

Management strategies for fibromyalgia

Kim Francis Le Marshall
Geoffrey Owen Littlejohn

Departments of Rheumatology
and Medicine, Monash Medical Centre
and Monash University, Victoria,
Australia

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Clinical question: What are the effective, evidence-based strategies available for the management of fibromyalgia?

Conclusion: There are a number of management strategies available with robust evidence to support their use in clinical practice.

Definition: Fibromyalgia is a complex pain syndrome characterized by widespread, chronic muscular pain and tenderness, disordered sleep, emotional distress, cognitive disturbance, and fatigue. Its prevalence is estimated to be 3%–5% in the population and higher yet in patients with comorbid rheumatic diseases.

Level of evidence: Systematic reviews, meta-analyses, randomized controlled trials (RCTs).

Search sources: PubMed, Cochrane Library, manual search

Consumer summary: Key messages for patients and clinicians are:

1. There are many effective pharmacological management strategies available for fibromyalgia.
2. A nonpharmacological, multicomponent approach utilizing education, aerobic exercise, psychological therapy, and other strategies is also effective for fibromyalgia.
3. Despite the significant and, at times, disabling physical and psychological symptoms, fibromyalgia can be a manageable condition with a potentially good outcome.

Keywords: fibromyalgia, pain, treatment, management, evidence

The evidence

What nonpharmacological strategies are effective?

Education

Level of evidence: RCT

Education alone may be beneficial in terms of self-efficacy, physical function, and quality of life.^{1,2}

Exercise and related therapies

Level of evidence: RCT, meta-analysis, systematic review

Aerobic exercise programs improve physical function, global well-being, fatigue, depressed mood, and health-related quality of life, and also help with pain reduction in fibromyalgia.^{3–5} One systematic review suggests that aerobic exercise should be land-based or water-based, of slight to moderate intensity, and undertaken two to three times per week.⁵ A graded and individualized approach to the intensity of the aerobic exercise undertaken is helpful, facilitating improved treatment adherence and fewer episodes of increased pain due to high intensity aerobic exercise.⁶ A meta-analysis of hydrotherapy⁷ demonstrates a similar reduction in pain and improved quality of life scores. Aerobic exercise (including hydrotherapy), in addition to education, may

Correspondence: Geoffrey Owen Littlejohn
Departments of Rheumatology and
Medicine, Monash Medical Centre and
Monash University, 246 Clayton Road,
Clayton, Victoria 3168, Australia,
Tel +61 3 9594 3565
Fax +61 3 9564 3512
Email geoff.littlejohn@monash.edu

produce outcomes superior to education alone. Strength training has less overall evidence than aerobic exercise but may also reduce pain and improve physical function.⁸ Combined aerobic, strength, and flexibility exercises improve psychological health status and health-related quality of life scores.⁹ Combined strength and endurance training appears to improve strength, physical function, and other symptoms of fibromyalgia, such as fatigue.¹⁰ There is RCT evidence that tai-chi may be superior to education and stretching exercises alone on the Fibromyalgia Impact Questionnaire and for quality of life outcomes.¹¹ Other strategies, such as yoga, mindfulness meditation, and Qijong movement therapy are also likely to be beneficial but have less evidence of additional benefit over education alone.¹²

Psychological therapy

Level of evidence: RCT, meta-analysis, systematic review
Psychological therapies for fibromyalgia show much heterogeneity, making direct comparison of strategies difficult. Psychological therapies may produce improvements in pain, sleep, emotional distress, catastrophizing, and physical function, although results of trials are variable.^{13,14} Cognitive behavioral therapy has the most evidence, improving ability to cope with pain and health care-seeking behavior.^{15,16}

Multicomponent therapy

Level of evidence: RCT, meta-analysis
Multicomponent therapy, including exercise, education, and cognitive behavioral therapy, improves pain, fatigue, depressive symptoms, quality of life, and physical fitness, although there is only evidence for sustained improvement (more than seven months) with physical fitness.¹⁷ Education combined with aerobic and flexibility exercises appears to be more effective than education alone, with greater improvements in pain, self-efficacy, physical function, and quality of life.² There is RCT evidence for cognitive behavioral therapy producing modest additional improvement in physical function when combined with exercise and pharmacological therapy.¹⁸

Repetitive transcranial magnetic stimulation

Level of evidence: RCT
Repetitive transcranial magnetic stimulation of the motor cortex is thought to reduce pain by activating pain modulation pathways. A 21-week RCT of repetitive transcranial magnetic stimulation therapy in fibromyalgia showed significant improvements in pain and quality of life scores (fatigue, sleep, and morning lethargy).¹⁹ Further evidence is needed in this area.

What pharmacotherapies are effective?

Drugs targeting central sensitization: gabapentin and pregabalin

Level of evidence: RCT, meta-analysis, systematic review
Central sensitization is thought to play a key role in propagating fibromyalgia pain.²⁰ Spinal cord dorsal neurons display enhanced excitability translating innocuous sensory input from mechanoreceptors into pain signals.²¹ This process is facilitated by the neurotransmitters, substance P and glutamate. Pregabalin and gabapentin (α -2-delta ligands) bind to the α -2-delta subunit of the voltage-dependent calcium channels of dorsal neurons, reducing the release of substance P and glutamate.

Three large meta-analyses^{22–24} indicate that pregabalin and gabapentin are effective in reducing pain, while improving sleep and health-related quality of life in fibromyalgia. Pregabalin has sustained outcomes to six months.²⁵ There is more evidence for pregabalin overall, but no evidence of superiority to gabapentin. Pregabalin has similar efficacy at doses from 300 mg up to 600 mg daily and may cause more side effects (including dizziness and somnolence) at higher doses. For a $\geq 30\%$ pain reduction, the number needed to treat (NNT) is approximately seven, and for a $\geq 50\%$ pain reduction, the NNT is closer to 10. These pain outcomes have been shown to correlate with substantial improvements in “real world” outcomes, such as quality-adjusted life years and work attendance.²⁶

Drugs targeting the diffuse noxious inhibitory control system

Tricyclic antidepressants: amitriptyline and cyclobenzaprine
Serotonin norepinephrine reuptake inhibitors: milnacipran and duloxetine

Level of evidence: RCT, meta-analysis, systematic review
The diffuse noxious inhibitory control system helps to downregulate sensory input, including pain, via central descending antinociceptive pathways.^{27,28} It is thought to be dysfunctional in fibromyalgia due to reduced levels of the key neurotransmitters, serotonin and norepinephrine. Drugs that are able to increase the levels of these neurotransmitters are effective in the treatment of fibromyalgia.

Meta-analysis²⁴ and systematic review²⁹ of these agents shows that each is effective for pain reduction in fibromyalgia. Adjusted indirect comparison suggests that amitriptyline may be superior in this respect, but in the face of variable methodological quality and limited long-term data in the underlying RCTs, this finding is difficult to interpret. The NNT for a $\geq 30\%$ pain reduction is 3.54 for amitriptyline

(95% confidence interval [CI] 2.74–5.01), 8.21 for duloxetine (95% CI 5.91–13.26), and 10.96 for milnacipran (95% CI 8.27–16.26). Each agent may have a slightly different profile in terms of efficacy (Table 1). There are long-term data available for duloxetine³⁰ and milnacipran³¹ but not for amitriptyline. Cyclobenzaprine also improves pain and sleep and has similar outcomes to amitriptyline in meta-analysis.³²

Tramadol

Level of evidence: RCT

Apart from tramadol, there is no RCT evidence for use of opioid analgesia in fibromyalgia. Tramadol is an atypical opioid analgesic that also inhibits serotonin and norepinephrine reuptake, providing a plausible mechanism for it to be effective in treatment of fibromyalgia. There is RCT evidence^{33,34} that tramadol (with acetaminophen) produces improvement in the Fibromyalgia Impact Questionnaire and reduces pain, with 18% more than placebo achieving $\geq 30\%$ pain reduction (95% CI 8%–28%, $P < 0.01$; NNT = 5.5) and 16% more than placebo achieving $\geq 50\%$ pain reduction (95% CI 7%–26%, $P < 0.01$; NNT = 6).

Dopamine agonists

Level of evidence: RCT

Dopamine is a centrally acting neurotransmitter that has effects on sleep, behavior, and the autonomic nervous system. Pramipexole, a dopamine agonist, produced improvement in pain, fatigue, and global function in one small 14-week RCT, in which 28% more than placebo achieved $\geq 50\%$ pain reduction ($P = 0.03$; NNT = 4).³⁵ Further evaluation of pramipexole is warranted.

Sodium oxybate

Level of evidence: RCT

Sodium oxybate has a complex mechanism of action, including effects on sleep, and dopaminergic, noradrenergic, serotonergic, and glutaminergic neurons,³⁶ potentially allowing for a therapeutic role in fibromyalgia. Sodium oxybate appears to improve sleep physiology on polysomnographic testing and to reduce pain and fatigue in fibromyalgia.^{37,38} Sodium

Table 1 Outcome profile for each agent in fibromyalgia

Outcome	Amitriptyline	Duloxetine	Milnacipran
Pain	✓	✓	✓
Fatigue	✓	✗	✓
Sleep	✓	✓	✗
HRQOL	✗	✓	✓

✓ indicates beneficial outcome; ✗ indicates no beneficial outcome.

Abbreviation: HRQOL, health-related quality of life.

oxybate 4.5 g daily produced $\geq 30\%$ pain reduction in 54.2% of patients (NNT = 6; 95% CI 4–12) while sodium oxybate 6 g daily produces $\geq 30\%$ pain reduction in 58.5% (NNT = 5; 95% CI 3–8). Prescription of sodium oxybate requires due care from the physician given its potential for abuse.

Selective serotonin reuptake inhibitors

Level of evidence: RCT

There is both supportive and contrary RCT evidence for the use of selective serotonin reuptake inhibitors, such as fluoxetine, in fibromyalgia.^{39–41} Overall, selective serotonin reuptake inhibitors appear to be less effective for pain reduction than other agents. Selective serotonin reuptake inhibitors that are highly selective for serotonin rather than serotonin and norepinephrine appear less effective in fibromyalgia (eg, citalopram).⁴² One RCT⁴⁰ showed that fluoxetine reduces pain and improves the outcome on the Fibromyalgia Impact Questionnaire, but the placebo group had unusually poor outcomes,⁴³ making interpretation difficult.

Nonsteroidal anti-inflammatory drugs and opioid analgesia

No RCT evidence supports the use of nonsteroidal anti-inflammatory drugs or opioids other than tramadol in fibromyalgia.

Serotonin (5-HT₃) receptor antagonists

Level of evidence: RCT

There is some limited RCT evidence showing that tropisetron, a serotonin (5-HT₃) receptor antagonist, improves pain in fibromyalgia and may have a sustained effect.^{44,45} Further studies are warranted.

The practice

Concurrent pharmacological and nonpharmacological therapy

The combination of pharmacological therapy with nonpharmacological strategies (education, exercise, and psychological therapy) seems rational. This may require the expertise of a

physical therapist and psychologist in addition to the primary physician. Education should be provided by the physician, but can be supplemented by reputable online or written resources, and “help groups” may play a role also. Given the array of potentially beneficial management strategies

available for fibromyalgia, individual review of each strategy (including adherence) is warranted in patients to ensure that each therapy is given an optimal trial and unhelpful therapies are adjusted.

Multicomponent nonpharmacological therapy

The combination of education, exercise, and cognitive behavioral therapy seems to produce superior outcomes to each individual strategy alone.

Combination pharmacological therapy

Despite limited evidence supporting combination pharmacological therapy in fibromyalgia, its use is commonplace and anecdotally it can improve symptoms. Empirically, combining therapies with different targets seems logical. An open-label RCT shows improved pain and Patient Global Impression of Change scores with the addition of milnacipran to pregabalin in patients with fibromyalgia not responding to pregabalin monotherapy.⁴⁶ Obviously the potential benefits need to be weighed against potential side effects when considering combination pharmacological therapy. More trials are needed in this area.⁴⁷

Tailored pharmacological therapy

Patients often require individualized drug regimens. Doses utilized may be restricted by side effects. Low initial doses followed by dose escalation may be helpful. In clinical practice, the dose required to produce a beneficial outcome may be lower than the dose commonly used in trials (eg, pregabalin 150 mg daily may achieve a meaningful outcome for some patients with fibromyalgia).

Adequate management of peripheral pain

Analgesics, including nonsteroidal anti-inflammatory drugs and opioids, are helpful for management of peripheral pain-generating conditions, such as osteoarthritis, which may act as an additional peripheral pain stimulus and thereby augment central sensitization.⁴⁸

Potential pitfalls in management

Appropriate initial evaluation and accurate diagnosis of fibromyalgia is crucial. In addition, an understanding that comorbid rheumatic, medical, and psychiatric conditions, including depression and anxiety, commonly coexist with fibromyalgia is important. These conditions need to be identified, evaluated and treated accordingly. Finally, an awareness of common drug side effects is invaluable, while remaining sentient of the very rare side effect of serotonergic

syndrome, which may result from excess serotonin and norepinephrine reuptake inhibition.

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