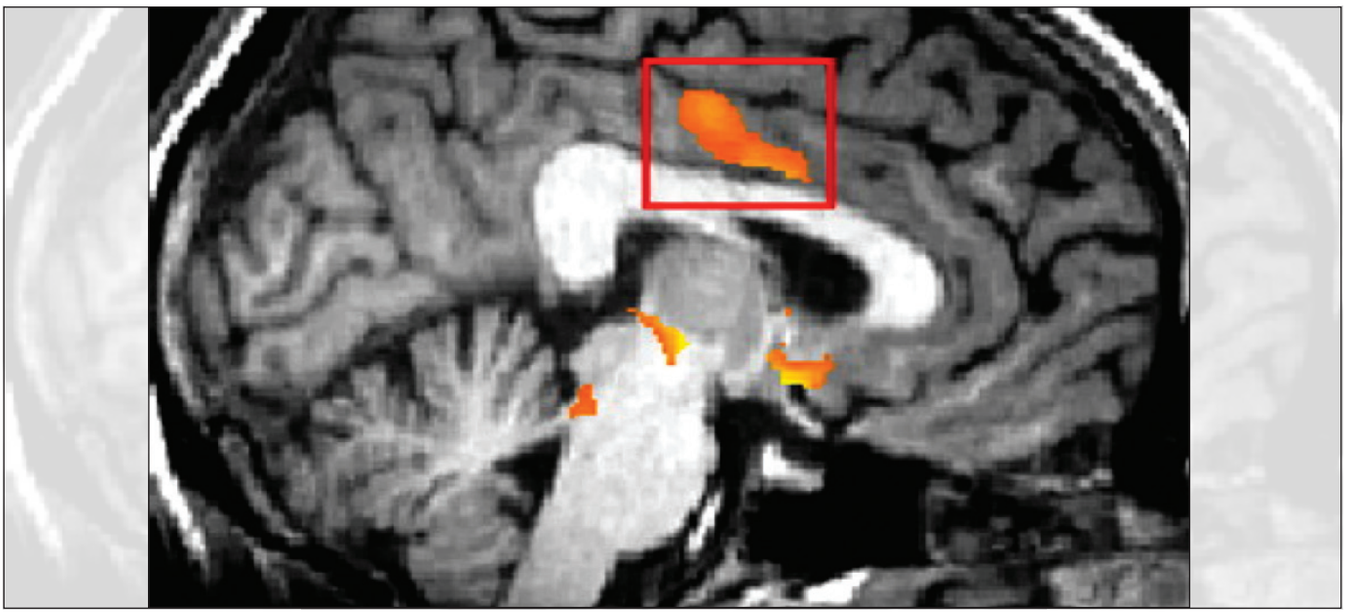
Update: Clinical Challenges in the Diagnosis And Management of Fibromyalgia



Fibromyalgia remains a challenge for many pain clinicians.

Progress is being made in understanding the pathophysiology of fibromyalgia. Treatment remains a collaborative effort incorporating both pharmaceutical and non-pharmaceutical options.

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Fibromyalgia (FM) is a complex disorder that is difficult to diagnose and treat. It is characterized by chronic pain that occurs throughout the body and is often accompanied by fatigue, non-restorative sleep, mood disorders, and variable somatic symptoms. The challenges of FM are multiple: The exact pathogenesis has been enigmatic, symptoms are variable, and treatment responses are unpredictable. The lack of diagnostic tests and the absence of a gold standard of treatment further complicate FM management.

The prevalence of FM ranges from 2% to 3% of the general population, with women affected between 6 to 9 times more commonly than men.[1] Although seen most commonly in middle-aged women, FM is also seen in children, teenagers, and the elderly.

The objective of this paper is to highlight the current knowledge of the pathogenesis and treatment of FM, identify attitudes and practice patterns of physicians treating these patients, and to suggest areas where improvement will enhance clinical care. The authors of the article were part of a Canadian taskforce to study FM. Taskforce participants included family physicians, anaesthesiologists, neurologists, psychiatrists, physiatrists, rheumatologists, nurses, chiropractors, physiotherapists, and a single naturopathic doctor.

Scientific Basis for Fibromyalgia

Recent neurophysiologic studies support the presence of pain in the body in the absence of identifiable physical abnormalites.[2-8] Abnormalities in pain processing have been identified at various levels in the peripheral, central, and sympathetic nervous systems, as well as the hypothalamic-pituitary-adrenal (HPA) axis stress-response system.[2-8] Documented abnormalities include evidence of peripheral sensitization and wind-up phenomenon; central sensitization with changes in functional magnetic resonance imaging (fMRI) and single photon emission computed tomography (SPECT) scans of the brain; increased levels of substance P in the cerebrospinal fluid; and impairment of diffuse noxious inhibitory control (DNIC). Recent research also points to interactions between peripheral, central bulbo-spinal, and central cortical mechanisms.[9,10]

Genetic factors may predispose some individuals to a dysfunctional stress response via the HPA axis.[11] In addition, there is increasing evidence that early-life adversity—such as the death of a mother, being in institutional care, or family financial hardships—are linked to chronic widespread pain in adult life.[12] These interacting factors combined with a stressful event—such as a viral illness, as reported by up to 30% of patients, trauma, or psychologic event—can lead to a vulnerable health status and may trigger FM in some patients.

Diagnosing Fibromyalgia

For many physicians, the diagnosis of FM is a challenge. Fibromyalgia, however, can be positively diagnosed and should no longer be seen as a diagnosis of exclusion. The 1990 American College of Rheumatology (ACR) diagnostic criteria[13] were developed as a research tool, but are often mistakenly used as a diagnostic instrument. The ACR criteria require the presence of widespread pain for at least 3 months' duration with the presence of at least 11 of 18 tender points in designated areas. These tender points, the only physical examination finding that has been used to help validate a diagnosis of FM, are a reflection of an overall reduction in pain threshold. The tender point examination, however, does not represent localized soft tissue pathology, is open to subjective interpretation, and its validity has been questioned in recent reports.

There is currently a move to eliminate the tender point examination from current criteria in favor of incorporating other clinically meaningful symptoms, including sleep disturbance, fatigue, mood disorder, cognitive changes, and various somatic symptoms frequently present in patients with FM. Other commonly described somatic complaints include an irritable bowel or bladder, migraines, restless leg syndrome, intolerance to external stimuli, and excessive sensitivity to medications.

As there is no single routine laboratory test that confirms a diagnosis of FM, it is recommended that only minimal testing, including ordering a complete blood count (CBC), erythrocyte sedimentation rate (ESR), thyroid function test, and creatinine kinase levels, be done in the first instance and that any other investigations or referrals to a specialist be driven by findings on clinical history and examination.[14] Appropriate additional testing may be required in selected patients to rule out conditions that can mimic FM, such as an endocrine disorder (hypothyroidism), rheumatic conditions (early inflammatory arthritis or

Making the Diagnosis

- A positive clinical diagnosis of FM should be made without extensive and unnecessary investigations: FM is not a diagnosis of exclusion.
- Diagnostic criteria currently based on medical history and physical examination should be revised to include the variety of symptoms important from the patient perspective of function and well-being.
- Only minimal testing, including a CBC, ESR, thyroid function tests, and creatinine kinase, should be done. Other investigations should be driven by findings on clinical history and examination.
- Body pain diagrams can be used as a useful tool for identifying that the pattern and distribution of pain are consistent with FM.
- Education of the patient regarding pathogenesis of FM and open discussion about expectations and a management plan are required.
- Primary care physicians should be provided with appropriate training and resources to diagnose and manage FM.
- Timely management of FM could improve patient outcome.
- Specialist referrals for FM may be delayed for up to a year in some provinces of Canada.
- Many insurers require that a specialist makes the diagnosis of FM.

polymyalgia rheumatica), or neurological disease (myopathy or multiple sclerosis). Excessive and unnecessary testing may be detrimental to a patient's well-being by promoting an illness-centered focus and fostering a sense of uncertainty.

While a positive diagnosis of FM may alleviate patient concerns and is associated with reduced healthcare utilization and decreased investigations, many clinicians continue to question the validity of reported functional disability.[15,16] A positive diagnosis also has medico-legal and work ability implications.

Improving the diagnostic abilities of primary care physicians could lead to more rapid and appropriate care.[17] Consultation with a specialist may be helpful for selected patients, but primary care physicians should coordinate patient management.[18]

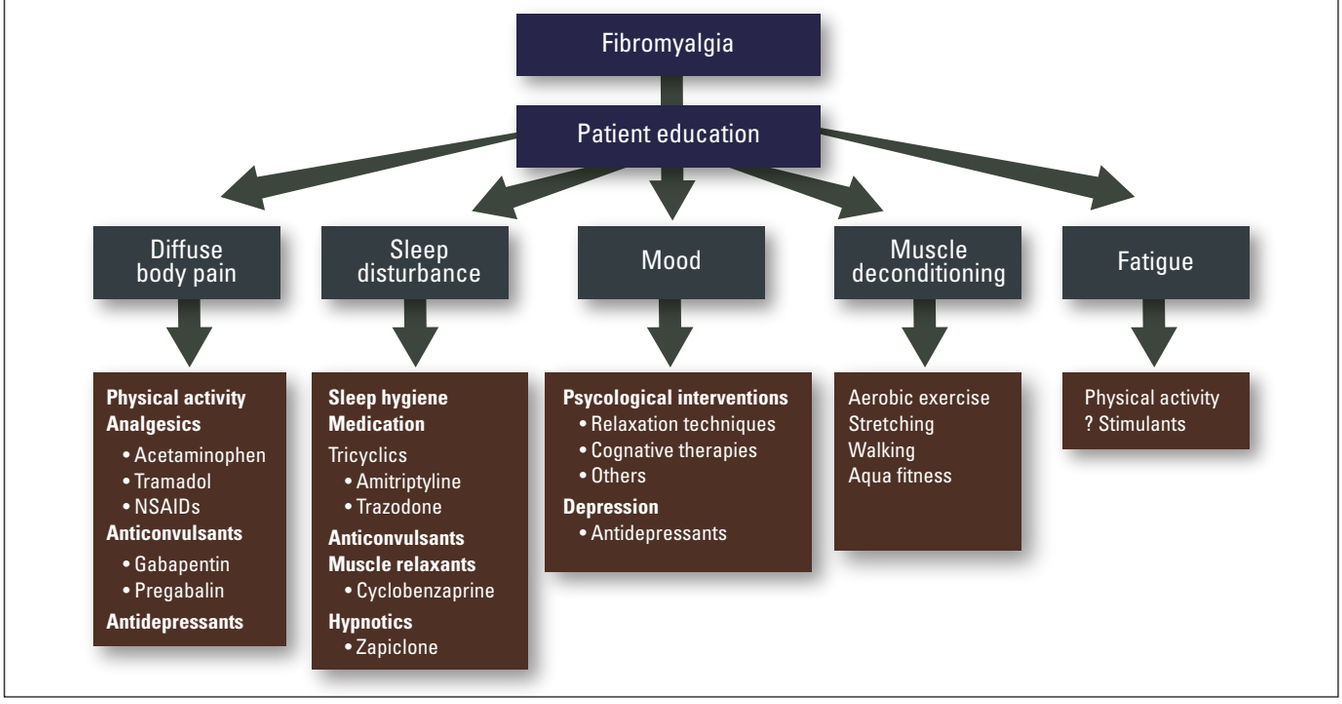
Fibromyalgia Treatments

The ideal FM treatment should take into account the various symptoms that may be present, including sleep disturbances, fatigue, mood disorder, cognitive impairment, and somatic symptoms, which all play a role in modulating the pain experience (see Algorithm). The goals of treatment should be to attain improvement in symptoms as well as function, encouraging the patient to be an active participant in self-management. Documentation of functional outcomes can be achieved by using the Brief Pain Inventory or the Fibromyalgia Impact Questionnaire (FIQ), although use of questionnaires in clinical practice is limited.[19]

Optimal treatment requires a multidisciplinary approach with a combination of non-pharmacological and pharmacological treatment modalities tailored to pain intensity, function, and associated comorbidities.[20,21] Patient education regarding pathogenesis and current treatment options should be initiated early. Patients should be strongly encouraged to work and do other normal activities. Once the patient stops working, getting back into the workforce is more difficult.

Maintenance of healthy lifestyle habits should be the foundation of managing FM. These should include regular physical activity, attention to sleep hygiene, healthy eating habits with weight control, smoking cessation, and avoidance of excessive alcohol and caffeine consumption. Exercise programs (eg, aerobic, strength training, flexibility) should be recommended according to a patient's fitness level. For those unable to do weight-bearing exercise, aqua therapy may be useful.[22]

Treatment Algorithm for Fibromyalgia



Guidelines for the management of FM were published by the American Pain Society (APS) in 2005,[14] the European League Against Rheumatism (EULAR) in 2008,[20] and a German consensus group in 2009.[23] There is, however, generally limited use of treatment algorithms in clinical practice.

Nonpharmacological Treatment Options for Fibromyalgia

As noted, non-pharmacological treatment options should be considered for all patients with FM (see Table 1). There is strong evidence in support of aerobic exercise, cognitive behavioral therapy (CBT), patient education, and multi-disciplinary therapy (at least one educational or other psychological therapy with at least one exercise therapy).[21]

According to a recent review, CBT provides worthwhile improvements in pain-related behavior, self-efficacy, coping strategies, and overall physical functioning.[24] Water exercise has been shown to improve both physical and emotional aspects of FM.[25,26] There is moderate evidence in support of the use of acupuncture, hypnotherapy, biofeedback, and balneotherapy (spa therapy).[21] There is limited evidence for spinal manipulation, movement-body awareness, vitamins, herbs, and dietary modifications.[27]

Pharmacological Treatments for Fibromyalgia

Because patients with FM frequently report excessive sensitivity to medications, pharmacologic treatments should be introduced at low doses, with a plan to gradually increase dosages to therapeutic levels. In this way, better tolerability may be achieved, and there's a better chance of patients continuing treatments.

To date, pharmacologic treatments for FM have focused mainly on pain modulation. A variety of medications have been used to affect peripheral sensitization (eg, gabapentinoids (α2-δ ligands), are analgesic, or work via augmenting descending pain inhibitory mechanisms (eg, antidepressant and dopaminergic agents).[28] Current guidelines indicate that there is strong evidence to support the use of tricyclic antidepressants (TCAs), dual (ie, serotonin and norepinephrine) reuptake inhibitors (SNRIs; duloxetine HCl, milnacipran HCl), and α2-δ ligands (pregabalin, gabapentin).[23] Currently, pregabalin, duloxetine, and milnacipran are approved by the US Food and Drug Administration for the treatment of FM (see Table 2).

Amitriptyline

Amitriptyline is still the most commonly prescribed drug for the pharmacologic treatment of FM. Although relatively inexpensive, use is limited by side effects (eg, mouth dryness, weight gain, and drowsiness) and questions regarding long-term sustained efficacy.[29]

Table 1. Evidence-Based Nonpharmacologic Treatments for FM

Exercise: • Cardiovascular exercise (strong evidence with meta-analysis of 40 trials including 6 with moderate- to high-quality RCTs). • Strengthening exercise (2 moderate- to high-quality RCTs) • Aquatic exercise (least evidence for stretching exercises alone)	**Other interventions with weak evidence:** • Chiropractic • Osteopathic manipulation • Massage therapy • Electrotherapy • Ultrasound
Psychological interventions: • Cognitive-behavioral therapy (good evidence including recent meta-analysis) • Patient education/self-management • Multidisciplinary treatment (usually combined with exercise) • Mindfulness-based stress reduction (weak evidence)	**Areas of potential research include:** • Botulinum-toxin A combined with manual therapy • Exercise to correct biomechanical factors for pain • Platelet-rich plasma prolotherapy injections for ligament laxity, chronic tendinosis • Functional medicine to correct intestinal dysbiosis, nutritional and hormonal deficiencies
Other interventions with modest evidence: • Acupuncture • Hypnotherapy • Biofeedback • Balneotherapy (medicinal bathing) • Transcranial electrical stimulation • Topical essential oils	

FM, fibromyalgia; RCT, randomized controlled trial.

Gabapentinoids

A recent meta-analysis summarized the randomized controlled trials for the currently available α2-δ ligand drugs (pregabalin-5 studies, gabapentin-1 study).[30] These drugs were found to have strong evidence for pain reduction, improved sleep, and improved health-related quality of life, but they did not improve depressed mood. There was also some impact on fatigue and anxiety.[30] The effects of gabapentinoids on pain appear to be independent of anxiolytic effects. The high doses of pregabalin used in trials (300 mg/d, 450 mg/d, 600 mg/d) may be used less commonly in clinical practice due to tolerability-related issues. These agents can be associated with troublesome side effects, including drowsiness, weight gain, and edema.

Antidepressants

SNRIs enhance the DNIC system via augmentation of serotonin and norepinephrine. Two agents—duloxetine and milnacipran—have been reported to improve pain and functioning in patients who have FM. Duloxetine's effect on pain has been shown to be independent of its effect on mood.[31,32] Long-term use has also been limited by side effects, including nausea, vomiting, insomnia, diarrhea, and dizziness.[32] These agents have a reported potential for interactions with other serotonin-elevating agents, such as tramadol. However, serotonin syndrome is rare, and with appropriate monitoring, it should not be an obstacle when selecting an effective pain-relieving strategy.[33]

Opioids

Studies of the use of opioids for managing pain associated with FM are lacking. There is conflicting evidence regarding the role of the endogenous opioid system in FM. Studies have reported both down- and up-regulation of opioid receptors, elevated levels of cerebrospinal fluid enkephalin, as well as variable responses to naltrexone—an opioid antagonist with effect on microglia activity (cells playing an increasingly important role in pain) in the central nervous system.[2] However, clinical experience suggests that opioids may be useful in selected patients, but clinicians need to prescribe opioids with caution because of side effects and concerns of misuse and addiction. The long-term effects of chronic opioid use in non-malignant pain are not yet fully clarified, but effects on mood and cognitive function need to be constantly re-evaluated. Extended-release formulas are believed to have a better tolerability profile than short-acting agents, but also with limited evidence. Tramadol is a novel analgesic that has an effect on serotonin and norepinephrine, as well as acting on the μ-opioid receptor. Two studies have shown a positive effect on pain with associated benefits to quality of life.[34,35]

NSAIDs generally are not effective for managing FM pain, but they may be used to treat pain associated with other co-existing conditions (eg, osteoarthritis). Physicians who prescribe NSAIDS should educate patients about the usual precautions regarding potential gastrointestinal and cardiovascular toxicity. Injection therapies with local anesthetics into trigger points and botulinum toxin type-A (biomechanical approach) have also been reported to help in pain palliation, but they require further placebo-controlled investigation.[36]

Emerging Treatment Options for Fibromyalgia

Novel pharmacological treatments for FM include dopamine agonists, such as pramipexole, the sleep-inducing agent sodium oxybate, and the cannabinoid group of molecules, exemplified by the synthetic cannabinoid nabilone. Pramipexole treatment was reported to provide improvements in pain, fatigue, and function in a 14-week, double-blind, placebo-controlled trial.[37]

Follow-up Evaluation

- Recording patient goals and their levels of achievement can be a useful strategy to follow patient outcome.
- The following tools were suggested:
  - **a.** FM Impact Questionnaire is a disease-specific composite instrument that measures function as well as symptoms in patients who have FM. A recent analysis indicated that a 14% change in the FIQ total score is clinically relevant.[44]
  - **b.** Pictorial Representation of Illness and Self Measure (PRISM) is quick and easy to perform in a physician's office. It was recently validated for chronic pain.[45]
- Current FM treatment paradigms are based on physicians' experience and patients' preference and tolerability, rather than on evidence from clinical trials.
- Treating the spectrum of symptoms that may be present in an individual patient is vital to successful management and improvement in well-being.
- FM patients in clinical practice often use multiple non-pharmacological and pharmacological treatment regimens.
- There is a need for improved long-term efficacy and safety data for all currently available agents.

Table 2. Evidence-Based Treatment Options for FM

Class	Generic (Brand)	Strength of Evidence	Usual Dose	Potential Side Effects	Comments
Tricyclic Antidepressants	Amirtriptyline (Elavil)	1A	10-50 mg qhs. In "sensitive" patients, start with 5 mg and titrate up more gradually. For ODB coverage of pregabalin, titrate up to 75 mg qhs.	Side effects may include dry mouth, drowsiness (do not prescribe for daytime use), weight gain, arrhythmias, and urinary retention. Risk of serotonin syndrome when combined with other TCAs, SSRIs, SNRIs, triptans, tramadol, and St. John's wort.	Contraindicated in patients taking MAOIs and in post–cardiac disease (MI) recovery. Nortriptyline has fewer side effects but is less potent (and fewer studies exist) for pain relief. Other options include desipramine, imipramine.
Alpha-2-Delta Ligands	Pregabalin (Lyrica)	1A	150-450 mg/d. Start with 75 mg at night and titrate up weekly. In "sensitive" patients, start with 25 mg and titrate up more gradually.	Side effects may include drowsiness, dizziness, dose-dependent weight gain, edema, and headache.	Adjust dose in renally impaired patients.
	Gabapentin (Neurontin)	1B	1,200-2,400 mg/d		Gabapentin is 6 to 7 times less potent than pregabalin and requires active transport in the gastrointestinal tract (more difficult and lengthier titration process compared with pregabalin).
SNRI	Duloxetine (Cymbalta)	1A	30-60 mg/d. Start with 30 mg at lunchtime (with food) and titrate up after 1 week. In "sensitive" patients, open up the capsule and take ½ with applesauce.	Side effects may include nausea, dry mouth, somnolence, constipation, sweating, and "serotonin syndrome."	Avoid use with other serotonergic agents (as listed for TCAs). Contraindicated in patients with hepatic insufficiency and those taking MAOIs. Other options include milnacipran (Savella) 1A.

Table 2. Evidence-Based Treatment Options for FM (continued)

Class	Generic (Brand)	Strength of Evidence	Usual Dose	Potential Side Effects	Comments
Muscle Relaxants	Cyclobenzaprine (Flexeril)	2A	10-40 mg/d. Start with 5-10 mg/d. Has tricyclic action, so begin in the evening or at nighttime and titrate up gradually.	Side effects and contraindications similar to amitriptyline.	
	Tizanidine (Zanaflex)	2B	4-12 mg/d. Start with ½ of a 4-mg tablet at nighttime. Titrate up with higher dose at nighttime.	Side effects include fatigue, dry mouth, dizziness, and hypotension. Rare risk of hepatic failure, so liver enzymes should be followed q3 mo.	An alpha-2 agonist; use with caution with other medications that can lower blood pressure.
Opioids	Tramadol (Tramacet)	2B	50-300 mg/d. Start with Tramacet (37.5 mg tramadol + acetaminophen 325 mg), taking 1 tid with food. Titrate up gradually and transition to controlled-release form Tridural and add acetaminophen prn for breakthough pain.	Side effects for opioids include nausea, constipation, sedation, itching, sweating, myoclonus, and hypogonadism. Tramadol also has SNRI action with similar side effects. Avoid or minimize use with concomitant serotonergic drugs.	Other options such as controlled-released opioids may be considered in severe, relcitrant neuropathic pain and palliative care conditions but are not routinely recommended for fibromyalgia.
Cannabinoid	Nabilone (Cesamet)	2A	0.5-6.0 mg/d. Start with 0.5 mg at nighttime. In "sensitive" patients, consider 0.25-mg capsule or have it compounded into a suspension. Titrate up gradually with higher dose at nighttime.	Side effects include nausea, fatigue, and dry mouth. Contraindicated in serious cardiovascular disease and history of psychosis.	Works synergistically with opioids. Less effective in omega-3 fatty acid deficiency. Other options include dronabinol (Marinol) (2.5 mg qhs à 10 mg tid), THC-CBD sublingual spray (Sativex) (1 spray in evening and qhs à 2 sprays qid) and medical marijuana (~10 mg THC in one joint [0.5 g cannabis] = 1 mg nabilone = 10 mg dronabinol = 4 THC-CBD sprays).

FM, fibromyalgia; MAOI, monoamine oxidase inhibitor; MI, myocardial infarction; prn, as needed; qhs, once daily at bedtime; qid, 4 times daily; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; THC-CBD, tetrahydrocannabinol-cannabidiol; tid, twice daily.

Reduction of pain and improvements in quality of sleep were observed in a study of sodium oxybate, 4.5 g and 6 g.[38] A recent small study of nabilone in FM reported improvements in the FIQ and the pain as measured by a visual analog scale.[39] However, the efficacy and safety of these novel agents require additional study.

There has been suggestion that subgrouping patients who have FM may facilitate treatments. Various subgroupings have been tested, categorizing patients according to psychological status, including depressed mood, anxiety, or a catastrophizing personality.[40]

Addressing *Pain* Symptoms

Because FM pain is mostly neurologically based, medications effective for the treatment of neuropathic pain (eg, gabapentinoids, SNRIs, cannabinoids) may be the most effective. Long-term studies to address adherence, efficacy, and outcome are still required. Regular re-evaluation is required to determine continued efficacy and to manage side effects.

Depressed Mood

The frequency and severity of depressive symptoms in FM may vary depending on whether a patient is in a primary or tertiary care setting, with more severe symptoms in tertiary care patients. Psychosocial distress is a predictor of onset of chronic widespread pain in population studies conducted in England.[41,42] Although SSRIs are useful in treating depression, they have limited effect on other FM symptoms. Thus, SNRIs and TCAs are better choices, although the low doses of TCAs commonly used will not have much of an effect on mood. Tailored treatments should also take into account the anxiety in FM patients.[30] Medications, such as gabapentin, pregabalin, and cannabinoids, have anxiolytic effects, as well as potential relief of insomnia and pain associated with FM.

Sleep Disturbances and Fatigue

Non-restorative sleep is associated with widespread pain.[43] Other sleep disorders, such as restless leg syndrome or sleep apnea should be specifically addressed. Education about the importance of getting enough sleep should be the first step in a treatment plan. Medications, such as benzodiazepines, opioids, and alcohol, that have a negative impact on sleep should be discouraged. Medications that show a positive impact on sleep include pregabalin,

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Current Challenges of Managing Fibromyalgia

- No objective diagnostic test available for use in clinical practice
- No gold standard of treatment
- Establishing achievable treatment outcomes
- Balancing the efficacy and side effects of a particular treatment, as well as patient adherence to treatment
- Physician's time and resources

Suggestions for Improving Fibromyalgia Management

- Educational programs for physicians on the management of chronic pain should be developed. Continuing medical education programs, workshops, and case studies were identified as efficient teaching methods. Local panels of pain experts could provide regular updates on current developments in the field (eg, clinical trials, updates on current recommendations and treatment strategies).
- Chronic pain-related lectures should be included in medical school curricula.
- Uniform approach and messages for all healthcare providers involved in FM treatment should be developed.
- Improvement in access to both pharmacological and non-pharmacological (eg, cognitive behavioral therapy, physiotherapy, rehabilitation centers, dietitians) treatment modalities is required. Timely access to pain clinics and pain specialists is also needed.
- A diagnostic procedure is required. Standardized diagnostic tools and/or tests—either a biological marker or imaging study—would be beneficial.
- Patient education tools (eg, reassurance, information about the disease, and coping strategies) should be developed. Information about available local resources (eg, support groups) and/or Internet-based programs should be accessible.
- Acceptance of FM as a chronic condition by authorities (eg, governing bodies, insurance providers, and employers) should be further improved. Development of public awareness strategies, as well as economic models, is required.

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nabilone, and sodium oxybate.

There have been no studies specifically addressing fatigue in FM. Exercise has been shown to improve function and is the only recommended treatment for fatigue at this time. Stimulating agents, such as modafinil or methylphenidate, are used occasionally and with caution as they may aggravate anxiety and have potential for abuse.

Patient Outcomes

There are no standardized tools for patient follow-up and ongoing evaluation. The evaluation of patient outcome depends on self-reporting of symptoms and function. Research data and evidence from clinical practice suggest that a proportion of patients improve considerably or even completely recover. This applies particularly to patients at the "mild end of the spectrum." Patients with severe symptoms often seen in specialty practices may therefore not be accurate representatives of the general FM population.

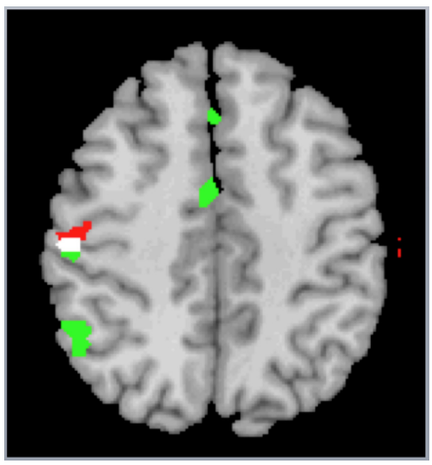
Caveats of Clinical Studies

Clinical trials are necessary to identify efficacy for a treatment intervention. They, however, do not accurately reflect real-world clinical practice. Patients in clinical trials are highly selected; those with severe co-morbidities are often excluded, and therefore may not accurately reflect the true patient population. Since there is no gold standard of treatment for FM, most studies compare a single active agent to placebo, with almost no studies examining the effect of a combination of treatments. Most FM-related clinical trials are also of short duration and, in many instances, involve a relatively small number of patients. In addition, the high-dose regimens (eg, pregabalin, pramipexole) used in clinical trials may not always be achieved in clinical practice due to problems with tolerability. Patients who have FM commonly report that they are hypersensitive and less tolerant to medications. As a result, the "start low and go slow" approach is often required.

Conclusions

Fibromyalgia is a legitimate disease characterized by the presence of multiple symptoms: widespread chronic pain, fatigue, mood, and sleep disturbances. The progress in the understanding of pathophysiological mechanisms of FM, however, has not been fully translated into clinical practice with regard to the diagnosis and management of patients. This condition remains a challenge from both a diagnostic and management perspective. Several effective pharmacological and non-pharmacological therapeutic options are available. However, tailoring treatments to the individual patient is crucial. Many patients are eventually treated pharmacologically, often with multiple agents. Vigilance regarding efficacy and toxicity of a treatment is required. Although FM should be managed pre-dominantly by primary care physicians, multidisciplinary support is ideal. The medical community and the public are gradually recognizing that this condition is unique, but with slower acceptance by governing bodies and insurance providers. ■

This condition remains a challenge from both a diagnostic and management perspective.



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References

1. McNally JD, Matheson DA, Bakowsky VS. The epidemiology of self-reported FM in Canada. *Chronic Dis Can.* 2006;27:9-16.
2. Abeles AM, Pillinger MH, Solitar BM, Abeles M. Narrative review: the pathophysiology of FM. *Ann Intern Med.* 2007;146:726-734.
3. Gracely RH, Grant MA, Giesecke T. Evoked pain measures in FM. *Best Pract Res Clin Rheumatol.* 2003;17:593-609.
4. Staud R. Biology and therapy of FM: pain in FM syndrome. *Arthritis Res Ther.* 2006;8:208.
5. Price DD, Staud R. Neurobiology of fibromyalgia syndrome. *J Rheumatol Suppl.* 2005;75:22-28.
6. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in FM. *Arthritis Rheum.* 2002;46:1333-1343.
7. Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. *Pain.* 2005;114:295-302.
8. Petzke F, Clauw DJ. Sympathetic nervous system function in fibromyalgia. *Curr Rheumatol Rep.* 2000;2:116-123.
9. Staud R, Nagel S, Robinson ME, Price DD. Enhance central pain processing in fibromyalgia patients is maintained by muscle afferent input: a randomized, double-blind, placebo-controlled study. *Pain.* 2009;145:96-104.
10. Goffaux P, de Sousa JB, Potvin S, Marchand S. Pain relief through expectation supersedes descending inhibitory deficits in fibromyalgia patients. *Pain.* 2009; 145:18-23.
11. McBeth J, Silman AJ, Gupta A et al. Moderation of psychosocial risk factors through dysfunction of the hypothalamic-pituitary-adrenal stress axis in the onset of chronic widespread musculoskeletal pain: findings of a population-based prospective cohort study. *Arthritis Rheum.* 2007;56:360-371.
12. Jones GT, Power C, Macfarlane GJ. Adverse events in childhood and chronic widespread pain in adult life: Results from the 1958 British Birth Cohort Study. *Pain.* 2009;143:92-96.
13. Wolfe F, Smythe HA, Yunus MB et al. The American College of Rheumatology 1990 Criteria for the Classification of FM. Report of the Multicenter Criteria Committee. *Arthritis Rheum.* 1990;33:160-172.
14. Burckhardt C, Goldenberg DL, Crofford LJ et al. Guideline for the Management of Fibromyalgia Syndrome Pain in Adults and Children. APS Clinical Practice Guidelines Series, No. 4; 2005. Available at: http://www.ampainsoc.org/pub/fibromyalgia.htm. Accessed January 17, 2011.
15. Hughes G, Martinez C, Myon E, Taïeb C, Wessely S. The impact of a diagnosis of fibromyalgia on health care resource use by primary care patients in the UK: an observational study based on clinical practice. *Arthritis Rheum.* 2006;54:177-183.
16. White KP, Nielson WR, Harth M, Ostbye T, Speechley M. Does the label "fibromyalgia" alter health status, function, and health service utilization? A prospective, within-group comparison in a community cohort of adults with chronic widespread pain. *Arthritis Rheum.* 2002;47:260-265.
17. Hunter J, Watt-Watson J, McGillion M et al. An interfaculty pain curriculum: lessons learned from six years experience. *Pain.* 2008;140:74-86.
18. Shir Y, Fitzcharles MA. Should rheumatologists retain ownership of FM? *J Rheumatol.* 2009;36:667-670.
19. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. . 1991;18:728-733.
20. Carville SF, Arendt-Nielsen S, Bliddal H et al. EULAR evidence-based recommendations for the management of fibromyalgia syndrome. *Ann Rheum Dis.* 2008;67:536-541.
21. Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. *JAMA.* 2004;292:2388-2395.
22. Munguia-Izauierdo D, Legaz-Arrese A. Assessment of the effects of aquatic therapy on global symptomatology in patients with fibromyalgia syndrome: a randomized controlled trial. *Arch Phys Med Rehabil.* 2008;89:2250-2257.
23. Häuser W, Thieme K, Turk DC. Guidelines on the management of fibromyalgia syndrome – a systematic review. 2010;14(1):5-10.
24. Bennett R, Nelson D. Cognitive behavioral therapy for fibromyalgia. *Nat Clin Pract Rheumatol.* 2006;2:416-424.
25. Mannerkorpi K, Nordeman L, Ericsson A, Arndorw M; GAU Study Group. Pool exercise for patients with fibromyalgia or chronic widespread pain: a randomized controlled trial and subgroup analyses. *J Rehabil Med.* 2009;41:751-760.
26. Tomas-Carus P, Gusi N, Häkkinen A, Häkkinen K, Raimundo A, Ortega-Alonso A. Improvements of muscle strength predicted benefits in HRQOL and postural balance in women with fibromyalgia: an 8-month randomized controlled trial. *Rheumatology (Oxford).* 2009;48:1147-1151.
27. Schneider M, Vernon H, Ko G, Lawson G, Perera J. Chiropractic management of fibromyalgia syndrome: a systematic review of the literature. *J Manipulative Physiol Ther.* 2009;32:25-40.
28. Clauw DJ. Pharmacotherapy for patients with fibromyalgia. *J Clin Psychiatry.* 2008;69 Suppl 2:25-29.
29. Nishishinya B, Urrutia G, Walitt B et al. Amitriptyline in the treatment of fibromyalgia: a systematic review of its efficacy. *Rheumatology (Oxford).* 2008;47:1741-1746.
30. Häuser W, Bernardy K, Uçeyler N, Sommer C. Treatment of fibromyalgia syndrome with gabapentin and pregabalin – a meta-analysis of randomized controlled trials. *Pain.* 2009;145:69-81.
31. Arnold LM, Hudson JI, Wang F et al. Comparisons of the efficacy and safety of duloxetine for the treatment of fibromyalgia in patients with versus without major depressive disorder. *Clin J Pain.* 2009;25:461-468.
32. Chappell AS, Littlejohn G, Kajdasz DK, Scheinberg M, D'Souza DN, Moldofsky H. A 1-year safety and efficacy study of duloxetine in patients with fibromyalgia. *Clin J Pain.* 2009;25:365-375.
33. Wedge MK. The truth behind tramadol and antidepressants: an interaction of concern? *Can Pharm J.* 2009;142:71-73.
34. Bennett RM, Kamin M, Karim R, Rosenthal N. Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: a double-blind, randomized, placebo-controlled study. *Am J Med.* 2003;114:537-545.
35. Russell IJ, Kamin M, Bennett RM, Schnitzer TJ, Katz WA. Efficacy of tramadol in treatment of pain in fibromyalgia. *J Clin Rheumatol.* 2000;6:250-257.
36. Ko GD, Whitmore S, Huang D, McDonald R. Effective pain palliation in fibromyalgia syndrome patients with Botulinum Toxin Type-A: case series of 25. *J Musculoskel Pain.* 2007;15:55-66.
37. Holman AJ, Myers RR. A randomized, double-blind, placebo-controlled trial of pramipexole, a dopamine agonist, in patients with fibromyalgia receiving concomitant medications. *Arthritis Rheum.* 2005;52:2495-2505.
38. Russell IJ, Perkins AT, Michalek JE; Oxybate SXB-26 Fibromyalgia Syndrome Study Group. Sodium oxybate relieves pain and improves function in fibromyalgia syndrome: a randomized, double-blind, placebo-controlled, multicenter clinical trial. *Arthritis Rheum.* 2009;60:299-309.
39. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. *J Pain.* 2008;9:164-173.
40. Giesecke T, Williams DA, Harris RE et al. Subgrouping of fibromyalgia patients on the basis of pressure-pain thresholds and psychological factors. . 2003;48:2916-2922.
41. Gupta A, Silman AJ, Ray D et al. The role of psychosocial factors in predicting the onset of chronic widespread pain: results from a prospective population-based study. *Rheumatology (Oxford).* 2007;46:666-671.
42. Gormsen L, Rosenberg R, Bach FW, Jensen TS. Depression, anxiety, health-related quality of life and pain in patients with chronic fibromyalgia and neuropathic pain. *Eur J Pain.* 2010;14(2):127.e1-8.
43. Chiu YH, Silman AJ, Macfarlane GJ et al. Poor sleep and depression are independently associated with a reduced pain threshold. Results of a population based study. *Pain.* 2005;115:316-321.
44. Bennett RM, Bushmakin AG, Cappelleri JC, Zlateva G, Sadosky AB. Minimal clinically important difference in the fibromyalgia impact questionnaire. *J Rheumatol.* 2009;36:1304-1311.
45. Kassardjian CD, Gardner-Nix J, Dupak K, Barbati J, Lam-McCullock J. Validating PRISM (Pictorial Representation of Illness and Self Measure) as a measure of suffering in chronic non-cancer pain patients. *J Pain.* 2008;9:1135-1143.