

# Fibromyalgia treatment update

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## Purpose of review

Fibromyalgia is a common chronic pain disorder characterized by complex symptomatology and few consistently effective treatments. The purpose of this review is to highlight the recent literature from April 2005 through September 2006 involving treatment options.

## Recent findings

Prior evidence suggests that medication and self-management approaches to care can improve symptoms, function and well-being in this patient population. Recent studies examining the efficacy of two serotonin and norepinephrine-reuptake inhibitors – duloxetine and milnacipran – and the anticonvulsant pregabalin are encouraging. Studies evaluating different forms of exercise continue to support the belief that increased physical activity is an essential component of any treatment plan for the patient with fibromyalgia. Three studies added to the understanding of treatment adherence. Finally, three studies evaluating the efficacy of acupuncture in the treatment of fibromyalgia showed conflicting results, but added to the knowledge needed for clinicians to have substantive conversations with patients.

## Summary

Recent studies support the recommendation of a multimodal approach to treatment involving individualized, evidence-based pharmacotherapy and self-management. Treatment goals should include the improvement of symptoms, primarily pain and sleep, and the promotion of positive health behaviors with the aim of improving physical function and emotional well-being.

## Keywords

fibromyalgia, guidelines, self-management, treatment

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## Abbreviations

**FIQ** Fibromyalgia Impact Questionnaire  
**VAS** visual analog scale

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## Introduction

Fibromyalgia is a common, multidimensional disorder with complex symptomatology and relatively poor treatment outcomes [1,2<sup>••</sup>]. Fibromyalgia is characterized by widespread pain for longer than 3 months and bilateral sites of amplified tenderness [3]. In most patients, fibromyalgia is associated with fatigue, sleep dysfunction, stiffness, depression, anxiety, cognitive disturbance, or exercise intolerance [2<sup>••</sup>,3,4], and is reported to be more common in women and individuals with other rheumatic conditions [5]. The prevalence of fibromyalgia is estimated to be 2% in the USA [6,7<sup>•</sup>] and Canada [8]. The etiology and pathophysiology of fibromyalgia remain unclear. Current hypotheses center on atypical sensory processing in the central nervous system and dysfunction of skeletal muscle nociception and the hypothalamic–pituitary–adrenal axis [9–11,12<sup>••</sup>].

Current treatments for fibromyalgia include medical, self-management and alternative interventions. The number of published studies, particularly randomized controlled trials, has risen steadily over the past decade. Treatment remains inadequate to reliably resolve persistent symptoms and improve functional limitations and quality of life in most patients. One reason for unsatisfactory outcomes may be the absence of an evidence-based standard of care. To address this void, a recent report commissioned by the American Pain Society provides a comprehensive assessment of the research supporting treatment choices for the patient with fibromyalgia and presents clinical practice guidelines, which are summarized in Table 1 [1,13<sup>••</sup>]. This paper will highlight studies evaluating treatment options for the patient with fibromyalgia published from April 2005 through September 2006.

## Outcome measures

Change in pain intensity and the impact of fibromyalgia on a person's functional status are the most common outcomes in fibromyalgia research. Pain, a subjective outcome, is highly variable in the fibromyalgia population [14<sup>•</sup>] and is commonly assessed by the visual analog scale (VAS). The typical VAS scale is 100 mm in length and anchored by the extremes of the characteristic being assessed; that is, absence of pain or most pain ever experienced. The VAS scale is also used to assess other common symptoms, including general fatigue, tiredness upon awakening, sleep and mood [15]. Other methods of assessing symptoms include the paper and electronic diary [16,17<sup>•</sup>] and symptom-specific

**Table 1 Treatment phases for fibromyalgia**


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1. Diagnose
Verify diagnosis
Assess and address associated comorbid conditions
Depression, anxiety and sleep disorders should be addressed independent of fibromyalgia symptoms
Educate patient
The Arthritis Foundation ( <a href="http://www.arthritis.org">www.arthritis.org</a> ), National Fibromyalgia Association ( <a href="http://www.fmaware.org">www.fmaware.org</a> ), and Fibromyalgia Association UK ( <a href="http://www.fibromyalgia-associationuk.org">www.fibromyalgia-associationuk.org</a> ) are good resources
2. Treat
Low-dose tricyclic antidepressants or cyclobenzaprine
Amitriptyline (25–50 mg at bedtime) has shown to improve sleep and well-being
Cyclobenzaprine (10–30 mg at bedtime) has shown similar outcomes to Amitriptyline
Increase physical activity in daily life and start a program of regular exercise
A pedometer can help patients monitor and increase daily physical activity
Exercise program should include moderate aerobic activities (i.e. walking, pool-based, bicycling, low-impact group exercise class)
Gentle strengthening and stretching activities can be included to meet the patient's overall health needs
Volume and intensity of activities should match patient's level of fitness and exercise experience
Refer for cognitive behavioural therapy
Shows promising results
Well-run group activities can add value to therapy experience
Combine interventions
Multimodal therapy of medication, exercise and education or cognitive behavioral therapy is recommended for optimal treatment
3. Refine treatment
Refer to rheumatologist, physiatrist, psychiatrist, psychologist, pain-management specialist, sleep specialist or other healthcare professional as needed
Managing fibromyalgia is best accomplished when the patient and healthcare providers work as a team
Initiate use of select serotonin-reuptake inhibitor (fluoxetine, 20–80 mg) with tricyclic, dual reuptake inhibitors (duloxetine, milnacipran, venlafaxine), pregabalin, or tramadol with or without acetaminophen
Continue to try different combinations of treatment options

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Modified from Goldenberg *et al.* [1].

questionnaires – short-form McGill Pain Questionnaire [18], the Beck Depression Inventory [19], and Beck Anxiety Inventory [20]. Discussion of what determines a ‘clinically’ significant improvement in an outcome such as pain is ongoing. However, a 30% improvement in a variable (i.e. from 7.5 to 5.25 on a VAS) is a recommended threshold for determining clinical efficacy [21].

Levels of physical and emotional function are important outcomes for chronic-pain-intervention studies [22<sup>•</sup>] and are increasingly used in fibromyalgia research [1,2<sup>••</sup>]. The Fibromyalgia Impact Questionnaire (FIQ) [15,23<sup>•</sup>], the most commonly used measure of function in this patient population, is a 10-item, reliable, responsive instrument that assesses physical function, common fibromyalgia symptoms and general well-being over the previous 7 days. A change in the total score of 20% or greater has been suggested to be clinically significant [23<sup>•</sup>]. Subscales of the Short-Form 36 Health Survey (SF-36) are increasingly being used as a generic measure of physical and emotional function and quality of life [24]. The SF-36 is a valid and reliable self-administered measure in populations with musculoskeletal conditions [25]. The distance walked in 6 min objectively assesses mobility in individuals with physical limitations and has been validated in the fibromyalgia population as a measure of function [26]. Recently, Mannerkorpi and Hernelid [27] reported on the Leisure Time Physical Activity Instrument and Physical Activity at Home and Work Instrument to address the issue of quantifying

physical activity in this often sedentary population. More detailed descriptions of outcome measures used in fibromyalgia research can be found in recent review articles [2<sup>••</sup>,28<sup>•</sup>].

### Medical management

Currently, no drug, modality or clinical intervention is approved by the US Federal Drug Administration or other governing body for the treatment of fibromyalgia. Whereas several new drugs are in trials [29,30], investigators continue to search for ways to apply currently available medications and other medical interventions to improve the clinical outcomes of fibromyalgia patients.

### Medication

Drugs remain the primary treatment option for fibromyalgia and the tricyclic antidepressants and their analogs are the drugs of choice [13<sup>••</sup>]. Meta-analyses support the moderate effectiveness of these drugs [31,32]. Arnold and colleagues [31], in their meta-analysis of nine placebo-controlled, randomized trials of tricyclic antidepressants, reported mean ( $\pm$ standard error) effect sizes of 0.565 ( $\pm$ 0.084) for pain, 0.521 ( $\pm$ 0.092) for fatigue and 0.690 ( $\pm$ 0.088) for sleep and clinical improvement in 25–37% of study participants. The mechanisms for their effectiveness may include a direct effect of the drugs on norepinephrine and serotonin reuptake to improve sleep, comorbid depression, stress and anxiety and inhibition of pain pathways and pain recognition [17<sup>•</sup>,33].

The newest direction of pharmacotherapy is in the area of dual reuptake inhibitors and an antiepileptic. Approved by the US Food and Drug Administration for depression, duloxetine and milnacipran are serotonin and norepinephrine-reuptake inhibitors that have shown encouraging results in preliminary studies with fibromyalgia. Arnold and colleagues [34], in a 12-week, randomized, double-blind, placebo-controlled, multicenter trial with duloxetine, reported sizable improvement in pain severity, tender-point count and sensitivity, stiffness and quality of life in women with fibromyalgia. These changes were observed independent of the presence of comorbid depression. Interestingly, males in the study did not show a significant improvement on any outcome measure. These findings were confirmed in a subsequent study by Arnold *et al.* [35]. Three hundred and fifty-four patients, 26% of whom had major depressive disorder, were randomized to one or two doses of duloxetine (60 mg either daily or twice daily) or placebo. Both duloxetine groups demonstrated greater improvement in pain severity compared to placebo and this effect was independent of changes in mood. More than half (54–55%) of participants randomized to duloxetine experienced  $\geq 30\%$  improvement in pain compared to 33% in the placebo group. No differences in outcomes were observed between the two doses.

Milnacipran, another dual reuptake inhibitor currently used to treat depression, was examined for its analgesic properties in 125 patients with fibromyalgia [17]. The Phase II trial randomized participants into a milnacipran daily, milnacipran twice daily or placebo group. Pain intensity was the primary outcome and collected via electronic and paper diaries several times a day. After the 12-week study, the twice-daily milnacipran group showed significantly greater improvement on measures of pain intensity, fatigue, morning stiffness, physical function and global well-being compared to placebo. No serious adverse events were reported.

The antiepileptic pregabalin is approved in the USA for treating neuropathic pain in diabetic peripheral neuropathy and postherpetic neuralgia. In a recent study, Crofford and colleagues [36] examined the effect of pregabalin for the treatment of fibromyalgia symptoms. In this large, 8-week, multicenter, double-blind, placebo-controlled, clinical trial 529 patients were randomized into three groups taking pregabalin (150, 300, and 450 mg/day) or a placebo. The highest dose of pregabalin resulted in statistically greater improvement in pain, fatigue, sleep and quality of life compared to changes in the placebo group. A recent abstract by Crofford and colleagues [37] reported the sustained analgesic effects of higher doses (300, 450, and 600 mg/day) of pregabalin over 26 weeks of treatment compared to placebo.

Several other notable studies published in the past year include new and current drug options. Twenty patients in an open-label, uncontrolled study with a progressive dose of pindolol showed improved FIQ scores after 12 weeks on the drug [38]. In a randomized, double-blind, placebo-controlled trial with the dopamine agonist pramipexole, participants reported improved pain, fatigue and function and weight loss (3.3 lb; 1.5 kg) after 14 weeks of treatment [39]. Tramadol combined with acetaminophen has shown to be beneficial in patients with fibromyalgia [40]. In a subsequent study, Bennett and colleagues [41], reporting an inverse relationship between pain and health-related quality of life in a large sample, evaluated the analgesic effect of tramadol/acetaminophen compared to placebo on fibromyalgia pain. Compared to the placebo group, participants in the tramadol group reported greater improvement in health-related quality of life, pain and several domains associated with physical function and work-related limitations.

### Nonmedication

In a novel approach to pain treatment, Sampson and colleagues [42] reported pilot data using repetitive transcranial magnetic stimulation in four women with fibromyalgia. The participants, who were also diagnosed with comorbid depression and borderline personality disorder, reported a mean reduction in pain of 82%, with two of the four reporting complete resolution of pain. The positive findings in this nonpharmacological approach to depression should garner more interest as a possible treatment for fibromyalgia.

### Self-management

In this review, self-management will be defined as the activities a patient has an active role in performing that promote health and well-being, while improving one or more fibromyalgia-specific symptom and functional status. The area of patient self-management is a rapidly growing aspect of care for the person with a chronic illness and has been an integral part of treatment for other chronic conditions [43,44]. We will focus on exercise here.

### Exercise

Since the first study showed the benefit of exercise to individuals with fibromyalgia nearly 25 years ago [45], the number of studies evaluating various forms of aerobic and strength training exercise in people with fibromyalgia has grown exponentially. In the past year, studies evaluating pool and resistance exercise reported positive outcomes. Water-based exercise has been shown to be beneficial in patients with fibromyalgia [46,47]. In a recent study, Assis and colleagues [48] found 15 weeks of moderately intense deep-water running and land-based fitness training both effective for improving pain, mood, fitness, quality of life and function in 60 sedentary women

severely impacted by fibromyalgia (FIQ score >60). Another study by Gusi and colleagues [49] using a 12-week training and 24-week detraining period reported that a pool-based, walking intervention improved lower-extremity muscle strength, health-related quality of life and pain in women with fibromyalgia compared to a group that did no exercise. After detraining, strength and quality of life improvements were maintained, whereas pain severity was not.

Strength training, particularly in older adults, has become an expanding area of research due to its many health and function-related benefits [50]. Valkeinen and colleagues [51<sup>•</sup>] published two papers detailing findings from their intense 21-week strength training intervention. The first paper included 26 older women with fibromyalgia randomized to training or no training. Training resulted in sizeable increases in muscle strength (33–36%), quadriceps cross-sectional area (5%), and voluntary activation of muscles (47–57%) compared to women who did not exercise [51<sup>•</sup>]. Serum levels of growth hormone, testosterone, insulin-like growth factor-1, dehydroepiandrosterone sulfate and cortisol were not affected by the exercise. Notably, no adverse events were reported from the intense training. In the second study, 13 older women with fibromyalgia and 10 older women without fibromyalgia performed the same exercise intervention. Although baseline levels were lower in the fibromyalgia group, both groups had similar increases in muscle strength, exercise-related pain, exercise-induced muscle fatigue, and blood lactate levels [52<sup>•</sup>]. These data demonstrate the plasticity of muscle to improve in strength is similar in women with and without fibromyalgia.

Lemstra and Olszynski [53] examined a 6-week program involving group exercise, rheumatologist and physical-therapist counseling, pain, stress management and nutrition education and massage therapy on symptoms and function in 79 women with fibromyalgia. The 43 participants randomized to standard care plus group adjunct treatment reported improved health status, severity and duration of pain, and disability related to pain, compared to patients receiving standard care only. All improvements, except health status level, were sustained at 15 months.

### Adherence

Adherence to any therapeutic intervention is critical for its effectiveness. Dobkin and colleagues [54<sup>•</sup>] reported that patient–physician agreement on the patient’s well-being and a lower level of patient distress predicted greater adherence to general treatment for fibromyalgia. Additionally, better adherence to medication was seen in patients experiencing greater pain and better emotional health. In additional papers, Dobkin and colleagues [55,56] reported on the difficulty in starting and

maintaining a home-based exercise program of aerobic and flexibility training in a small sample of women with fibromyalgia. Findings suggested that addressing pain, stress and obstacles to exercise and individualizing the exercise activities for the person’s level of fitness and physical limitations could improve adherence to habitual exercise involvement.

### Complementary therapies: acupuncture

In recent years, complementary and alternative therapies have garnered increased attention as potential treatments for fibromyalgia and are used by patients [57]. Acupuncture is a treatment in traditional Chinese medicine with more than 2500 years of history for use in chronic pain and has been suggested for use in fibromyalgia [58,59]. According to traditional Chinese medicine, fibromyalgia is caused by dysfunction of the liver, spleen and kidney that interrupts or depletes the body’s internal energy (Qi) and blood flow, resulting in clinical symptoms [60]. Two recent randomized controlled studies examining acupuncture in fibromyalgia samples contribute to the body of well designed studies in this area; however, the studies do little to clarify the role of acupuncture as a possible treatment for fibromyalgia.

In a well designed study, Assefi and colleagues [61<sup>•</sup>] randomized 100 acupuncture-naïve, fibromyalgia patients into one of four groups (actual acupuncture designed to treat fibromyalgia and three sham acupuncture). Participants received two treatment sessions per week for 12 weeks. After good adherence to the interventions ( $\geq 80\%$  of 24 sessions), no differences were seen between groups in any of the outcome variables – pain, fatigue, sleep quality, overall well-being and physical and mental function. Similar findings were seen in a study by Harris and colleagues [62], where the level of analgesia reported was independent of needle placement or stimulation.

Conflicting findings were reported by Martin and colleagues [63] from a randomized controlled trial in 50 patients with fibromyalgia, half of whom received six sessions of actual acupuncture and the other half sham acupuncture over 3 weeks. FIQ scores improved in both acupuncture and sham groups during treatment (6.7 compared with 4.0 points). One month after treatment ended, the acupuncture group maintained the improvement while the sham group scores receded toward baseline, resulting in a mean difference of 7.4 points on the FIQ total score ( $P < 0.007$ ). Significant differences were also observed between groups in scores for pain severity, fatigue, and anxiety 1 month after treatment. Differences between groups in all measures were not sustained at 7-month follow-up.

The studies by Assefi, Harris and Martin *et al.* provide examples of methodologic differences that may explain

their disparate findings and intrinsic challenges associated with acupuncture trials. First, acupuncture is known to have a powerful placebo effect in these types of trials [64] and individuals with fibromyalgia have shown a strong placebo response in other blinded intervention trials [35<sup>\*</sup>]. Second, needling has beneficial effects on the variables being measured in these studies independent of placement location [62]. Additionally, needling results in similar physiological responses in people with and without fibromyalgia [65]. Third, it is not known what dose of acupuncture is sufficient to produce reliable results in fibromyalgia patients. The three studies used different numbers of sessions in their intervention, with Martin having the fewest. A final difference is the source of study participants and a possible selection bias. This may best explain the difference in findings of Assefi and Martin *et al.* Assefi and colleagues [61<sup>\*</sup>] recruited patients from outside their clinic, whereas participants in the study by Martin *et al.* [63] were recruited after successfully completing an affiliated fibromyalgia-treatment program. Patients who had recently succeeded in the treatment program had additional interaction time with clinical staff. This interaction history may have translated to greater confidence in the clinicians performing the study intervention and an increased credibility of the research team, which could have promoted a placebo effect.

At this time, the benefits of acupuncture for treating fibromyalgia remain unclear and require well designed controlled trials to identify its potential role in managing this patient population. Treatment should center on evidence-based interventions. However, because studies have not reported safety issues unique to the person with fibromyalgia, acupuncture could be considered as an option in certain patients who are unresponsive or resistant to pharmacotherapy and self-management approaches.

## Conclusion

The past year has seen several studies that raise optimism for a more reliable and effective treatment for fibromyalgia. Both pharmacological and nonpharmacological approaches to treatment improved a variety of symptoms, function and well-being. Duloxetine, milnacipran and pregabalin show promise for the remediation of pain, fatigue, sleep disruption, morning stiffness and improvement of function and quality of life. Exercise on land and in the water continues to demonstrate physical, emotional and functional benefits. Insight into treatment adherence suggests a good patient-clinician relationship that addresses pain and stress and individualizing the exercise program may facilitate adherence to fibromyalgia treatment. Finally, the role of acupuncture in treating fibromyalgia remains to be determined.

The combination of pharmacotherapy and nonpharmacological interventions remains the recommendation for

treating fibromyalgia. Future studies must evaluate longer-term effectiveness of interventions in racially, ethnically and age-representative samples to more closely mimic clinical reality. Additionally, the development of a core group of outcome measures would allow appropriate comparison of interventions and the faster development of a uniform standard of care for this population.

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## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 209–211).

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