyalgia. Some believe that a label of fibromyalgia may harm patients. However, studies suggest that the opposite is true: establishing a diagnosis of fibromyalgia can provide substantial relief for patients.[32] In fact, once the diagnosis is established, there may be decreased health care utilization, with fewer referrals and reduced diagnostic testing seeking causes of pain.[33] Ms P was relieved once her diagnosis of fibromyalgia was established. Once she knew the cause of her pain, she could concentrate on treatment.

Figure. Example of a Patient Self-report Survey for the Assessment of Fibromyalgia Based on Criteria in the 2011 Modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia[7]

Widespread Pain Index
(1 point per check box; score range: 0-19 points)

1. Please indicate if you have had pain or tenderness **during the past 7 days** in the areas shown below.
   Check the boxes in the diagram for each area in which you have had pain or tenderness.



Symptom Severity
(score range: 0-12 points)

2. For each symptom listed below, use the following scale to indicate the severity of the symptom **during the past 7 days**.
   - **No problem**
   - **Slight or mild problem**: generally mild or intermittent
   - **Moderate problem**: considerable problems; often present and/or at a moderate level
   - **Severe problem**: continuous, life-disturbing problems

	No problem	Slight or mild problem	Moderate problem	Severe problem
Points	0	1	2	3
A. Fatigue	☐	☐	☐	☐
B. Trouble thinking or remembering	☐	☐	☐	☐
C. Waking up tired (unrefreshed)	☐	☐	☐	☐

3. During the **past 6 months** have you had any of the following symptoms?

Points	0	1
A. Pain or cramps in lower abdomen	☐ No	☐ Yes
B. Depression	☐ No	☐ Yes
C. Headache	☐ No	☐ Yes

Additional criteria (no score)

4. Have the symptoms in questions 2 and 3 and widespread pain been present at a similar level for at **least 3 months**?
   ☐ No ☐ Yes

5. Do you have a disorder that would otherwise explain the pain?
   ☐ No ☐ Yes

ACR indicates American College of Rheumatology. Scoring information is shown in blue. The possible score ranges from 0 to 31 points; a score ≥13 points is consistent with a diagnosis of fibromyalgia. Additional scoring information and a printer-ready version of this survey that patients can complete are available online (eFigure 1 and eFigure 2 in the Supplement).

Treatment of Fibromyalgia

Fibromyalgia is best approached by integrating pharmacological and nonpharmacological treatments while engaging patients as active participants in the process. Fibromyalgia can be diagnosed and treated in the primary care setting. Referral to specialists should be necessary only for patients in whom the diagnosis is uncertain (eg, to a rheumatologist or neurologist, depending on symptoms) or for patients refractory to therapy (eg, to multidisciplinary pain clinics) or with significant comorbid psychiatric issues (eg, to a psychiatrist or psychologist). Developing treatment teams is useful, even if they are only virtual teams. The team should include clinicians with expertise in patient education (eg, midlevel practitioners or nurse educators), exercise therapy (eg, physical or occupational therapists), and cognitive behavioral therapy.

The **Table** summarizes the recommendations of the Canadian National Fibromyalgia Guideline Advisory Panel.[34] These and other guidelines generally recommend that all patients should receive education about the nature of this condition (ie, that the pain is not due to damage of painful regions and is not progressive) as well as about the importance of playing an active role in their own care. In particular, the importance of stress reduction, sleep, and exercise should be continually reinforced. Pharmacological therapies can be helpful in alleviating some symptoms, but patients rarely achieve meaningful improvements without adopting these core self-management strategies.

Pharmacological Therapies

The general approach to pharmacological therapy is summarized in **Box 2**. Effective pharmacological therapies generally work in part by reducing the activity of facilatory neurotransmitters (eg, gabapentinoids reduce glutamate[46,47]) or by increasing the activity of inhibitory neurotransmitters such as norepinephrine and serotonin (eg, tricyclics, serotonin norepinephrine reuptake inhibitors[48,49]) or γ-aminobutyric acid (eg, γ-hydroxyglutamate[43,50]). The hyperactive endogenous opioid system[51] in fibromyalgia may explain why opioids appear to be ineffective[15,52] and low-dose naltrexone[44] is a promising new treatment. Several drugs or classes of drugs have strong evidence (level 1A evidence) for efficacy in treating fibromyalgia,[53] including tricyclic compounds[40] (amitriptyline, cyclobenzaprine), gabapentinoids[54] (pregabalin, gabapentin), serotonin norepinephrine reuptake inhibitors (duloxetine,[55] milnacipran[56]), and γ-hydroxybutyrate.[43] Drugs with more limited

evidence of efficacy include older selective serotonin reuptake inhibitors with greater noradrenergic activity when used at higher doses (eg, fluoxetine,[57] paroxetine, sertraline), low-dose naltrexone,[58] esreboxetine[59] (a serotonin norepinephrine reuptake inhibitor not available in the United States), and cannabanoids.[60] When treating polygenic chronic illnesses, it is often necessary to use combinations of several drugs having differing mechanisms of action.

Drugs frequently used to treat peripheral pain such as nonsteroidal anti-inflammatory drugs, opioids, and corticosteroids do not effectively treat fibromyalgia pain. In fact, all oral analgesics (eg, nonsteroidal anti-inflammatory drugs and opioids) are only modestly effective for treating chronic pain (ie, work well in only a third of patients).[61] There is evidence that opioids might worsen fibromyalgia-related hyperalgesia and other centralized pain states, leading to opioid-induced hyperalgesia.[15]

Nonpharmacological Therapies

The 3 best-studied nonpharmacological therapies are education, cognitive behavioral therapy, and exercise. All have strong (level 1A evidence) evidence for efficacy in fibromyalgia. The magnitude of the treatment response for these therapies often exceeds that for pharmaceuticals. The greatest benefit is observed for improved function, which should be the main treatment goal for treating chronic pain.[62,63] These treatments can result in sustained (eg, >1 year) improvements. Access, adherence, and compliance to treatment are the most important limitations when trying to implement them in clinical practice.

Complementary and alternative therapies can be useful as treatment adjuncts for fibromyalgia. As with other disorders, relatively few controlled trials support their use. Trigger-point injections, chiropractic manipulation, tai chi, yoga, acupuncture, and myofascial release therapy all have some evidence of efficacy and are among the more commonly used treatments.[64] Some evidence suggests that these treatments give patients a greater sense of control over their illness. Giving patients a choice of therapies may improve the likelihood for a placebo response by activating the body's internal analgesic mechanisms. Despite the absence of high-quality evidence regarding their efficacy, alternative therapies may be useful as long as they do not cause harm since options for treating chronic pain are limited.

Although fibromyalgia is generally not thought to be caused by peripheral damage or inflammation, some evidence exists supporting treatment of peripheral pain generators. Conceivably, peripheral nociceptive input drives central sensitization.[13,65] Patients with fibromyalgia and concomitant osteoarthritis or myofascial pain had improvement in their overall fibromyalgia pain and tenderness when treated with local therapies.[66] Some patients with fibromyalgia also have been shown to have small fiber neuropathy on biopsy.[67] The treatment implications of this observation remain unclear.

Various neurostimulatory therapies can effectively treat musculoskeletal pain. Transcutaneous electrical nerve stimulation has been used to treat peripheral musculoskeletal pain with some success. Newer central neurostimulatory therapies are in development that presumably stimulate brain structures involved in pain processing and are showing promise in treating centralized pain states such as fibromyalgia.[39,68]

Box 1. Characteristics of Fibromyalgia and Other Centralized Pain Syndromes

- Character and quality of pain
  - Diffuse or multifocal, often waxes and wanes, and is frequently migratory in nature
  - Often accompanied by dysesthesia or paresthesias and described as more "neuropathic" (eg, with terms such as numbness, tingling, burning)
  - Patients may note discomfort when they are touched or when wearing tight clothing
- History of pain in other body regions earlier in life
- Accompanying comorbid symptoms also of central nervous system origin
  - Often fatigue, sleep disturbances, memory, and mood difficulties accompany centralized pain states such as fibromyalgia
  - Several of these symptoms will typically improve along with pain when individuals are successfully treated with appropriate pharmacological or nonpharmacological therapies
- Symptoms suggesting more global sensory hyperresponsiveness
  - Sensitivity to bright lights, loud noises, and odors and even many visceral symptoms may be in part due to a global sensory hyperresponsiveness seen in conditions such as fibromyalgia
  - Often leads to a "pan-positive review of symptoms" that has often mischaracterized these individuals as "somatizers" as the biology of somatization is increasingly recognized as that of sensory hyperresponsiveness[30]

Recommendations for Ms P

Ms P has a fairly typical history for fibromyalgia. In addition to her pain symptoms, she has a sense of helplessness and hopelessness and she is frustrated. Of note was Ms P's frustration while she struggled to obtain a diagnosis. Rarely, providing a diagnosis might be ill advised. This may the case for a child or adolescent who might use a fibromyalgia diagnosis as a reason to restrict activities. More commonly, patients are relieved to have a diagnosis established. Once the diagnosis is established, health care utilization may decrease as fruitless searches for the cause of pain are no longer needed.

Referral to a specialist was not necessary because Ms P's symptoms were long-standing and typical of fibromyalgia and there were many treatment options yet to be tried. Once a diagnosis of fibromyalgia is given, providing patient education is helpful (level 1A evidence[1]). Patient education may be provided by a physician or other health care practitioner. Education delivered in 1 long or several shorter sessions emphasizes that fibromyalgia symptoms are not due to damage or inflammation of tissues, that pharmacological therapies have limited efficacy, and that it is important for patients to use self-management therapies (for example, https://fibroguide.med.umich.edu). The importance of behavioral therapies should be emphasized, as should be normalization of sleep patterns and institution of exercise therapy. Patients should understand that these treatments often will be more effective than pharmacological treatments.[1]

Table. Summary of Treatment Guidelines[34]

Treatment	Cost	Details	Evidence Level	Adverse Effects	Clinical Pearls
General recommendations					
Patient education[35]	Low	Incorporate principles of self-management including a multimodal approach	1A		Following initial diagnosis, spend several visits (or use separate educational sessions) to explain the condition and set treatment expectations
Nonpharmacological therapies					
Graded exercise[36]	Low	Aerobic exercise has been best studied but strengthening and stretching have also been shown to be of value	1A	Worsening of symptoms when program is begun too rapidly	Counsel patients to "start low, go slow" For many patients, focusing first on increasing daily "activity" is helpful before actually starting exercise
Cognitive behavioral therapy (CBT)[37]	Low	Pain-based CBT programs have been shown to be effective in one-on-one settings, small groups, and via the Internet	1A	No significant adverse effects of CBT per se but patient acceptance is often poor when viewed as a "psychological" intervention	Internet-based programs are gaining acceptance and are more convenient for working patients
Complementary and alternative medicine (CAM) therapies[38]	Variable	Most CAM therapies have not been rigorously studied	1A	Generally safe	Evidence emerging that CAM treatments such as tai chi, yoga, balneotherapy, and acupuncture may be effective Allowing patients to choose which CAM therapies to incorporate into an active treatment program can increase self-efficacy
Central nervous system (CNS) neurostimulatory therapies[39]		Several types of CNS neurostimulatory therapies have been effective in fibromyalgia and other chronic pain states		Headache	These treatments continue to be refined as optimal stimulation targets, "dosing," etc, become understood
Pharmacological therapies		Therapies best chosen based on predominant symptoms and initiated in low doses with slow dose escalation	5, Consensus		Prescribing patients a drug regimen that helps improve symptoms prior to initiating nonpharmacological therapies can help improve adherence
Tricyclic compounds[40,41]		Amitriptyline, 10-70 mg once daily before bedtime Cyclobenzaprine, 5-20 mg once daily before bedtime	1A	Dry mouth, weight gain, constipation, "groggy" or drugged feeling	When effective, can improve a wide range of symptoms including pain, sleep, bowel, and bladder symptoms Taking several hours prior to bedtime improves adverse effect profile
Serotonin norepinephrine reuptake inhibitors[40]	Duloxetine is generic; milnacipran is not	Duloxetine, 30-120 mg/d Milnacipran, 100-200 mg/d	1A	Nausea, palpitations, headache, fatigue, tachycardia, hypertension	Warning patients about transient nausea, taking with food, and slowly increasing dose can increase tolerability Milnacipran might be slightly more noradrenergic than duloxetine and thus potentially more helpful for fatigue and memory problems but also more likely to cause hypertension
Gabapentinoids[42]	Gabapentin is generic, pregabalin not	Gabapentin, 800-2400 mg/d in divided doses Pregabalin, up to 600 mg/d in divided doses	1A	Sedation, weight gain, dizziness	Giving most or all of the dose at bedtime can increase tolerability
γ-Hydroxybutyrate[43]	For treating narcolepsy/ cataplexy	4.5-6.0 g per night in divided doses	1A	Sedation, respiratory depression, and death	Shown as efficacious but not approved by Food and Drug Administration because of safety concerns
Low-dose naltrexone[44]	Low	4.5 mg/d	2 small single-center randomized trials[a]		
Cannabanoids[45]	NA	Nabilone, 0.5 mg orally at bedtime to 1.0 mg twice daily	1A[a]	Sedation, dizziness, dry mouth	No synthetic cannabinoid has US approval for treatment of pain
Selective serotonin reuptake inhibitors (SSRIs)[40]	SSRIs that should be used in fibromyalgia are all generic	Fluoxetine, sertraline, paroxetine	1A	Nausea, sexual dysfunction, weight gain, sleep disturbance	Older, less selective SSRIs may have some efficacy in improving pain, especially at higher doses that have more prominent noradrenergic effects Newer SSRIs (citalopram, escitalopram, desvenlafaxine) are less effective or ineffective as analgesics
Nonsteroidal anti-inflammatory drugs		No evidence of efficacy; can be helpful for comorbid "peripheral pain generators"	5D	Gastrointestinal, renal, and cardiac adverse effects	Use the lowest dose for the shortest period of time to reduce adverse effects
Opioids		Tramadol with or without acetaminophen, 50-100 mg every 6 h No evidence of efficacy for stronger opioids	5D	Sedation, addiction, tolerance, opioid-induced hyperalgesia	Increasing evidence suggests that opioids are less effective for treating chronic pain than previously thought and their risk-benefit profile is worse than other classes of analgesics

[a] Evidence rated by author; not rated by Canadian National Fibromyalgia Guideline Advisory Panel.

There are many pharmacological treatment options for Ms P, including limiting the use of cyclobenzaprine to a low dose (5-10 mg) at bedtime, optimizing the dose of pregabalin by giving most or all of the dose at bedtime to decrease her grogginess, and adding a serotonin norepinephrine reuptake inhibitor (all level 1 evidence[1]). More importantly, it appears that she has not been informed about the nonpharmacological therapies that should be the mainstay of treating chronic pain, including education, exercise, and cognitive behavioral therapy. If these are not readily available locally, web-based programs are available that have been tested and shown to be effective.[69]

Box 2. General Approach to Pharmacological Therapy

All patients should receive

- Education about nature of disorder
- Counseling regarding role of exercise, cognitive behavioral techniques

Pharmacological therapy should be guided by predominant symptoms that accompany pain

- All patients should have a good therapeutic trial of a low-dose tricyclic compound (eg, cyclobenzaprine, amitriptyline, nortriptyline)
- Patients with comorbid depression or fatigue should next try a serotonin norepinephrine reuptake inhibitor
- Patients with comorbid anxiety or sleep issues should next try a gabapentinoid
- It is often necessary to use several of these classes of drugs together
- Use of opioids is discouraged
- Nonsteroidal anti-inflammatory drugs and acetaminophen can be used to treat comorbid "peripheral pain generators"

Therapies that have been less well studied but show promise

- Complementary and alternative therapies
- Drugs including low-dose naltrexone, cannabinoids
- Cortical electrostimulatory therapies

Questions and Discussion

QUESTION Is progress being made in developing animal models that may result in new treatment modes?

DR CLAUW Many animal models of hyperalgesia/allodynia exist, but these lack the other features of the human fibromyalgia "phenotype." Moreover, animal studies are usually performed on inbred strains of animals that do not exhibit the genetic heterogeneity humans have. Classic animal models also measure "pain behaviors" mediated by spinal reflexes and generally do not probe the central nervous system response to peripheral stimuli. So, phenotypically relevant animal models using operant paradigms as outcomes will likely be very useful for bidirectional translation.

QUESTION Will injury occur if fibromyalgia patients push themselves to continue exercising even while in pain?

DR CLAUW In general, and not just for fibromyalgia but for almost every chronic pain condition, activity and exercise are beneficial and not harmful. Nearly any type of exercise is good for fibromyalgia or any form of chronic pain. Patients should be advised to start with modest exercise and build up their activity level slowly. Many patients tend to try to do too much too soon, leading to worsened pain.

QUESTION How much of a problem is secondary gain resulting from disability financial support as an alternative to work in fibromyalgia patients?

DR CLAUW There will always be individuals who fake or magnify symptoms to benefit financially, but this is seen in a minority of patients. More problematic is the nonvolitional worsening occurring when patients with pain enter the disability and compensations systems. As eloquently noted by Hadler, "If you have to prove that you're sick, you can't get well."[70] I think that chronic pain patients are very deserving of disability but find that they almost always clinically worsen when they get involved in disability or litigation. The disability system results in frustration, anxiety, isolation, and inactivity, all of which are counterproductive to rehabilitation approaches that benefit chronic pain patients. Clinicians should be aware that there are few, if any, diseases where "objective" factors correlate well with disability. They should not expect this to be the case in fibromyalgia.[71]

QUESTION How should physicians manage a clinic visit with a patient like this to avoid feeling like they are manipulated by their patient?

DR CLAUW If clinicians treat fibromyalgia or other chronic pain conditions with drugs alone, they will fail. This is akin to treating diabetes with insulin or drugs alone, without any corresponding attempt to modify diet or weight. In contrast to diseases like diabetes or hypertension that lack physical symptoms, patients with chronic pain hurt, motivating them to be more adherent to nondrug therapies. Be on the offensive. Be persistent in encouraging your patients about doing exercise and trying web-based nondrug therapies. Do not be defensive and think that every time these patients come in, changing to a different drug is the only available approach. If practitioners use nondrug therapies more aggressively and use fewer opioids, nonsteroidal anti-inflammatory drugs, and procedures and more centrally acting analgesics, fibromyalgia is easier to manage.

ARTICLE INFORMATION

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