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Strategies for Managing Fibromyalgia

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ABSTRACT

The presentation of fibromyalgia is heterogeneous, and the treatment approach should be individualized for each patient, depending on the severity of the patient's pain, the presence of other symptoms or comorbidities, and the degree of functional impairment. The management of fibromyalgia includes the identification and treatment of all pain sources that may be present in addition to fibromyalgia, such as peripheral pain generators (e.g., comorbid osteoarthritis or neuropathic pain) or visceral pain (e.g., comorbid irritable bowel syndrome). It is also important to address other symptoms or disorders that commonly occur in patients with fibromyalgia, such as fatigue, sleep disturbances, cognitive impairment, stiffness, and mood or anxiety disorders. Finally, the treatment should strive to improve the patient's function and global health status. In most cases, the management of fibromyalgia involves both pharmacologic and nonpharmacologic treatments. This report provides an in-depth review of randomized, controlled trials for pharmacologic and nonpharmacologic approaches to fibromyalgia therapy.

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The presentation of fibromyalgia is heterogeneous, and the treatment approach should be individualized for each patient, based on the severity of the patient's pain, the presence of other symptoms or comorbidities, and the degree of functional impairment. The management of fibromyalgia involves the treatment of not only pain but also the other symptoms or disorders that commonly occur in patients with fibromyalgia, such as fatigue, sleep disturbances, cognitive impairment, stiffness, and mood or anxiety disorders (Table 1).

The serotonin and norepinephrine reuptake inhibitors that have been studied in randomized controlled trials of fibromyalgia include cyclic medications, such as the tricyclic antidepressants and cyclobenzaprine, and selective serotonin and norepinephrine reuptake inhibitors, such as duloxetine and milnacipran. Selective serotonin reuptake inhibitors (e.g., fluoxetine, paroxetine, and citalopram) have also been studied in fibromyalgia, with inconsistent results. Other medications that have received attention in the treatment of fibromyalgia are the α_2-δ ligands, pregabalin and gabapentin. Tramadol and other analgesics have been evaluated in controlled studies with mixed results. In addition, studies have been conducted on the serotonin 5-HT_3 receptor antagonist tropisetron, the sedative hypnotics sodium oxybate, zolpidem, and zopiclone, the *N*-methyl-D-aspartate (NMDA) receptor antagonist dextromethorphan, and the dopamine D_3 receptor agonist pramipexole.

Mease[1] reviews the serotonin and norepinephrine reuptake inhibitors elsewhere in this supplement. This review focuses on other randomized controlled trials of pharmacologic and nonpharmacologic treatments for fibromyalgia.

PHARMACOLOGIC TREATMENTS FOR FIBROMYALGIA

α_2-δ Ligands

Pregabalin and gabapentin are α_2-δ ligands that have analgesic, anxiolytic, and anticonvulsant activity. The analgesic action of both drugs is thought to be mediated through the α_2-δ protein, an auxiliary subunit of voltage-dependent calcium channels. Pregabalin and gabapentin reduce the synaptic release of several neurotransmitters believed to play a role in pain processing, including glutamate and substance P, by binding to α_2-δ subunits and thereby modulating the influx of calcium ions into hyperexcited neurons. This at-

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tenuation of synaptic activity by pregabalin and gabapentin may account for their reduction of neuronal excitability in vivo and ultimately their analgesic action.[2-4]

Pregabalin is approved by the US Food and Drug Administration (FDA) for the management of neuropathic pain associated with diabetic peripheral neuropathy, management of postherpetic neuralgia, adjunctive therapy for adult patients with partial onset seizures, and the management of fibromyalgia.[5] The recommended dose of pregabalin for fibromyalgia is 300 to 450 mg/day.

Table 1 Overall Treatment Goals in Fibromyalgia Management

- Reduce pain and tenderness
- Ameliorate multidimensional symptoms, including:
  - Fatigue
  - Cognitive impairment
  - Disrupted sleep
  - Mood and anxiety symptoms
  - Stiffness
- Restore functionality and improve quality of life

Four randomized, placebo-controlled clinical trials of pregabalin in the treatment of fibromyalgia have been published (Table 2).[6-9] The first published study of pregabalin in fibromyalgia was a multicenter, randomized, placebo-controlled, 8-week monotherapy trial that tested the safety and efficacy of pregabalin (150, 300, or 450 mg/day) administered 3 times daily in equal doses in 529 patients with fibromyalgia (91% women).[6] The primary outcome measure was the endpoint mean weekly pain score derived from a daily pain diary in which patients rated their pain on a numerical scale from 0 (no pain) to 10 (worst possible pain). The significant outcomes ($P < 0.05$) for pregabalin 450 mg/day, compared with placebo, were the primary outcome of the mean weekly pain (diary) score and secondary outcomes that included the Short-Form McGill Pain Questionnaire (SF-MPQ) total score,[10] the visual analogue scale (VAS) pain score, the daily sleep (diary) score, the Medical Outcomes Study (MOS)-Sleep Problems Index,[11] the Multidimensional Assessment of Fatigue (MAF),[12] the Clinical

Table 2 Randomized, Double-Blind, Placebo-Controlled Trials of Pregabalin in Fibromyalgia

Study	Treatment Groups	Duration	Significant Efficacy Outcomes (Treatment vs. Placebo)
Crofford et al (2005)[6]	Placebo (n = 131) Pregabalin 150 mg/day (n = 132) Pregabalin 300 mg/day (n = 134) Pregabalin 450 mg/day (n = 132)	8 wk	• Primary: mean endpoint pain score, daily diary (450 mg/day) • Secondary: ≥50% improvement from baseline pain (450 mg/day); ≥30% improvement from baseline pain (450 mg/day); SF-MPQ VAS total, sensory, and affective (450 mg/day); sleep quality, daily diary (300 and 450 mg/day); MOS-Sleep Problems Index (all doses); MAF (300 and 450 mg/day); SF-36 social functioning, bodily pain, and vitality (450 mg/day); SF-36 general health (all doses)
Mease et al (2008)[7]	Placebo (n = 190) Pregabalin 300 mg/day (n = 185) Pregabalin 450 mg/day (n = 183) Pregabalin 600 mg/day (n = 190)	13 wk	• Primary: mean endpoint pain score, daily diary (all doses); PGIC (all doses) • Secondary: sleep quality, daily diary (all doses); MOS-Sleep Problems Index (all doses); MOS-Sleep Scale sleep disturbance (all doses), sleep quantity (all doses), awaken short of breath (450 and 600 mg/day), sleep quantity (all doses), sleep adequacy (450 mg/day), somnolence (450 and 600 mg/day)
Arnold et al (2008)[8]	Placebo (n = 184) Pregabalin 300 mg/day (n = 183) Pregabalin 450 mg/day (n = 190) Pregabalin 600 mg/day (n = 188)	14 wk	• Primary: mean endpoint pain score, daily diary (all doses); PGIC (all doses); FIQ (450 and 600 mg/day) • Secondary: ≥50% improvement from baseline pain (all doses); ≥30% improvement from baseline pain (all doses); sleep quality, daily diary (all doses); MOS-Sleep Problems Index (all doses); HADS (600 mg/day)
Crofford et al (2008)[9]	Placebo (n = 287) Pregabalin 300, 450, or 600 mg/day (n = 279)†	26 wk*	• Primary‡: Time to loss of therapeutic response, pooled doses • Secondary: Time to worsening: PGIC; FIQ total; MOS-Sleep Problems Index; MAF; SF-36 PCS, and MCS

FIQ = Fibromyalgia Impact Questionnaire; FM = fibromyalgia; HADS = Hospital Anxiety and Depression Scale; MAF = Multidimensional Assessment of Fatigue; MCS = Mental Component Summary; MOS = Medical Outcomes Study; PCS = Physical Component Summary; PGIC = Patient Global Impression of Change; SF-36 = Short Form 36 Health Survey; SF-MPQ = Short-Form McGill Pain Questionnaire; VAS = visual analogue scale.

*The 26-week double-blind treatment phase was preceded by a 6-week open-label phase (N = 1,051); response to open-label treatment with pregabalin was required for entry into the double-blind phase.

†Based on pain control and patient tolerability.

‡Loss of therapeutic response defined as <30% improvement in VAS pain or worsening of FM symptoms.

Adapted from *Arthritis Rheum,*[6] *J Rheumatol,*[7] *J Pain,*[8] and *Pain.*[9]

Global Impression of Change (CGI-C), the Patient Global Impression of Change (PGIC), and the Short Form 36 Health Survey (SF-36) domains of social functioning, bodily pain, vitality, and general health perception.[13] A significantly larger proportion of patients receiving pregabalin 450 mg/day (28.9%) experienced ≥50% reduction in the pain (diary) score compared with the placebo group (13.2%, $P = 0.003$). Compared with placebo, pregabalin 300 mg/day significantly improved sleep, as measured by both the daily sleep diary and the MOS-Sleep scale, and significantly improved fatigue, the SF-36 domain of general health perception, and the global changes assessments by the patients and clinicians (all $P < 0.05$). Patients taking pregabalin 150 mg/day also reported improved sleep on the MOS-Sleep scale and improvement in general health perception, compared with placebo. Most adverse events were mild-to-moderate in severity. The most common side effects were dizziness and somnolence; these tended to be dose-related across the pregabalin groups. Other side effects that were more frequent in the pregabalin group included abnormal thinking, euphoria, dry mouth, peripheral edema, and weight gain.

The second study of pregabalin in fibromyalgia was a multicenter, randomized, placebo-controlled, 13-week monotherapy trial that assessed the safety and efficacy of pregabalin 300, 450, or 600 mg/day dosed twice a day in equal doses in 748 patients with fibromyalgia (94% women).[7] As in the first study, the primary outcome measure was the endpoint mean weekly pain score derived from a daily pain diary in which patients rated their pain on a numerical scale of 0 (no pain) to 10 (worst possible pain). In addition, if the primary outcome was met, a further objective was to assess the efficacy of pregabalin in the management of fibromyalgia, which included improvement in 2 additional outcomes, the PGIC and the Fibromyalgia Impact Questionnaire (FIQ).[14] All 3 doses of pregabalin were significantly better than placebo ($P < 0.05$) at improving mean weekly pain score and the PGIC. However, improvements in the FIQ total score were numerically, but not significantly, greater for the pregabalin groups compared with the placebo group. Compared with placebo, all 3 pregabalin groups showed significant improvement in daily sleep (diary) score ($P < 0.0001$) and the MOS-Sleep Problems Index ($P < 0.05$). Unlike the first study, fatigue, as measured by the MAF, did not improve significantly with pregabalin compared with placebo. In addition, the proportion of patients classified as responders (defined in this study as ≥30% decrease in mean pain score) were 43%, 43%, and 44% among patients receiving pregabalin 300, 450, and 600 mg/day, respectively, compared with 35% for placebo, which did not reach significance for any pregabalin dosage. The most common adverse events among patients treated with pregabalin were dizziness and somnolence, which, like the other side effects observed, tended to be dose-related across the treatment groups. Other side effects that were more frequent in the pregabalin group (reported by ≥5% of patients in any treatment group) included weight gain, dry mouth, nausea, blurred vision, abnormal thought, constipation, headache, increased appetite, amnesia, euphoria, ataxia, asthenia, uncoordination, nervousness, and peripheral edema.

The third study of pregabalin in fibromyalgia was a multicenter, randomized, double-blind, placebo-controlled trial in which 750 patients (95% female) were randomized to pregabalin 300 mg/day, 450 mg/day, 600 mg/day, or placebo, dosed twice daily, for 14 weeks, following 1 week of single-blind administration of placebo.[8] Consistent with the previous trials of pregabalin, the primary outcome was comparison of endpoint mean pain scores, derived from daily diary ratings of pain intensity (0 to 10 scale), between each of the pregabalin groups and the placebo group. If positive, additional primary efficacy parameters included the PGIC and the FIQ total score. Compared with patients given placebo, mean improvements in pain scores at endpoint in all pregabalin-treated groups were significantly greater ($P < 0.001$). In addition, compared with placebo, significantly more patients treated with pregabalin reported improvement on the PGIC ($P < 0.01$) and, for the 450 mg/day and the 600 mg/day doses, significant improvements in the total FIQ score ($P < 0.01$). Secondary outcomes that improved significantly in the pregabalin groups compared with placebo included the MOS-Sleep Problems Index ($P < 0.05$) and the daily sleep-quality diary ($P < 0.001$). Fatigue, as measured by the MAF, did not improve significantly with pregabalin compared with placebo, but pregabalin 450 mg/day and 600 mg/day significantly improved the vitality score on the SF-36 compared with placebo ($P < 0.05$). Compared with placebo, pregabalin 600 mg/day significantly improved the Hospital Anxiety and Depression Scale (HADS) anxiety score,[15] the SF-36 mental health domain score, and the SF-36 Mental Component Summary (MCS) score (all $P < 0.05$). In addition, pregabalin 450 mg/day significantly improved the SF-36 social functioning domain score ($P < 0.05$). A significantly larger proportion of patients receiving pregabalin 300 mg/day (42%), 450 mg/day (50%), and 600 mg/day (48%) experienced a ≥30% reduction in the pain (diary) score compared with the placebo group (30%) (all $P < 0.05$). As in previous trials of pregabalin in fibromyalgia, most adverse events were mild-to-moderate in severity and tended to be dose-related. Dizziness and somnolence were the most common adverse events associated with pregabalin treatment. Other events reported by ≥5% of patients in any of the treatment groups and more common in the combined pregabalin groups included increased weight, peripheral edema, fatigue, blurred vision, constipation, disturbance in attention, balance disorder, euphoric mood, sinusitis, back pain, dry mouth, increased appetite, and memory impairment. In this study, all pregabalin-treated patients were started at 150 mg/day and titrated every 3 to 4 days; all patients received 300 mg/day by the end of the first week. Patients in the 450 mg/day and 600 mg/day groups continued escalating to their randomized dose by the end of week 2. Slower escalation to higher

dosages may decrease the incidence of adverse events and should be explored in future trials.

Because fibromyalgia is a chronic condition, randomized controlled trials beyond the time frame of 8 to 14 weeks are needed to assess the long-term efficacy of treatments. A recent 6-month study of pregabalin treatment assessed the durability of the effect of pregabalin monotherapy on fibromyalgia pain.[9] The trial included an open-label pregabalin treatment period in which all patients received 6 weeks of pregabalin treatment (300, 450, or 600 mg/day). Response to pregabalin treatment after the initial 6 weeks was defined by pain reduction ≥50% and a patient rating of "much improved" or "very much improved" on the PGIC. In the double-blind phase, all patients who responded to pregabalin treatment were randomized to continue treatment (300, 450, or 600 mg/day) or receive placebo for an additional 26 weeks or until they experienced a loss of therapeutic response. Loss of therapeutic response was defined as worsening of fibromyalgia symptoms necessitating change in treatment according to the investigators' clinical judgment or a <30% reduction in pain from the open-label baseline over 2 consecutive physician visits. Of the 1,051 patients (93% women) enrolled in the trial, 663 completed the open-label phase and were assessed for response. Of these patients, 566 were pregabalin responders who were randomized to double-blind treatment (287 randomized to placebo, 279 to pregabalin). Based on Kaplan-Meier estimates of time-to-event, significantly more patients on placebo (174 [61%]) lost therapeutic response compared with patients treated with pregabalin (90 [32%]) (P <0.0001). All secondary efficacy endpoints, including the PGIC, FIQ total score, MOS-Sleep Scale Overall Sleep Problems Index, MAF, and SF-36 MCS and Physical Component Summary (PCS) scores, showed significantly greater time to loss of therapeutic response for pregabalin compared with placebo (all P <0.0001). The most frequently reported adverse events during the open-label treatment were dizziness (36%), somnolence (22%), headache (14%), and weight increase (11%). Most of the adverse events were mild-to-moderate in intensity. A total of 196 patients (19%) withdrew from the open-label phase because of adverse events. During the double-blind phase, the most common adverse events in the pregabalin group were insomnia (6%), sinusitis, nausea, arthralgia, anxiety, and influenza (5% in each), upper respiratory tract infection (4%), and weight increase (4%). Adverse events led to withdrawal in the double-blind phase of 20 (7%) patients in the placebo group, compared with 12 (19%), 13 (18%), and 22 (15%) patients in the pregabalin 300, 450, and 600 mg/day groups, respectively.

In summary, the results of randomized controlled trials of pregabalin demonstrate that pregabalin monotherapy reduces pain and improves other key symptom domains of fibromyalgia, such as sleep, and is associated with improvements in function, health-related quality of life, and global assessments. In patients who respond to the drug, pregabalin dosed at 300, 450, and 600 mg/day (given in 2 divided doses) may have a durable effect of maintaining the patient's improvement in pain associated with fibromyalgia as well as improvements in sleep, fatigue, functional status, and measures of global assessment.

The α_2-δ ligand gabapentin is indicated by the FDA for adjunct therapy in adults with partial seizures and for postherpetic neuralgia. A multicenter, randomized, placebo-controlled, 12-week monotherapy trial tested the safety and efficacy of gabapentin in 150 patients with fibromyalgia (90% women) (Table 3).[16] Gabapentin was administered 3 times daily at 1,200 to 2,400 mg/day. The primary outcome measure was the Brief Pain Inventory (BPI) average pain severity score, which assesses average pain severity during the past 24 hours using a numerical scale from 0 (no pain) to 10 ("pain as bad as you can imagine").[17] The outcomes that significantly improved with gabapentin (median dose 1,800 mg/day), compared with placebo, were the primary outcome of the BPI average pain severity score, as well as improvements in the secondary outcomes of BPI average pain interference score, FIQ total score, Clinical Global Impression of Severity (CGI-S), PGIC, MOS-Sleep Problems Index, and the SF-36 vitality domain score (all P <0.05). The mean tender point pain threshold and the Montgomery Asberg Depression Rating Scale (MADRS)[18] did not significantly improve with gabapentin treatment compared with placebo. Significantly more patients treated with gabapentin (38 [51%]) compared with placebo (23 [31%]) (P = 0.014) experienced a response to treatment, defined as a ≥30% reduction in pain from baseline to endpoint. Most adverse events were mild-to-moderate in severity. The side effects reported by ≥5% of the gabapentin-treated patients and more common in the gabapentin group compared with the placebo group were headache, dizziness, sedation, somnolence, edema, lightheadedness, insomnia, diarrhea, asthenia, depression, flatulence, nervousness, weight gain, amblyopia, anxiety, and dry mouth. In summary, the results of this randomized controlled study demonstrated that monotherapy with gabapentin 1,200 to 2,400 mg/day (3 times daily dosing), when taken for up to 12 weeks, significantly reduces pain and improves other important symptom domains of fibromyalgia, including sleep, and is associated with improvements in functionality and global assessments.

In deciding on which α_2-δ ligand to initiate in treating fibromyalgia, the potentially lower cost of a generic agent like gabapentin must be weighed against the greater amount of clinical trial data for pregabalin and its FDA approval for this indication.

Sedative-Hypnotic Medication

Many patients with fibromyalgia experience disrupted or nonrestorative sleep and benefit from treatment to improve sleep. Three studies reported that the nonbenzodiazepine sedatives zolpidem and zopiclone improved sleep in patients with fibromyalgia but did not improve pain.[19-21] Another study found no significant benefit of the benzodiazepine bromazepam over placebo in the treatment of fibromyalgia.[22]

Table 3 Other Pharmacologic Treatments of Significant Benefit Versus Placebo in Fibromyalgia Management

Class/Drug	Study	Trial Design	Significant Efficacy Outcomes (Treatment vs. Placebo)
α_2-δ Ligands			
Gabapentin	Arnold et al (2007)[16]	• Randomized DBPCT (N = 150) • Treatment: PBO (n = 75) or gabapentin 1,200-2,400 mg/day, flexible dosing (n = 75) • Duration: 12 wk	• BPI average pain severity • BPI average pain interference • ≥30% reduction in pain • FIQ total • CGI-S • PGI-I • MOS-Sleep Problems Index • SF-36 vitality
Sedative hypnotics			
Sodium oxybate	Russell et al (2009)[23]	• Randomized DBPCT (N = 188) • Treatment: PBO (n = 64) or sodium oxybate 4.5 (n = 58) or 6 g/day (n = 66) • Duration: 8 wk	• Composite responder* (both doses) • Pain VAS (both doses) • ≥20% and ≥30% reduction in pain (both doses) • FIQ total, days felt good, job ability, pain, fatigue, tired upon wakening, and stiffness (both doses); FIQ physical impairment (4.5 g/day) • ≥20% and ≥30% reduction in FIQ total (both doses) • PGIC of "very much better" or "much better" (4.5 g/day) • CGI-C of "very much better" or "much better" (6 g/day) • Jenkins Scale for Sleep (both doses) • SF-36 vitality and pain (both doses)
Opiates			
Tramadol	Russell et al (2000)[36]	• OL lead-in (N = 100) followed by randomized DBPCT (N = 69) • DB treatment: PBO (n = 34) or tramadol 50-400 mg/day (n = 35) • Duration: 6 wk (DBPCT)	• Time to exit due to inadequate pain relief • Pain VAS • Pain relief rating scale
Tramadol + acetaminophen	Bennett et al (2003)[37]	• Randomized DBPCT (N = 313) • Treatment: PBO (n = 157) or 37.5 mg tramadol/325 mg acetaminophen tablet, 4-8 tablets/day (flexible dosing) (n = 156) • Duration: 13 wk	• Time to discontinuation for any reason or due to lack of efficacy • Pain VAS • Pain relief rating scale • Tender point count • FIQ total, physical impairment, feel good, do job, pain, rest, stiffness, and anxiety • SF-36 PCS, physical functioning, physical role limit, and bodily pain • ≥30% and ≥50% reduction in pain
5-HT_3 receptor antagonists			
Tropisetron	Färber et al (2000)[40]	• Randomized DBPCT (N = 418) • Treatment: PBO (n = 103), tropisetron 5 mg/day (n = 102), 10 mg/day (n = 100), or 15 mg/day (n = 98) • Duration: 10 days	• Body pain diagram (5 and 10 mg/day) • Pain VAS (5 mg/day) • Tender point count (5 mg/day) • ≥35% reduction in pain (5 mg/day)
	Späth et al (2004)[41]	• Randomized DBPCT (N = 21) • Treatment: PBO (n = 12) or tropisetron 5 mg IV (n = 9) • Duration: 5 days	• Body pain diagram

Table 3 Continued

Class/Drug	Study	Trial Design	Significant Efficacy Outcomes (Treatment vs. Placebo)
NMDA receptor antagonists			
Dextromethorphan + tramadol	Clark et al (2000)[44]	• OL lead-in (N = 48) followed by randomized DBPCT (N = 28) • DB treatment: PBO + tramadol 200 mg/day (n = 12) or dextromethorphan 50 to 200 mg/day + tramadol 200 mg/day (n = 16) • Duration: 30 days (DBPCT)	• Time to discontinuation from the study
Dopamine D_3 receptor agonists			
Pramipexole	Holman et al (2005)[47]	• Randomized DBPCT (N = 60) • Treatment: PBO (n = 21) or pramipexole 4.5 mg/day (n = 39) • Duration: 14 wk	• MDHAQ pain, fatigue, global status, and function • FIQ total • Moderate or better improvement in patient assessment of pain • ≥50% reduction in pain

BPI = Brief Pain Inventory; CGI-C = Clinical Global Impression of Change; CGI-S = Clinician Global Impression of Severity; DB = double-blind; DBPCT = double-blind, placebo-controlled trial; FIQ = Fibromyalgia Impact Questionnaire; IV = intravenous; MDHAQ = Multidimensional Health Assessment Questionnaire; MOS = Medical Outcomes Study; NMDA = *N*-methyl-D-aspartate; OL = open-label; PBO = placebo; PCS = Physical Component Summary; PGIC = Patient Global Impression of Change; PGI-I = Patient Global Impression of Improvement; SF-36 = Short Form 36 Health Survey; VAS = visual analogue scale.

*Composite responder defined as patient experiencing simultaneous improvements in the following domains: ≥20% decrease from baseline in pain VAS score; ≥20% decrease from baseline in FIQ total score; PGIC rating of "very much better" or "much better."

Adapted from *Arthritis Rheum*,[16,23,44,47] *J Clin Rheumatol*,[36] *Am J Med*,[37] *Scan J Rheumatol Suppl*,[40] and *Scan J Rheumatol*.[41]

Sodium oxybate is the sodium salt of γ-hydroxybutyrate (GHB), a metabolite of the neurotransmitter γ-aminobutyric acid (GABA), with marked sedative properties. An 8-week study of sodium oxybate monotherapy evaluated 4.5 or 6 g/day taken in 2 equally divided doses (bedtime and 2.5 to 4 hours later) in 188 patients with fibromyalgia (Table 3).[23] The primary outcome was a composite score of change from baseline in 3 co-primary measures, the pain VAS from electronic diaries, the FIQ, and the patient global assessment. The primary outcome improved significantly with both dosages of sodium oxybate compared with placebo ($P < 0.05$). Both dosages were also significantly superior to placebo in improvement in sleep quality ($P < 0.01$), but the tender point count improved only at the higher sodium oxybate dose compared with placebo. The most common side effects were nausea and dizziness. GHB is associated with a high likelihood of abuse, cases of date rape, and, along with pentobarbital and methaqualone, is more likely to be lethal at supratherapeutic doses than other hypnotics.[24,25] Sodium oxybate was granted orphan drug status by the FDA for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy. Because of the risk of abuse, sodium oxybate is only available through a risk management program that was designed to educate physicians and patients about the safe use of the drug and to minimize potential diversion or abuse by limiting distribution through a central pharmacy.[26] This risk management program appears to be effective in preventing diversion and limiting abuse in patients with narcolepsy, although the evaluation of the program is ongoing.[26] Safer alternatives for the management of insomnia in patients with fibromyalgia include low-dose tricyclic agents.[27,28] More recently, the α_2-δ ligands pregabalin and gabapentin have also been used for this purpose because they have sedative properties, improve slow-wave sleep, and relieve pain.[29,30]

Opiates

Several opiate medications have been evaluated in patients with fibromyalgia. Intravenous administration of morphine in 9 patients with fibromyalgia did not reduce pain intensity in a small, double-blind, placebo-controlled study. A 4-year, nonrandomized study found that patients with fibromyalgia taking opiates did not report significant reduction in pain at the 4-year follow-up, and experienced increased depression in the last 2 years of the study.[31] Despite the lack of data supporting the use of opiates in fibromyalgia, a survey of US academic medical centers found that about 14% of patients with fibromyalgia are treated with opiates.[32] The use of opiates in fibromyalgia continues to be controversial, not only because of the lack of supportive efficacy data, but also because of the abuse potential of opiates and the emerging evidence of opioid-induced hyperalgesia. Recent preclinical studies suggest that chronic use of opioids induces neuroadaptive changes that are mediated, in part, through the neurokinin-1 receptor and result in enhancement of nociceptive input.[33] The potential development of opioid-induced hyperalgesia might limit the usefulness of opioids in controlling chronic pain over the long term.[34]

Tramadol is a novel analgesic with weak agonist activity at the μ-opiate receptor combined with dual serotonin and norepinephrine reuptake inhibition. A double-blind crossover study compared single-dose intravenous tramadol 100 mg with placebo in 12 patients with fibromyalgia.[35] Patients receiving tramadol experienced a 20.6% reduction in pain compared with a 19.8% increase in pain in the placebo group; however, the study size was too small to detect statistical significance. Another study of tramadol began with a 3-week open-label phase of tramadol 50 to 400 mg/day followed by a 6-week double-blind phase wherein enrollment was restricted to patients who tolerated tramadol and perceived benefit (Table 3).[36] The primary measure of efficacy was the time to exit from the double-blind phase because of inadequate pain relief. A total of 100 patients with fibromyalgia were enrolled in the open-label phase; 69% tolerated and perceived benefit from tramadol and were randomized to tramadol or placebo. Significantly fewer patients receiving tramadol compared with placebo ($P = 0.015$) discontinued during the double-blind phase because of inadequate pain relief. Finally, a multicenter, double-blind, randomized, placebo-controlled, 91-day study examined the efficacy of a combination analgesic tablet containing tramadol (37.5 mg) and acetaminophen (325 mg) in 315 patients with fibromyalgia.[37] Patients taking tramadol and acetaminophen (4.0 $\pm$ 1.8 tablets/day) were significantly more likely than placebo-treated subjects to continue treatment ($P < 0.05$) and experience an improvement in pain and physical function. Improvements in SF-36 physical functioning, role-physical, bodily pain, and PCS scores were significantly greater in the tramadol/acetaminophen group than the placebo group ($P < 0.05$). The most common side effects in the tramadol/acetaminophen group were nausea, dizziness, somnolence, and constipation. Although tramadol is currently marketed as an analgesic without scheduling under the Drug Enforcement Administration (DEA) Controlled Substances Act, it should be used with caution because of recent reports of classic opioid withdrawal with discontinuation and dose reduction, and reports of abuse and dependence.[38] In addition, some states (e.g., Kentucky) have listed tramadol as a scheduled controlled substance. Although the abuse potential of tramadol exists, a large study (N = 11,352) suggests that it might be less than for other opioids.[39]

Serotonin 5-HT_3 Receptor Antagonists

Clinical trials of the 5-HT_3 receptor antagonist tropisetron have been conducted in patients with fibromyalgia (Table 3). One randomized, placebo-controlled, double-blind, 10-day trial in 418 patients with fibromyalgia evaluated the short-term efficacy of tropisetron at doses of 5, 10, and 15 mg/day.[40] Significant reduction in pain was noted only in those patients taking tropisetron at 5 mg/day and 10 mg/day compared with placebo ($P < 0.05$), suggesting a bell-shaped dose-response curve. Another randomized placebo-controlled trial of 21 women with fibromyalgia evaluated intravenous bolus injections of 5 mg/day tropisetron for 5 days and found significant improvement for body map pain score in the tropisetron group compared with placebo ($P = 0.038$) but not for pain VAS score ($P = 0.063$).[41] The pro- and antinociceptive effects of 5-HT_3 receptor blockade might be related to the presence of 5-HT_3 receptors on both the inhibitory dorsal horn interneurons and the primary afferent fibers that relay nociceptive information from peripheral nociceptors to the dorsal horn. The balance of these opposing effects may be dose-dependent and contribute to unpredictable results with tropisetron.[42]

NMDA Receptor Antagonists

NMDA receptor antagonists may inhibit or attenuate central sensitization and potentially reduce pain associated with fibromyalgia.[43] In 1 clinical study, 48 women with fibromyalgia were treated with an open-label combination of tramadol 200 mg/day and increasing doses of the NMDA receptor antagonist dextromethorphan (50 to 200 mg/day) titrated to therapeutic effect or tolerability (Table 3); 28 patients (58%) responded to the addition of dextromethorphan and entered a double-blind phase,[44] in which they were randomized to dextromethorphan and tramadol or tramadol and placebo. A Kaplan-Meier analysis showed that significantly fewer patients on dextromethorphan and tramadol discontinued treatment compared with patients given tramadol plus placebo ($P = 0.018$). Another study found that the reduction in wind-up from repeated thermal and mechanical pressure stimulation of the skin by dextromethorphan did not significantly differ between patients with fibromyalgia and normal controls.[45] The results of this study suggest that patients with fibromyalgia do not have substantially altered NMDA receptor mechanisms, and that other mechanisms, such as enhanced descending facilitation, should be considered for the development of pain associated with fibromyalgia.

Dopamine D_3 Receptor Agonists

Excessive adrenergic arousal may fragment sleep, and enhancement of dopaminergic neurotransmission at the D_3 receptors in the mesolimbic hippocampus may reduce expression of arousal and improve sleep.[46] Pramipexole, a dopamine D_3 receptor agonist, was added to existing pharmacologic and nonpharmacologic therapies in patients with fibromyalgia in a 14-week, single-center, randomized, placebo-controlled study (Table 3).[47] Compared with the placebo group, those patients receiving pramipexole titrated over 12 weeks to 4.5 mg every evening had significant improvements in pain, fatigue, function, and global status ($P < 0.05$). A gradual titration of pramipexole was well tolerated; weight loss and increased anxiety were significantly more common in patients receiving pramipexole. Sleep was not assessed in the study, despite the proposed role of dopamine D_3 receptor agonists in reducing adrenergic arousal in patients with fibromyalgia. The results of the study were also difficult to interpret because the participants

were taking concomitant medications for fibromyalgia (e.g., approximately 50% were taking narcotic analgesics).

Anti-inflammatory Drugs

The corticosteroid prednisone was found to be ineffective in fibromyalgia management in a double-blind placebo-controlled clinical trial.[48] Consistent with this finding, corticosteroids in general are not recommended for the treatment of fibromyalgia. Patients with fibromyalgia frequently use nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, although there is no evidence from clinical trials that they are effective when used alone in the treatment of fibromyalgia, and patients typically report that they offer only minimal relief of pain. In 1 randomized controlled trial, ibuprofen (600 mg administered 4 times daily) was not more effective than placebo in reducing pain associated with fibromyalgia.[49] The lack of a significant inflammatory component in the pathophysiology of fibromyalgia may explain the poor response of fibromyalgia to NSAID monotherapy. However, studies have documented some benefit of ibuprofen and naproxen in fibromyalgia management when combined with tricyclics (e.g., amitriptyline or cyclobenzaprine)[50,51] or benzodiazepines.[52] Patients with fibromyalgia who have a peripheral pain generator that could be aggravating their condition, such as comorbid osteoarthritis or other painful inflammatory conditions, would likely benefit from the addition of NSAIDs in the management of their pain.

NONPHARMACOLOGIC TREATMENTS FOR FIBROMYALGIA

Exercise

The rationale for using exercise as a treatment modality in fibromyalgia is that patients often become sedentary because of symptoms such as pain and fatigue. The deconditioning that results from lack of physical activity can make the symptoms of fibromyalgia worse.[53,54] Exercise may help to reverse the effects of deconditioning and improve fitness, but the exact mechanism by which exercise improves fibromyalgia symptoms is still unclear. A recent Cochrane Review of exercise in the treatment of fibromyalgia[55] assessed exercise trials up to and including July 2005. The review concluded that moderate-intensity aerobic training for 12 weeks may improve overall well-being and physical function, but probably leads to little or no difference in pain or tender points. Although there are limited studies evaluating strength training, this form of exercise for 12 weeks may result in reductions in pain and tender points, as well as improvement in overall well-being. According to the recent Cochrane Review,[55] it is unknown whether exercise training for >12 weeks would improve other symptoms of fibromyalgia, and adherence to exercise programs is problematic. It is also unknown whether flexibility training, combined types of exercise, or programs combining exercise with nonexercise strategies would improve fibromyalgia.

Another review of exercise studies in fibromyalgia[56] concluded that, for many patients with fibromyalgia, a gradual increase in exercise, as tolerated, to reach a goal of 30 to 60 minutes of low-to-moderate–intensity land-based aerobic exercise (e.g., walking, running, stationary bike, full-body exercise, aerobic sports) ≥2 to 3 times a week for >10 weeks appears to be associated with positive short-term benefits, with maintenance of those effects achieved with ongoing exercise. Table 4 summarizes some of the recent exercise studies in fibromyalgia.[57-62] A number of clinical trials have indicated that pool-based exercises in warm water (e.g., walking, running, water-resistance training) may also be beneficial for patients with fibromyalgia, particularly patients with symptoms of depression or anxiety.[63] Supervised group exercise interventions may be preferable to home-based exercise regimens, especially in helping patients initiate an exercise program and in enhancing adherence. Factors that were found to contribute to low adherence to exercise included disability, stress, exacerbation of pain, depression, low exercise self-efficacy (i.e., low confidence in the ability to exercise under adverse conditions), barriers to exercise, and low social support.[56]

Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT), in principle, may help patients improve the way they think about and cope with fibromyalgia. However, therapies with cognitive restructuring and coping components have not been found to be significantly better than education or attention control in clinical studies. In 1 controlled study, 131 outpatients were randomized to a 12-session combined educational and cognitive group intervention, an attention control consisting of group education plus group discussion, or a waiting list control.[64] There was very little improvement across any of the groups. The attention control group did somewhat better than the combined education and cognitive intervention group, with improved pain coping and pain control ($P < 0.01$), but neither group experienced reduction in pain intensity.

Another controlled study of 71 patients with fibromyalgia evaluated a 10-week program consisting of weekly 90-minute group sessions of education, relaxation training, goal setting, and activity pacing, with the involvement of a support person to promote adaptive coping skills and adherence to the program.[65] The treatment resulted in significant reductions in depression, self-reported pain behavior, observed pain behavior, and pressure pain thresholds, but pain intensity levels were not reduced. Furthermore, the effect of this treatment program was no better than an education control that included lectures and group discussion.

CBT that is targeted to a specific outcome such as function might be efficacious in patients with fibromyalgia. In 1 study, 145 patients with fibromyalgia were randomized to either standard medical care that included pharmacologic treatment and suggestions for aerobic fitness, or the same

Table 4 Aerobic Exercise in the Treatment of Fibromyalgia: Recent Clinical Trials

Clinical Trial	Design	Significant Efficacy Outcomes, Exercise Treatment vs. Control
Richards and Scott (2002)[57]	• RCT (N = 132) • Exercise: graded intensity, aerobic, supervised • Control: relaxation, flexibility training • Treatment duration: 3 mo • Study duration: 12 mo	• Patient-reported global impression of change (3 mo) • Tender point count (3 and 12 mo)
King et al (2002)[58]	• RCT (N = 152) • Exercise: graded intensity, aerobic, supervised, with or without self-management education • Control: written instructions for basic stretches and general coping strategies • Treatment duration: 3 mo • Study duration: 6 mo	• CPSS-coping with other symptoms (3 mo, exercise + education compliers only)
van Santen et al (2002)[59]	• RCT (N = 143) • Exercise: high intensity, mixed exercise, supervised • Control: usual care • Treatment duration: 24 wk • Study duration: 24 wk	• No significant improvements
van Santen et al (2002)[60]	• Randomized trial (N = 37) • Exercise: high intensity, aerobic, supervised • Control: low intensity, aerobic, supervised • Treatment duration: 20 wk • Study duration: 20 wk	• No significant improvements
Schachter et al (2003)[61]	• RCT (N = 143) • Exercise: graded low intensity, aerobic, unsupervised home-based, video-based • Control: monthly group discussion without educational information • Treatment duration: 16 wk • Study duration: 16 wk	• No significant improvements
Da Costa et al (2005)[62]	• RCT (N = 79) • Exercise: graded intensity, home-based individualized, mixed exercise prescription from an exercise physiologist • Control: usual care • Treatment duration: 3 mo • Study duration: 12 mo	• FIQ total (6 and 12 mo) • VAS pain, upper body (6 and 12 mo)

CPSS = Chronic Pain Self-Efficacy Scale; FIQ = Fibromyalgia Impact Questionnaire; RCT = randomized controlled trial; VAS = visual analogue scale. Adapted from *BMJ*,[57] *J Rheumatol*,[58-60] *Phys Ther*,[61] and *Rheumatology (Oxford)*.[62]

standard medical treatment plus the addition of 6 CBT group sessions over a 4-week period that were specifically aimed at improving physical function.[66] Patients in both groups were contacted monthly by phone to track healthcare use; cognitive behavioral skills were also tracked in those assigned to the therapy. Significantly more (25%) of the 62 patients who completed the CBT protocol achieved a clinically meaningful and sustained improvement in physical function compared with the control group (12% of 60 completers) ($P < 0.05$). Despite these positive results, there was a low level of adherence to the CBT, with only 15% of the patients consistently achieving their stated monthly cognitive behavioral goals.

Recent work on psychological therapy in fibromyalgia has identified important patient characteristics that may predict responsiveness to different treatment approaches. One study evaluated both CBT and operant behavioral therapy (based on the principles of operant conditioning and antecedents and consequences of behavior) compared with attention control.[67] All treatments consisted of 15 weekly 2-hour sessions co-led by a psychologist and a rheumatologist, with spouses attending 4 of the sessions. CBT focused on the patients' thinking and involved problem solving, pain coping strategies, and relaxation. The operant behavioral therapy was based on changing observed pain behaviors and included video feedback of pain expressions, contingent positive reinforcement of pain-incompatible behaviors, and punishment of pain behaviors. The attention control regimen included general therapist-guided discussions. At the 12-month follow-up, patients in the 2 therapy groups experienced significant reduction in pain intensity and physical impairment ($P < 0.05$). Notably, at baseline, patients who

responded to operant behavioral therapy had more pain behaviors, physical impairment, physician visits, solicitous spouse behaviors, and higher levels of catastrophizing compared with nonresponders (all $P < 0.01$). The CBT responders, compared with nonresponders, had higher levels of affective distress, lower coping, less solicitous spouse behaviors, and lower pain behaviors at baseline. The study results suggest that when using psychological treatments in patients with fibromyalgia, it may be important to match treatments to patient characteristics in order to improve outcomes.

Education

Education about fibromyalgia is an important therapeutic option that can be combined with other treatment approaches. A study of 600 patients with fibromyalgia found that patients who participated in a social support and education group, which met for 10 weekly 2-hour sessions, followed by 10 monthly sessions, experienced significantly less helplessness compared with both a social support control group and a no-treatment control group that completed assessment interviews (both $P < 0.001$).[68] However, attendance rates for the interventions were low, with patients attending only about 40% of all meetings.

A 12-week study evaluated a supervised aerobic exercise program, a self-management education program, and the combination of exercise and education in 152 women with fibromyalgia.[58] The supervised exercise occurred 3 times a week for an average duration of 20 to 40 minutes and included walking, pool exercises, or low-impact aerobics. The education group, which focused on self-management skills, met once a week for 1.5 to 2 hours per session. The control group was given written instructions for basic stretches and general coping strategies. All groups were given a log book to document the course of fibromyalgia and weekly goals, and all patients were contacted once or twice to ensure compliance with the log book documentation and to answer any questions about their condition. For patients who complied with the protocol (only about half of the group), the combination of supervised exercise and group education improved self-efficacy for coping with some symptoms compared with the control group ($P < 0.01$).

A recent study evaluated the potential effect of 4 common self-management interventions in 207 women with fibromyalgia who were randomly assigned to 16 weeks of (1) group aerobic and flexibility exercise; (2) strength training, aerobic, and flexibility exercise; (3) the Arthritis Foundation's Fibromyalgia Self-Help Course; or (4) a combination of strength training, aerobic, flexibility exercises, and the Fibromyalgia Self-Help Course.[69] The study found that a structured exercise program for 1 hour twice weekly involving progressive walking and flexibility movements, with or without moderate strength training, improved physical function in women with fibromyalgia who were also actively treated with medication. The beneficial effects of exercise were enhanced with the addition of the group-based self-management education. The results suggest the need to include appropriate exercise and education in the treatment of fibromyalgia.

OTHER NONPHARMACOLOGIC TREATMENTS: COMPLEMENTARY AND ALTERNATIVE MEDICINE

A review of studies conducted between 1975 and 2002[70] evaluating the use of complementary and alternative medicine in fibromyalgia found that among the 5 classifications of complementary and alternative medicine—(1) alternative medical systems (e.g., acupuncture, homeopathy), (2) biological-based therapy (e.g., nutritional supplements and dietary modifications), (3) energy therapies (e.g., magnetic therapy), (4) manipulative and body-based systems (e.g., chiropractic care, massage), and (5) mind-body interventions (e.g., relaxation, biofeedback, and hypnotherapy)—no single treatment approach was consistently effective. In this review, acupuncture had the strongest evidence for efficacy, and there was also moderate support for magnesium supplementation, *S*-adenosyl-L-methionine supplementation, and massage therapy. A more recent systematic review of randomized clinical trials of acupuncture in American College of Rheumatology (ACR)-defined fibromyalgia included 5 trials, each with a sham treatment control group.[71] The review concluded that there is no evidence from rigorous clinical trials that acupuncture is an effective treatment for fibromyalgia symptoms.

Other studies of the nonpharmacologic treatment of fibromyalgia through alternative medicine have had mixed results. A group treatment with a combination of mindfulness meditation and Qigong movement therapy was tested in 128 patients with fibromyalgia who were randomly assigned to either an 8-week course of this therapy or a control education support group.[72] The study found no significant differences between groups in change in pain, tenderness, walking, mood, or impact of fibromyalgia. A small, open, pilot study of T'ai Chi exercise in which 39 patients had twice-weekly 1-hour T'ai Chi exercise sessions for 6 weeks reported significant improvement in symptom management and health-related quality of life ($P < 0.05$), but there was a higher than expected dropout rate (only 21 patients completed ≥ 10 of the 12 exercise sessions).[73] Another study evaluated the efficacy of relaxing yoga compared with relaxing yoga plus touch in 40 women with fibromyalgia.[74] Both groups, which met for 8 weekly 50-minute sessions, showed improvement in the impact of fibromyalgia and pain. However, this study, like the T'ai Chi study above, was limited by the lack of adequate controls.

In conclusion, nonpharmacologic treatments have an important role in the management of fibromyalgia. There is a need for improved access to treatment centers that offer these types of interventions. In addition, future studies should focus on ways to improve the adherence to nonpharmacologic therapies. Further studies are also needed to assess the efficacy of the combination of pharmacologic

and nonpharmacologic strategies in the management of fibromyalgia.

SUMMARY

Fibromyalgia presents a host of symptoms spanning pain, fatigue, sleep disturbances, stiffness, and mood disorders. Treatment strategies under investigation for the management of these multiple symptom domains include pharmacologic approaches with mechanistically distinct drugs and diverse nonpharmacologic approaches. The α_2-δ ligand pregabalin is approved by the FDA for the management of fibromyalgia; pregabalin monotherapy is efficacious against multiple symptom domains of fibromyalgia, including pain. Gabapentin likewise significantly improves pain and other fibromyalgia symptom domains, underscoring the value of this mechanistic class of drugs in fibromyalgia therapeutics development. Another important class of drugs to emerge for the management of multiple fibromyalgia symptoms is the serotonin and norepinephrine dual reuptake inhibitors, notably duloxetine and milnacipran, which target descending antinociceptive pathways in central pain processing. Both duloxetine[75] and milnacipran[76] are approved for the management of fibromyalgia. Additional pharmacologic interventions under investigation for fibromyalgia are sedative-hypnotic medications, 5-HT_3 receptor antagonists, and dopamine D_3 receptor agonists. It is generally thought that pharmacologic treatment should be accompanied by nonpharmacologic interventions. Promising nonpharmacologic approaches under development for the management of fibromyalgia include exercise, CBT, and education.

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