Review

Biology and therapy of fibromyalgia

New therapies in fibromyalgia

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Abstract

Fibromyalgia is a chronic, musculoskeletal pain condition that predominately affects women. Although fibromyalgia is common and associated with substantial morbidity and disability, there are no US Food and Drug Administration-approved treatments. However, progress has been made in identifying pharmacological and non-pharmacological treatments for fibromyalgia. Recent pharmacological treatment studies have focused on selective serotonin and norepinephrine reuptake inhibitors, which enhance serotonin and norepinephrine neurotransmission in the descending pain pathways and lack many of the adverse side effects associated with tricyclic medications. Promising results have also been reported for medications that bind to the $\alpha_2\delta$ subunit of voltage-gated calcium channels, resulting in decreased calcium influx at nerve terminals and subsequent reduction in the release of several neurotransmitters thought to play a role in pain processing. There is also evidence to support exercise, cognitive behavioral therapy, education, and social support in the management of fibromyalgia. It is likely that many patients would benefit from combinations of pharmacological and non-pharmacological treatments, but more study is needed.

Introduction

This review focuses on recent randomized, controlled studies of pharmacological and non-pharmacological therapies for fibromyalgia. Clinical recommendations for the management of fibromyalgia will be based on the available evidence from these trials. Although much work remains, progress has been made in identifying potentially efficacious treatments for fibromyalgia. The treatment of fibromyalgia is a rapidly growing area of research, and it is likely that treatment options will continue to expand for patients with fibromyalgia.

Although fibromyalgia causes substantial morbidity and disability, there are no US Food and Drug Administration (FDA)-approved or European Medicines Agency (EMEA)-approved treatments. Strategies that are being pursued to develop better treatments for fibromyalgia include the development of large, multicenter, well-controlled clinical trials to test the efficacy of a variety of therapies. The results of the clinical trials will help to identify which patients might benefit from a particular treatment, whether that treatment approach is pharmacological, non-pharmacological or a combination of different therapies. The ultimate goal of fibromyalgia treatment is to develop an individualized treatment approach that takes into account the nature of the patient's fibromyalgia symptoms and their severity, the level of function and stressors, and the presence of medical and psychiatric comorbidity.

New developments in the pharmacological treatment of fibromyalgia

Serotonin and norepinephrine reuptake inhibitors

There is emerging evidence that fibromyalgia is associated with aberrant central nervous system processing of pain [1-4]. Although the American College of Rheumatology criteria for fibromyalgia [5] require tenderness in 11 out of 18 discrete regions, patients with fibromyalgia have increased sensitivity to pressure pain throughout the body. Fibromyalgia patients often develop an increased response to painful stimuli (hyperalgesia) and experience pain from normally non-noxious stimuli (allodynia) [6]. Both hyperalgesia and allodynia reflect an enhanced central nervous system processing of painful stimuli that is characteristic of central sensitization [7].

Serotonergic and noradrenergic neurons are implicated in the mediation of endogenous pain inhibitory mechanisms through the descending inhibitory pain pathways in the brain and spinal cord [8-10]. Dysfunction in serotonin and norepinephrine in these pain inhibitory pathways may contribute to the central sensitization and hyperexcitability of the spinal

ACSM = American College of Sport Medicine; APS = American Pain Society; BID = twice a day; CBT = cognitive behavioral therapy; CST = coping skills training; FDA = Food and Drug Administration; FIQ = Fibromyalgia Impact questionnaire; GHB = gamma-hydroxybutyrate; NMDA = N-methyl-D-aspartate; NSAID = non-steroidal anti-inflammatory drug; QD = once a day; SF-36 = Medical Outcomes Study Short Form 36; SNRI = selective serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

and supraspinal pain transmitting pathways and manifest as persistent pain associated with fibromyalgia and some other chronic pain conditions [11-15]. Medications that increase the activity of serotonin and norepinephrine may correct a functional deficit of serotonin and norepinephrine neurotransmission in these descending inhibitory pain pathways and, therefore, help reduce pain.

Systematic reviews

Three recent meta-analyses of fibromyalgia pharmacological trials assessed the efficacy of medications that inhibit the reuptake of serotonin and/or norepinephrine. The first meta-analysis [16] assessed nine placebo-controlled trials of the cyclic drugs that inhibit the reuptake of both serotonin and norepinephrine, including the tricyclics amitriptyline [17-20], dothiepin, which is structurally similar to amitriptyline and doxepin [21], cyclobenzaprine [18,22-24], which possesses structural and pharmacological properties of other tricyclics [25], clomipramine [26], and the tetracyclic maprotiline [26]. Seven outcome measures were assessed, including: the patients' self-ratings of pain, stiffness, fatigue and sleep; the patient and the physician global assessment of improvement; and tender points. The largest effect was found in measures of sleep quality, with more modest changes in tender point measures and stiffness. Thus, the most consistent improvement could be attributed to the sedative properties of these medications.

The results of another meta-analysis of randomized, placebo-controlled studies of cyclobenzaprine was consistent with the Arnold and colleagues [16] meta-analysis. Cyclobenzaprine treatment resulted in moderate improvement in sleep, modest improvement in pain, and no improvement in fatigue or tender points [27].

A third meta-analysis of antidepressants in the treatment of fibromyalgia [28] evaluated 13 trials of antidepressants, most of which studied the cyclic drugs amitriptyline [17-20,26, 29-32], clomipramine [26], and maprotiline [26]. The meta-analysis also included trials of the selective serotonin reuptake inhibitors (SSRIs) fluoxetine [20,33] and citalopram [34], as well as a reversible inhibitor of the monoamine oxidase-A enzyme, moclobemide [29], and the dietary supplement S-adenosylmethionine [35,36]. Outcome measures included the number of tender points, and patients' self-ratings of pain, sleep, fatigue, and overall well being. The pooled results showed a significant symptomatic benefit of antidepressants that was moderate for sleep, overall well being, and pain severity, and mild for fatigue and number of tender points. The magnitude of benefit was similar to that found in the Arnold and colleagues [16] meta-analysis. Because only three trials of SSRIs were included in the meta-analysis, it was not possible to assess the relative efficacy of SSRIs.

The trials of SSRIs in fibromyalgia have shown mixed results, suggesting that medications with selective serotonin effects are less consistent than those with dual effects on norepinephrine and serotonin in the relief of pain associated with fibromyalgia. Citalopram, which has the highest selectivity for the serotonin reuptake transporters among the SSRIs, was not effective for the treatment of fibromyalgia in two small controlled studies [33,37]. On the other hand, the SSRIs fluoxetine and paroxetine CR, which may have additional effects on norepinephrine at adequate doses [38,39], have been shown to be effective for fibromyalgia in recent studies [40,41].

Although the meta-analyses indicated that the overall effect of the cyclic drugs on most symptoms of fibromyalgia was modest, possibly related to the low doses that were typically studied, tricyclics continue to be frequently recommended for the treatment of patients with fibromyalgia [42]. Furthermore, even at low doses, many patients experience problems with the safety and tolerability of these medications related to their anticholinergic, antiadrenergic, antihistaminergic, and quinidine-like effects [43].

Recently, fibromyalgia trials have focused on new selective serotonin and norepinephrine reuptake inhibitors (SNRIs), which are potent dual reuptake inhibitors but, unlike the tricyclics, do not interact with adrenergic, cholinergic or histaminergic receptors, or sodium channels, and, therefore, lack many side effects of tricyclics. Preliminary, open trials of the SNRI venlafaxine were promising [44,45], but one study, a six-week, randomized, placebo-controlled, double-blind trial of a fixed, low dose of venlafaxine (75 mg/day) [46], found that venlafaxine improved some but not all measures of pain. The short duration of this trial and low dose of venlafaxine may explain the discrepant results. To date, two randomized, placebo-controlled studies of the SNRI duloxetine and one study of the SNRI milnacipran in the treatment of fibromyalgia have been published, and are described below.

Duloxetine

Duloxetine, a new, potent SNRI with dual reuptake inhibition of serotonin and norepinephrine over the entire clinically relevant dose range [47], is a safe, tolerable, and effective antidepressant [48-50] that also significantly reduces painful physical symptoms associated with major depressive disorder [51]. In non-depressed patients with diabetes, duloxetine effectively reduces diabetic peripheral neuropathic pain [52,53], supporting an analgesic effect of duloxetine that is independent of its effects on mood. Duloxetine is currently indicated by the FDA for the treatment of major depressive disorder in adults and diabetic peripheral neuropathic pain in adults [54].

The first study of duloxetine in fibromyalgia was a randomized, placebo-controlled, double-blind, parallel-group, multi-site, 12-week monotherapy study of duloxetine titrated to 60 mg twice a day (BID) that included 207 patients with fibromyalgia with or without current major depressive disorder [55]. Co-primary outcome measures were the Fibromyalgia Impact

questionnaire (FIQ) total score and pain score [56]. The FIQ is a self-report instrument in which patients rate their overall symptoms and function over the previous week. Duloxetine-treated patients compared with placebo-treated patients improved significantly more on the FIQ total score, but not on the FIQ pain score. However, duloxetine-treated patients had significantly greater improvement in secondary measures of pain, including the Brief Pain Inventory (short form) [57] average pain severity score, which measured pain over the past 24 hours from 0 (no pain) to 10 (pain as bad as you can imagine), and the average pain interference score, which assessed interference from 0 (does not interfere) to 10 (completely interferes) with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. Duloxetine-treated patients compared with patients on placebo also experienced significant improvement in tender point number and mean tender point pain thresholds that were assessed using a Fischer dolorimeter [58] applied to the 18 tender point sites defined by the American College of Rheumatology criteria. Other secondary measures that significantly improved in the duloxetine-treated group compared with the placebo group included the FIQ stiffness score, Clinical Global Impression of Severity scale [59], and the Patient Global Assessment of Improvement scale. Quality of life measures that significantly improved in the duloxetine group compared with the placebo group included the Quality of Life in Depression Scale total score [60], the Sheehan Disability Scale total score [61], and the Medical Outcomes Study Short Form 36 (SF-36) physical subscore and scores for bodily pain, general health perception, mental health, physical functioning, and vitality [62].

Significantly more duloxetine-treated female patients (30.3%) had a clinically meaningful (≥50%) decrease in the FIQ pain score compared with placebo-treated female patients (16.5%). In addition, the Brief Pain Inventory average pain severity score decreased by ≥50% in significantly more duloxetine-treated women (30%) than women on placebo (16%). However, duloxetine-treated male patients failed to significantly improve on any efficacy measure. The reasons for the sex differences in response to duloxetine are unclear, but may be related to the small male subgroup (23 (11%) of 207 patients), or to possible sex differences in fibromyalgia that affect treatment response.

The duloxetine trial was one of the first fibromyalgia clinical trials to assess baseline psychiatric comorbidity using a structured psychiatric clinical interview and to include patients with and without current major depressive disorder in order to evaluate the impact of major depressive disorder on the response to treatment with duloxetine. Of importance is that duloxetine reduced pain severity regardless of the presence or absence of major depressive disorder. In addition, the treatment effect of duloxetine on significant pain reduction in female patients was independent of the effect on depressive or anxiety symptoms. Therefore, the effect of duloxetine on the reduction of pain associated with fibromyalgia appears to be independent of its effect on mood.

Duloxetine was well tolerated, and there was no significant difference in the number of patients who discontinued due to adverse events. Duloxetine-treated patients reported insomnia, dry mouth, and constipation significantly more frequently than placebo-treated patients. Most treatment-emergent adverse events were of mild or moderate severity.

The second, randomized, placebo-controlled, double-blind, parallel-group, multi-site, 12-week study of duloxetine monotherapy in fibromyalgia tested the safety and efficacy of both 60 mg BID and a lower dose of 60 mg once a day (QD) in 354 women with fibromyalgia with or without current major depressive disorder [63]. This study included only women to confirm the results of the first duloxetine trial in which women, but not men, responded significantly to duloxetine compared with the same sex placebo-treated patients on efficacy measures. The primary outcome measure was pain severity as measured by the Brief Pain Inventory (short form) average pain severity score (score range 0 to 10). Compared with the placebo group, the duloxetine 60 mg QD group and the duloxetine 60 mg BID group experienced significantly greater improvement in the Brief Pain Inventory average pain severity score, beginning at week 1 and continuing through week 12. Significantly more patients treated with duloxetine 60 mg QD (41%) and duloxetine 60 mg BID (41%) compared with placebo (23%) had a ≥50% reduction in the Brief Pain Inventory average pain severity score. Compared with placebo, duloxetine 60 mg QD or duloxetine 60 mg BID resulted in significantly greater improvement in the remaining Brief Pain Inventory pain severity and interference scores, and other secondary outcomes, including the FIQ, Clinical Global Impression of Severity, and the Patient Global Impression of Improvement. Consistent with the first duloxetine study, several quality of life measures significantly improved in both duloxetine groups compared with the placebo group, including the Quality of Life in Depression Scale total score, the Sheehan Disability Scale total score, and the SF-36 mental subscore, bodily pain, mental health, role limit emotional, role limit physical, and vitality. There were no significant differences between duloxetine 60 mg QD and duloxetine 60 mg BID treatment groups in efficacy outcomes. However, only the duloxetine 60 mg BID dose, compared with placebo, significantly improved the tender point assessments. This suggests that the higher dose may be necessary to improve pressure pain thresholds, which have been found to be less responsive to treatment in previous fibromyalgia trials using tricyclics [16,28]. As in the first study of duloxetine, the treatment effect of duloxetine on pain reduction was independent of the effect on mood and the presence of major depressive disorder.

The most frequent side effect in patients in the duloxetine 60 mg QD and 60 mg BID groups was nausea, and side

effects were generally mild to moderate in severity for most patients. Significantly more patients in the duloxetine 60 mg BID group than the placebo group discontinued treatment due to adverse events. This finding differs from the previous duloxetine trial of 60 mg BID in which there were no differences between treatment groups in discontinuation due to treatment-emergent adverse events. The difference between the studies might be explained by the slower titration of duloxetine in the first study, in which duloxetine was titrated from a starting dose of 20 mg QD to 60 mg BID over 2 weeks. In the second study, patients were started on 60 mg QD and titrated to 60 mg BID over just three days. This suggests that some patients would benefit from a lower duloxetine starting dose and slower titration.

The results of both duloxetine studies in fibromyalgia provide evidence that duloxetine 60 mg QD and 60 mg BID for up to 12 weeks are safe and effective in the treatment of fibromyalgia in women with or without major depressive disorder.

Milnacipran

Milnacipran is another selective SNRI that has been approved for treatment of depression since 1997 in parts of Europe, Asia, and elsewhere, but is currently unavailable in the US. Milnacipran is a dual serotonin and norepinephrine reuptake inhibitor within its therapeutic dose range and also exerts mild N-methyl-D-aspartate (NMDA) inhibition [64].

In a double-blind, placebo-controlled, multicenter trial, 125 patients (98% women) with fibromyalgia were randomized to receive placebo or milnacipran monotherapy for 4 weeks of dose escalation to the maximally tolerated dose followed by 8 weeks of stable dose (25 to 200 mg/day) [65]. The study evaluated the efficacy and safety of two different dosing regimens of milnacipran (QD versus BID) for the treatment of fibromyalgia. The primary outcome measure was based on change of average daily pain scores recorded on an electronic diary (e-diary), comparing the two-week baseline period to endpoint (last two weeks on treatment). The majority of milnacipran-treated patients, 92% of completers on the BID regimen and 81% on the QD regimen, titrated to the highest daily dose (200 mg). Although the primary outcome measure of daily e-diary pain scores did not significantly improve in either patients on BID milnacipran or those on the QD regime compared to placebo, patients treated with milnacipran on a BID schedule experienced significant improvement in the weekly e-diary pain scores, paper pain scores, and the McGill Pain Questionnaire present pain intensity score [66] compared to those on placebo. Furthermore, significantly more patients receiving milnacipran BID (37%) reported a reduction in the weekly average pain scores by 50% or more, compared with 14% of patients in the placebo group. Milnacipran-treated patients on the QD schedule did not exhibit the same degree of improvement in pain, suggesting that dosing frequency is important in the use of milnacipran for pain associated with fibromyalgia. The QD regime may have resulted in inadequate drug levels of milnacipran and less effective pain relief by the end of the day because of milnacipran's short half-life of 6 to 8 hours. Both milnacipran groups (QD and BID dosing), compared with the placebo-treated patients, had significantly greater improvement in other secondary measures, including the patient global impression of change score, and the physical function and 'days felt good' subscales of the FIQ. The BID milnacipran-treated group, compared to patients on placebo, also had significant improvement in the FIQ scores for pain, fatigue, and morning stiffness.

Milnacipran was generally well tolerated and most adverse events were rated as mild or moderate in severity. Overall, 14.4% of patients discontinued the study due to adverse events, including 7 (13.7%) from the milnacipran BID group, 10 (21.7%) from the milnacipran QD group, and 1 (3.6%) from the placebo-treated group. Headache and gastrointestinal complaints (nausea, abdominal pain, gastrointestinal upset, and constipation) were the most frequent reasons for early discontinuation. Other reasons included orthostatic dizziness, exacerbation of hypertension, depression, lethargy, increased sweating, and hot flashes. The QD group experienced a higher incidence of adverse events than the BID group, suggesting that the QD dose was not as well tolerated as BID dosing.

As in the duloxetine trials, patients were evaluated for psychiatric comorbidity and those with and without current major depressive disorder were included. Unlike the results of the duloxetine trials in which both depressed and non-depressed patients responded similarly to duloxetine, statistically greater improvement in pain reduction was seen in non-depressed patients versus depressed patients treated with milnacipran. Although this finding needs to be replicated in a larger clinical trial, the positive response in non-depressed patients suggests that, like duloxetine, the pain relieving effects of milnacipran do not occur only through improvement in mood.

Summary of serotonin and norepinephrine reuptake inhibitors

The earlier evidence from studies of cyclic agents and the new studies of selective SNRIs support the efficacy of medications with dual effects on serotonin and norepinephrine in fibromyalgia. In recent trials, the SNRIs were found to improve pain and other important symptom domains of fibromyalgia in addition to improving function, quality of life, and global well-being (Table 1). Most studies of tricyclic drugs used low doses, an approach that may have been influenced by concern about the undesirable side effects of the tricyclics. Recent studies of selective SNRIs have assessed a wider range of doses, which have been well tolerated by most patients and effective in reducing many of the symptoms and impact of fibromyalgia. Fibromyalgia trials have not directly compared selective SNRIs with tricyclics, and it is unknown whether the selective SNRIs are more

Table 1

Randomized, double-blind, placebo-controlled trials of serotonin and norepinephrine reuptake inhibitors and alpha 2 delta ligands in fibromyalgia

Study	Drug (mg/day)	Study design (no. of patients)	Duration (weeks)	Outcomes that significantly improved with treatment over placebo
SNRI				
Arnold *et al*. [55]	Duloxetine (120)	Duloxetine v placebo, parallel (207)	12	Primary measure: FIQ total score (FIQ pain score improved in women only) Secondary measures: FIQ stiffness scores, BPI pain severity and interference from pain, tender points, CGI-S, PGI-I, QLDS, SDS, SF-36 physical subscore and bodily pain, general health perception, mental health, physical function, vitality scores
Gendreau *et al*. [65]	Milnacipran (up to 200)	Milnacipran v placebo, parallel (125)	12	Secondary measures: Pain (weekly e-diary pain score, paper daily and weekly scores, present pain score), patient global impression of change, FIQ physical function, days felt good, pain, fatigue, and morning stiffness scores
Arnold *et al*. [63]	Duloxetine (60 and 120)	Duloxetine v placebo, parallel (354)	12	Primary measure: BPI average pain severity Secondary measures: BPI interference from pain, FIQ total score, tender points (120 mg only), CGI-S, PGI-I, QLDS, SDS, SF-36 mental subscore and scores for social function (60 mg only), physical function (120 mg only), bodily pain, mental health, role limit emotional and physical, and vitality
Alpha 2 delta				
Crofford *et al*. [67]	Pregabalin (150, 300, and 450)	Pregabalin v placebo, parallel (529)	8	Primary measure: mean daily pain score (daily diaries) (450 mg only) Secondary measures: sleep quality diary (300 mg, 450 mg), MAF global fatigue (300 mg, 450 mg), patient and clinician global impression of change (300 mg, 450 mg), SF-36 general health (150 mg, 300 mg, 450 mg), vitality (450 mg), bodily pain (450mg), social functioning (450 mg)

BPI, Brief Pain Inventory; CGI-S, Clinician global impression of severity; FIQ, Fibromyalgia Impact Questionnaire; MAF, Multidimensional Assessment of Fatigue; PGI-I, Patient global impression of improvement; QLDS, Quality of Life in Depression Scale; SDS, Sheehan Disability Scale; SF-36, Medical Outcomes Study Short Form.

effective than the tricyclics in the treatment of fibromyalgia. However, the new selective SNRIs provide an alternative for patients who have tolerability or safety concerns related to the side effects of tricyclics.

Alpha 2 delta ligands

In parallel with the development of selective SNRIs for fibromyalgia, another approach is being explored using medications that bind to the $\alpha_2\delta$ subunit of voltage-gated calcium channels, resulting in decreased calcium influx at nerve terminals and subsequent reduction in the release of several neurotransmitters thought to play a role in pain processing, such as glutamate and substance P [10,67]. Pregabalin is an alpha 2 delta ligand that has analgesic, anxiolytic-like, and anticonvulsant activity and is approved by the FDA for the treatment in adults of diabetic peripheral neuropathic pain, postherpetic neuralgia, and adjunctive therapy in partial onset seizures [54].

A multicenter, randomized, placebo-controlled, 8 week, monotherapy trial 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% female) [67]. The primary outcome measure was a daily paper pain diary in which patients selected a number on a numerical scale from 0 (no pain) to 10 (worst possible pain) that best described their pain during the past 24 hours. The outcomes that responded significantly to pregabalin 450 mg/day compared with placebo were the mean weekly pain (diary) score, the Short-form McGill Pain Questionnaire total score and VAS pain score [68], daily sleep (diary) score (a 0 to 10 numerical scale on the quality of sleep), the Medical Outcomes Study Sleep scale [69], Multidimensional Assessment of Fatigue [70], Clinical/Patient Global Impression of Change, and SF-36 domains of social functioning, bodily pain, vitality, and general health perception. A significantly larger proportion of patients receiving pregabalin 450 mg/day (28.9%) exper-

ienced a ≥50% reduction in the pain (diary) score compared with the placebo group (13.2%). Compared with placebo, pregabalin 300 mg/day significantly improved sleep as measured by both the daily sleep diary and the Medical Outcomes Study Sleep scale, significantly improved fatigue, the SF-36 domain of general health perception, and the global change assessments by the patients and clinicians. Patients taking 150 mg/day of pregabalin also reported improved sleep on the Medical Outcomes Study Sleep Scale and improvement in general health perception compared with placebo.

Pregabalin was generally well tolerated and most adverse events were mild or moderate in severity. The most common side effects were dizziness and somnolence, which tended to be dose related across the pregabalin groups. Few patients withdrew due to these symptoms. The median duration of dizziness in patients who did not withdraw from the study was 15 days in those taking 450 mg/day of pregabalin; the mean duration for somnolence was 18 days in the same group. Other side effects that were more frequent in the pregabalin group included abnormal thinking, euphoria, dry mouth, peripheral edema, and weight gain.

Unlike the duloxetine and milnacipran studies, patients in the pregabalin trial were not evaluated for the presence of comorbid psychiatric disorders. However, anxiety and depressive symptoms were assessed using the Hospital Anxiety and Depression Scale [71], and the mean baseline scores were mild. There were no significant changes in the Hospital Anxiety and Depression Scale anxiety or depressive scores at endpoint from those at baseline, which suggests that the improvement in pain was probably independent of any improvement in anxiety or depressive symptoms.

Another recent study examined the effects of pregabalin compared with alprazolam and placebo on aspects of sleep in 24 healthy adult volunteers who received pregabalin 150 mg three times a day, alprazolam 1 mg three times a day, or placebo three times a day for three days [72]. Compared with placebo, pregabalin significantly increased slow-wave sleep both as a proportion of the total sleep period and the duration of stage 4 sleep. Alprazolam, on the other hand, significantly reduced slow-wave sleep. Both pregabalin and alprazolam produced significant reduction in sleep-onset latency compared with placebo. Pregabalin also significantly reduced the number of awakenings of more than 1 minute in duration. Pregabalin's enhancement of slow-wave sleep could be very important in many patients with fibromyalgia in whom there is a reduction in slow-wave sleep.

In summary, the results of the first published, randomized, controlled trial of an alpha 2 delta ligand, pregabalin, in fibromyalgia demonstrated that pregabalin monotherapy reduced pain and improved other key symptom domains of fibromyalgia, such as fatigue and sleep. In addition, pregabalin treatment was associated with improvement in health-related quality of life and global assessments.

Sedative-hypnotic medication

Although there continues to be debate about the role of sleep disturbance in the pathogenesis of fibromyalgia, many patients with fibromyalgia experience disrupted or non-restorative sleep and benefit from treatment. A few controlled studies have examined sedative hypnotics in the treatment of fibromyalgia. The short-acting non-benzodiazepine sedatives zolpidem and zopiclone improved sleep in patients with fibromyalgia but did not improve pain, limiting their usefulness in fibromyalgia as monotherapy [73-75]. While the combination of alprazolam and ibuprofen was somewhat beneficial in a pilot trial of fibromyalgia [76], another study found no significant benefit of another benzodiazepine, bromazepan, over placebo in the treatment of fibromyalgia [77].

Gamma-hydroxybutyrate (GHB) is a precursor of gamma-aminobutyric acid (GABA) with marked sedative properties. Sodium oxybate, the sodium salt of GHB, was granted an Orphan Drug Status by the FDA for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy, which was classified as an orphan (rare) disease [54]. A preliminary, 4 week, double-blind, placebo-controlled crossover trial of 24 women with fibromyalgia suggested that sodium oxybate reduced symptoms of pain and fatigue, decreased the tender point index, and increased slow-wave sleep and decreased alpha intrusion on polysomnography [78]. A recently completed 8 week study of sodium oxybate monotherapy evaluated 4.5 g or 6 g per day taken in two equally divided doses (bedtime and 2.5 to 4 hours later) in 188 patients with fibromyalgia [79]. The primary outcome, a composite of changes from baseline in three co-primary, self-report measures (pain visual analog scale from electronic diaries, the FIQ, and the patient global assessment) improved significantly with both dosages of sodium oxybate compared to placebo. Both dosages were also significantly superior to placebo in improvement of sleep quality; the tender point count improved only in the higher sodium oxybate dose compared to placebo. The direct relationship between change in pain and insomnia suggested that the improvement in pain was related to improved sleep. Sodium oxybate was well tolerated; the most common side effects were nausea and dizziness.

Despite the results of this proof-of-principle study, GHB's abuse potential and its use in cases of date rape [80] will likely limit the usefulness of sodium oxybate in patients with fibromyalgia. A recent study evaluating the relative abuse liability of hypnotic drugs reported that GHB was associated with a high likelihood of abuse. Furthermore, GHB, along with pentobarbital and methaqualone, were more likely to be lethal at supratherapeutic doses than any of the other hypnotics [81]. Finally, patients with chronic pain may be especially at risk for the development of problematic hypnotic use [81].

Because of the risk of abuse, sodium oxybate for the treatment of narcolepsy is only available through a Risk Management Program that was designed to maximize physician and patient education about the safe use of the drug and minimize potential diversion or abuse by limiting distribution through a central pharmacy. This risk management program has appeared to be effective in preventing diversion and limiting abuse in patients with narcolepsy, although the evaluation of the program is ongoing [82]. It is not clear, however, whether this program would be effective in the much larger group of patients (mostly women) with fibromyalgia, who have chronic pain and frequent psychiatric comorbidities that might make them more vulnerable to the abuse potential of sodium oxybate.

Safer alternatives for the management of insomnia include low-dose tricyclic agents, and, more recently, the alpha 2 delta ligand pregabalin or a related compound, gabapentin, which have sedative properties, improve slow-wave sleep, and relieve pain [72,83].

Opiates

There is controversy about the use of opiates to manage the pain associated with fibromyalgia because of the abuse potential of these agents and the lack of data supporting their efficacy in fibromyalgia. However, a survey of academic medical centers in the US reported that about 14% of fibromyalgia patients were treated with opiates [84]. A small, double-blind, placebo-controlled study found that intravenous administration of morphine in nine patients with fibromyalgia did not result in a reduction of pain intensity [85]. A recent, four year, non-randomized study of opiates in fibromyalgia discovered that the fibromyalgia patients taking opiates did not experience significant improvement in pain at the four year follow-up compared with baseline, and reported increased depression in the last two years of the study [86]. These results suggest that opiates may not have a role in the long-term management of fibromyalgia. In addition, there is emerging evidence that opioid-induced hyperalgesia might limit the usefulness of opioids in controlling chronic pain [87]. Although the mechanisms by which opioids promote pain are not completely understood, recent animal studies suggest that chronic use of opioids induces neuroadaptive changes mediated, in part, through the NK-1 receptor, that result in enhancement of nociceptive input [88]. These results raise the possibility that prolonged treatment of pain with opiates may actually cause unintentional harm to patients [88].

Tramadol is a novel analgesic with weak agonist activity at the mu opiate receptor combined with dual serotonin and norepinephrine reuptake inhibition that may exert antinociceptive effects within both the ascending and descending pain pathways. Three controlled studies have evaluated the efficacy of tramadol in fibromyalgia. The first small study used a double-blind crossover design to compare single-dose intravenous tramadol 100 mg with placebo in 12 patients with fibromyalgia. Patients receiving tramadol experienced a 20.6% reduction in pain compared with an increase of 19.8% of pain in the placebo group [89]. The second study of tramadol began with a three week, open-label phase of tramadol 50 to 400 mg/day followed by a six-week double-blind phase in which only patients who tolerated tramadol and perceived benefit were enrolled [90]. The primary measure of efficacy was the time to exit from the double-blind phase because of inadequate pain relief. One hundred 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 on tramadol discontinued during the double-blind phase because of inadequate pain relief. This study is limited by the possible unblinding of patients in the double-blind phase after open-label treatment with tramadol. Finally, a multicenter, double-blind, randomized, placebo-controlled, 91 day study examined the efficacy of the combination of tramadol (37.5 mg) and acetaminophen (325 mg) in 315 patients with fibromyalgia. Patients taking tramadol and acetaminophen (4 ± 1.8 tablets per day) were significantly more likely than placebo-treated subjects to continue treatment and experience an improvement in pain and physical function [91]. Treatment emergent adverse events were reported by significantly more patients in the tramadol/acetaminophen group (75.6%) than the placebo group (55.8%). The most common side effects in the tramadol/acetaminophen group were nausea, dizziness, somnolence, and constipation. A *post hoc* analysis of the data from this trial revealed that the patients who had the most reduction in pain severity (≥25 mm on the 0 to 100 mm visual analog scale) from baseline had significantly greater improvement in health-related quality of life than those with less reduction in pain. When comparing treatment groups, improvements in the SF-36 physical functioning, role-physical, bodily pain, and physical component summary scores were significantly greater in the tramadol/acetominophen than the placebo group [92].

Although tramadol is currently marketed as an analgesic without scheduling under the US Controlled Substances Act, it is under review for possible control, and it should be used with caution because of recent reports of classic opioid withdrawal with discontinuation and dose reduction and increasing reports of abuse and dependence [93].

Other pharmacological studies in fibromyalgia

Preliminary evidence from randomized, controlled studies supports the possibility that other pharmacological approaches hold promise for fibromyalgia, but more study is needed. Among these possible medications are the 5-HT_3 antagonists (e.g., ondansetron and tropisetron), which have analgesic effects. A randomized, placebo-controlled, double-blind, 10 day trial in 418 patients with fibromyalgia evaluated the short-term efficacy of tropisetron at doses of 5 mg/day, 10 mg/day, and 15 mg/day. Significant reduction in pain was noted only in those patients taking 5 mg/day and 10 mg/day,

while the effects of tropisetron 15 mg/day were no different from placebo, suggesting a bell-shaped dose response curve [94]. Another, recent, randomized, placebo-controlled trial of 21 female fibromyalgia patients evaluated daily intravenous bolus injections of 5 mg tropisetron for 5 days and found significant improvement in pain in the tropisetron group compared to placebo [95]. 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 nociceptives to the dorsal horn may explain the pro- and anti-nociceptive effects of 5-HT_3 receptor blockade. The balance of these opposing effects may be dose-dependent and contribute to unpredictable results with tropisetron [96], but more study of longer-term treatment with 5-HT_3 antagonists is needed.

Central sensitization, a possible pathogenic mechanism of the chronic pain associated with fibromyalgia, is mediated, in part, by the binding of excitatory amino acids (glutamate and aspartate) to the NMDA receptor. NMDA antagonists may inhibit or attenuate central sensitization [97] and potentially reduce pain associated with fibromyalgia. In one clinical study, 48 female patients with fibromyalgia were treated with an open-label combination of tramadol 200 mg/day and increasing doses of dextromethorphan (50 to 200 mg/day), titrated to therapeutic effect or tolerability. Fifty-eight percent (28 of 48) responded to the addition of dextromethorphan and entered a double-blind phase in which the patients were randomized to dextromethorphan and tramadol or tramadol and placebo. A Kaplan-Meier drop-out analysis showed that significantly fewer patients on dextromethorphan and tramadol discontinued treatment compared with patients on tramadol alone [98]. More study of NMDA receptor antagonists is needed before clinical recommendations can be made regarding the use of these agents. Interestingly, a study looking at the effects of dextromethorphan on temporal summation of pain in patients with fibromyalgia compared to normal controls found that dextromethorphan had similar effects in both groups on reduction in wind-up from repeated thermal and mechanical pressure stimulation of the skin. These results suggest that patients with fibromyalgia do not have substantially altered NMDA receptor mechanisms and other mechanisms, such as enhanced descending facilitation, should be considered for the pain associated with fibromyalgia [99].

Finally, pramipexole, a dopamine 3 receptor agonist, was tested in patients with fibromyalgia in a 14 week, single-center, randomized, placebo-controlled study in which pramipexole was added on to existing pharmacological and non-pharmacological therapies [100]. The rationale for testing a dopamine 3 agonist in fibromyalgia is based on evidence that excessive adrenergic arousal may fragment sleep, and enhancement of dopaminergic neurotransmission at the D3 receptors in the mesoliombic hippocampus may reduce expression of arousal and improve sleep. Compared with the placebo group, those patients receiving pramipexole titrated over 12 weeks to 4.5 mg every evening had gradual and significant improvement in pain, fatigue, function, and global status. A gradual titration of pramipexole was well tolerated; weight loss and increased anxiety were significantly more common in patients on pramipexole.

Sleep was not assessed in the study, despite the proposed role of pramipexole in reducing adrenergic arousal in patients with fibromyalgia; therefore, the mechanism by which pramipexole improved the symptoms of fibromyalgia is unclear. The study was also difficult to interpret because the participants were taking concomitant medications (about half on narcotic analgesics) for fibromyalgia.

Limitations of pharmacological treatment studies in fibromyalgia

The pharmacological treatment studies of fibromyalgia are limited for several reasons. First, many of the medication trials were of short duration, and there is a need for more data on the long-term efficacy of medications in the treatment of fibromyalgia, a chronic condition. Second, although most fibromyalgia clinical trials assessed change in the intensity of pain as the primary outcome, they have inconsistently evaluated other associated symptoms, such as sleep disturbance, fatigue, depression, anxiety, cognition, or function and health-related quality of life, which reduce the comparability and clinical applicability of the trials. Third, medication clinical trials have used dissimilar measures to assess symptom and functional domains. Fourth, the primary outcome measure of most recent fibromyalgia trials has been the mean reduction of pain in the patients receiving a treatment compared with those receiving placebo. Although this approach provides information about the overall efficacy of a particular treatment in reducing pain, it does not determine the proportion of patients who experience clinically important improvement. Fifth, there is a lack of consensus about the definition of clinically meaningful reduction in pain for fibromyalgia clinical trials. In addition, it is unclear whether improvement in pain intensity alone should define response to treatment in fibromyalgia, which is a syndrome characterized by multiple symptoms in addition to pain. Standardized, operationally defined outcome measures of fibromyalgia activity and improvement would greatly enhance the comparability, validity, and clinical applicability of fibromyalgia trials. Sixth, patients with fibromyalgia frequently have comorbid disorders that may affect their response to treatment. Despite evidence of elevated prevalence rates of mood and anxiety disorders in patients with fibromyalgia and their possible prognostic significance, few clinical trials systematically evaluated patients for comorbid psychiatric disorders. Seventh, most trials excluded patients with pain from some other disorders, such as rheumatoid arthritis, inflammatory arthritis or autoimmune disease, and future trials should examine the efficacy of medications in these patients. Finally, the majority of patients studied in the trials were women, which reflects the much

higher prevalence of fibromyalgia in women [101]. The results of the studies may not, therefore, be generalizable to men with fibromyalgia.

Summary of pharmacological trials in fibromyalgia

Despite the limitations of the pharmacological trials, much progress has been made in identifying effective medication treatments for patients with fibromyalgia. Two recent pharmacological approaches have shown promise in large, multicenter, randomized, placebo-controlled trials: the SNRIs duloxetine and milnacipran, and the alpha 2 delta ligand pregabalin. All three medications reduced pain, the primary symptom of fibromyalgia, and improved other important symptom domains, some aspects of function, and global assessments, as summarized in Table 1. In addition to efficacy, their safety and tolerability also make them important options for patients with fibromyalgia. Table 2 outlines the conclusions that can be drawn from the results of the recent randomized, placebo-controlled pharmacological trials. Continued clinical trials of these medications, combinations of medications, and other drugs with alternative mechanisms of action are needed to identify effective and FDA-approved treatments for fibromyalgia.

Table 2

Summary of findings from pharmacological studies in fibromyalgia

1. Serotonin and norepinephrine reuptake inhibitors improve pain, other symptom domains, function, quality of life, and global well-being in patients with fibromyalgia.
2. Selective serotonin and norepinephrine reuptake inhibitors (SNRIs) offer an alternative to cyclic medications (e.g., tricyclics) that are associated with safety and tolerability concerns.
3. The effect of SNRIs on reduction in pain associated with fibromyalgia is independent of their effects on mood.
4. Alpha 2 delta ligands also improve pain, other symptom domains, function, and global well-being in patients with fibromyalgia.
5. Alpha 2 delta ligands improve slow wave sleep.
6. Drugs associated with high risk of abuse and dependence should be avoided. Opiates may contribute to hyperalgesia if used chronically.
7. Although studies are limited, combinations of medications (e.g., combination of an SNRI and alpha 2 delta ligand) may be an option for patients who do not fully respond to a single agent or who have problems with tolerability at higher doses.

New developments in the non-pharmacological treatment of fibromyalgia

Systematic reviews of non-pharmacological modalities

Several systematic reviews of non-pharmacological treatments for fibromyalgia have been published since 1999. The first review was a meta-analysis of pharmacological and non-pharmacological treatment studies of fibromyalgia completed between 1966 and 1996 [102]. Studies of patients with fibromyalgia were included in the analysis if they had sufficient statistical information to calculate effect sizes on the outcome variables of physical status, self-report of fibromyalgia symptoms, psychological status, or daily functioning. The meta-analysis included 33 pharmacological and 16 non-pharmacological treatment studies. The pharmacological treatments included: tricyclic agents (tricyclic antidepressants or the muscle relaxant cyclobenzaprine, which is structurally a tricyclic); S-adenosylmethionine (SAMe); alprazolam; 5-hydroxytryptophan; the SSRIs fluoxetine and citalopram; the non-steroidal anti-inflammatory drugs (NSAIDs) ibuprofen and naproxen; prednisone; zolpidem; topical capsaicin; a combination of malic acid and magnesium hydroxide; mexiletine (oral lidocaine); a combination of carisoprodol, paracetamol and caffeine; myanserine; chlormezanone; and an antidiencephalon immune serum. Non-pharmacological therapies included exercise, education, cognitive-behavioral therapy, electroacupuncture, acupuncture, and hypnotherapy. After combining effects sizes within the two classes of treatment for each outcome variable, both pharmacological and non-pharmacological treatments were associated with improvement in physical status, fibromyalgia symptoms, and psychological status; only non-pharmacological treatment improved daily functioning. Furthermore, non-pharmacological treatment was superior to pharmacological treatment on fibromyalgia symptoms. However, this meta-analysis was limited by pooling diverse pharmacological and non-pharmacological treatments, making it difficult to evaluate individual treatments, and by including studies that were of poor methodological quality.

Instead of evaluating non-pharmacological treatments as a group as was done in the Rossy and colleagues [102] meta-analysis described above, a subsequent systematic review focused only on mind-body therapies, which included autogenic training, relaxation exercises, meditation, cognitive-behavioral training, hypnosis, guided imagery, biofeedback, or education [103]. Thirteen randomized or quasi-randomized controlled trials conducted between 1966 and 1999 were evaluated with a best-evidence synthesis method that has been used in Cochrane systematic reviews. There were several important findings from this review. First, there was strong evidence that mind-body therapies were more effective for self-efficacy (a measurement of an individual's belief that she or he can cope effectively with a challenging situation) than waiting list or treatment as usual controls [104,105]. However, improvements in self-efficacy did not correspond to improvements in other clinical measures. Indeed, the results suggested that mind-body therapies were not consistently better than waiting list or treatment as usual controls in the modulation of pain or improvement in function. Second, there was strong evidence that exercise was more effective than mind-body therapies for short-term improvement in pain intensity or tender point pain threshold and physical function [106,107]. Third, patients with fibromyalgia who were also severely depressed did not respond well to mind-body therapies [104]. Finally, mind-body therapies with cognitive restructuring and coping components were not

significantly better than education or attention controls. For example, in a controlled study, 131 outpatients with fibromyalgia were randomized to one of 3 conditions: a 12 session, combined educational and cognitive group intervention; an attention control condition consisting of group education plus group discussion; and a waiting list control. For the sample as a whole, very little improvement was found. The patients in the attention control condition with group education and discussion did somewhat better than those in the combined education and cognitive intervention with improved pain coping and pain control, although neither group experienced improvement in pain intensity [105]. Another controlled study of 71 patients with fibromyalgia evaluated a 10 week behavioral treatment program that consisted of 90 minute weekly group sessions of education, training in relaxation, behavioral goal setting and activity pacing, and involvement of a support person to promote adaptive coping techniques and encourage adherence to the protocol. Both the behavioral treatment and an education control that consisted of lectures and group discussion resulted in significant reductions in depression, self-reported pain behavior, observed pain behavior, and myalgic scores (a measure of pressure pain threshold). Pain levels were not reduced in either condition. Furthermore, the effect of the behavioral treatment condition was no better than the education control [108].

Another recent systematic review of randomized, controlled trials of several non-pharmacological treatments for fibromyalgia completed between 1980 and 2000 assessed methodological quality according to a set of formal criteria adapted from other Cochrane systematic reviews [109]. Interventions tested in the 25 reviewed trials included exercise therapy, educational intervention, relaxation therapy, cognitive-behavioral therapy, acupuncture, and forms of hydrotherapy. Aerobic exercise (nine studies), education (four studies), and relaxation (four studies) were the most frequently evaluated interventions. Although there was a lack of strong evidence to support any single intervention, there was preliminary support of moderate strength for aerobic exercise. Overall, the methodological quality of the studies was judged to be fairly low, mostly as a result of small samples with low mean power to detect a medium effect. Furthermore, 16 studies had blinded outcome assessments, but patients were blinded in only 6 studies. In contrast to the Rossy and colleagues [102] meta-analysis, which found favorable results for non-pharmacological therapies when grouped together, at the level of the specific non-pharmacological modalities assessed in this review, the evidence supporting their use in fibromyalgia was inconclusive due to the methodological limitations of most of the studies.

Finally, a Cochrane review of randomized clinical trials assessed the effectiveness of multidisciplinary rehabilitation for patients with fibromyalgia [110]. The multidisciplinary program was required to consist of a physician's consultation, in addition to a psychological, social, or vocational intervention, or a combination of these. Only four randomized, controlled trials of fibromyalgia conducted between 1966 and 1998 met methodological inclusion criteria, although the overall quality of these studies was determined to be poor. Nonetheless, several findings from the review emerged that were consistent with some of the results from the above systematic reviews, which included some of the same studies. First, the effectiveness of aerobic exercise was neutral compared to stress management in the long-term treatment of pain, tenderness, or work capacity [107]. This conclusion differs from the Hadhazy and colleagues review [103], which focused on the short-term benefits of exercise among the participants who completed this trial [107]. Second, education combined with physical exercise was better than education alone in a long-term follow-up study [104]. Finally, as reviewed above, neither a combined education and cognitive group intervention nor behavioral therapy was more effective than education alone [105,108].

Systematic review of exercise therapy

The use of exercise as a therapy for fibromyalgia received support in the above reviews of non-pharmacological interventions. Another review focused specifically on exercise as a treatment for fibromyalgia. This Cochrane review included exercise trials conducted between 1966 and 2001 that were defined as high quality training studies, which met methodological quality criteria and included an exercise dosage that was consistent with the American College of Sport Medicine (ACSM) guidelines for healthy individuals [111]. For aerobic training, the ACSM guidelines indicate that the frequency of exercise is required to be at least 2 days per week at an intensity to achieve 40% to 85% of heart rate reserve or 55% to 90% predicted maximum heart rate. In addition, the duration of exercise must be at least 20 minutes duration (range 20 to 60 minutes), either as continuous exercise or spread intermittently throughout the day, and using any mode of aerobic exercise for a total time period of at least 6 weeks. The review identified 16 randomized clinical trials that evaluated the effects of 23 exercise interventions in fibromyalgia. Thirteen of these studies were judged to have moderate to high methodological quality, eight of which also met ACSM training guidelines. Among the latter eight studies, aerobic training was evaluated in four trials [107, 112-114], strength training in one [115], mixed exercise in one [106], and two trials included composite interventions of biofeedback plus aerobic training [114] or education plus aerobic training [116]. Modes of aerobic exercise that were studied included cycle ergometry [112], aerobic dance [113], whole body aerobics [107], and walking indoors [114]. A meta-analysis of the four trials of aerobic exercise showed that, compared to controls, those in the aerobic exercise groups experienced significant short-term improvements in cardiovascular fitness and tender points. However, the effect of aerobic exercise on pain was not significant.

The Cochrane review of exercise studies included the following conclusions. First, large improvements with exercise were seen for global well being, and moderate to large effects on self-reported physical function. Second, the effects of aerobic training on pain, fatigue, and sleep were weak and inconsistent. Third, there was no evidence that aerobic training improved psychological function. Fourth, it is unclear from the data whether mixed regimens of different exercises provided additional benefit beyond a single type of exercise. Fifth, there was evidence in one study to support the use of strength training, which improved pain, musculoskeletal performance and psychological function, but more study was recommended. Finally, only three of the studies examined long-term effects of the exercise intervention. Improvements in self-reported physical function and self-efficacy for function were seen at one year follow-up in one study [114], but another study found that, 4.5 years after the exercise intervention, improvements were not retained in the exercise group, although most were no longer exercising [107]. Lastly, an uncontrolled three and six month follow-up of participants in a program that included aerobic pool exercise and education found that participants reported significant improvements in the six minute walk test, fatigue, and self-efficacy [116].

Recent non-pharmacological treatment studies of fibromyalgia

Exercise

Exercise continues to be an active area of research in fibromyalgia treatment. Since 2001, several trials have been published that expand on the results of the earlier studies reviewed in the aforementioned systematic analysis, which focused on exercise that met ACSM guidelines for healthy individuals. Recent trials have attempted to assess other levels of exercise intensity, other forms of exercise, or exercise in combination with other non-pharmacological therapies for fibromyalgia.

Exercise intensity

A recent study of 143 women with fibromyalgia compared 24 weeks of mixed physical fitness training or biofeedback with usual medical care [117]. The fitness protocol was based on the ACSM guidelines and consisted of twice weekly supervised group exercise of 60 minutes duration in which patients performed aerobic exercise, stretching, flexibility and balance exercises, and isometric muscle strengthening; an additional third unsupervised weekly exercise session was also encouraged. The training intensity was left up to each individual, based on the patient's experience of pain or fatigue. The biofeedback training comprised individual 30 minute sessions twice weekly during 8 weeks with progressive relaxation practice using an audio tape twice daily at home; patients were instructed to continue twice daily relaxation exercises during the remaining 16 weeks of the study. Among the 118 participants who completed the study, no intervention led to significant or clinically relevant improvement in pain, patient global assessment of well being, functional ability, or psychological distress. Physical fitness actually worsened during the trial in all groups. Notably, in terms of training intensity and maximal heart rates achieved, the fitness intervention was actually low impact training despite efforts to encourage patients to follow a high impact version.

To assess the impact of exercise intensity on fibromyalgia symptoms, another study randomly assigned 37 women with fibromyalgia to either a high intensity aerobic fitness training regimen or a low intensity aerobic fitness training regimen [118]. The high intensity group had supervised exercise 3 times weekly for 60 minutes over 20 weeks, adapting the protocol used by McCain and colleagues [112]. The low intensity protocol consisted of twice weekly supervised exercise for 60 minutes for 20 weeks; an additional third, unsupervised 60 minute weekly session was also encouraged. The low intensity protocol was designed to meet ACSM guidelines for the development and maintenance of cardiorespiratory and muscular fitness. However, the training intensity was left up to each subject, who could stop or interrupt exercise as needed for pain or fatigue. The primary outcome was the patient global assessment of well being. The results indicated that neither intervention led to substantial improvement between baseline and 20 weeks. The most important change was a 20% increase in pain in the high intensity group. Furthermore, there was no significant difference between the high intensity and low intensity training in the improvement in physical fitness. Notably, about 50% of the subjects in both groups were unable to fully comply with the training sessions. By contrast, patients in the cardiovascular training group in the McCain and colleagues study [112] had better compliance and achieved a higher fitness level. However, this study included only those patients who could complete a treadmill exercise stress test, which may have selected for a more physically fit patient subgroup.

In an attempt to assess the effects of graded aerobic exercise in a more generalizable group of patients with fibromyalgia, a randomized, controlled trial evaluated a community-based exercise program in 132 patients with fibromyalgia that included all patients seen in an outpatient rheumatology clinic [119]. The patients were randomly assigned in equal proportions to either graded aerobic exercise or relaxation twice weekly for 12 weeks. The aerobic exercise group was given an individualized program of gradually increasing intensity, as tolerated, of either walking on a treadmill or cycling on an exercise bicycle. By the end of the 12 weeks the patients were doing two sessions of 25 minutes each of exercise at an intensity that made them sweat while allowing them to talk comfortably. The relaxation and flexibility group performed upper and lower limb stretches and practiced relaxation techniques for an hour twice weekly for 12 weeks. Both groups received information about fibromyalgia and were advised that exercise could improve their condition. The primary outcome was the change in self-rated global

impression of improvement. At the end of the intervention, significantly more patients in the exercise arm 24/69 (35%) were much better or very much better compared with the relaxation arm 12/67 (18%). At 12 months follow-up, the benefits were maintained in 26 (38%) and 15 (22%) of the participants, respectively (not significant). Furthermore, significantly more patients in the exercise group experienced a decrease in tender point counts at the 12 months follow-up. Although this study was adequately powered with a diverse group of fibromyalgia patients, involved a sufficient control group, and included a 1 year follow-up, the study was limited by compliance problems in that only 53% of the total group attended over one-third of the classes.

Compliance for exercise programs was addressed in another study that assessed whether a home-based, video-based, low-impact aerobic exercise program would improve physical function and symptoms of fibromyalgia [120]. In addition, the study compared the efficacy of one long exercise bout with two short exercise bouts per training day on physical function, fibromyalgia symptoms, and exercise adherence. A total of 143 women with fibromyalgia were randomly assigned to either a group that used a long bout of exercise, a group that used short bouts of exercise, or a group that performed no exercise. The 16 week, low-impact aerobics, videotaped program consisted of warm-up and cool-down segments and a training portion with rhythmic movements of all major muscle groups of the lower extremities, but minimal involvement of the upper extremities. The long bout of exercise program was to be performed once daily; the training segment progressed from 10 minutes per session to 30 minutes per session by week 9. The short bouts of exercise program was to be performed during two sessions per day separated by at least four hours. The short bouts of exercise training session began at 5 minutes per session and progressed to 15 minutes per session by week 9. Exercise intensity for both programs was modulated through the use of heart rate and rating of perceived exertion. Participants also attended monthly meetings in which they received instruction on how to monitor exercise intensity and to address problems related to the exercise program. The group leader also called each participant every four weeks to provide encouragement and to help with problem solving related to exercise difficulties. Both exercise groups were given an exercise and daily symptoms logbook. The control no-exercise group attended monthly group discussion sessions without educational information and received calls every four weeks for an assessment of their status. They were also asked to record symptoms in a daily log. After 16 weeks, there were no differences between the exercise groups and the no-exercise group for symptoms, disease severity, pain, self-efficacy, or psychological well-being. There were high attrition rates for both exercise groups and minimal changes in fitness levels. The authors concluded that a home-based, video-taped-based, low impact aerobic exercise is not an ideal combination of mode and method for delivery of exercise programs for individuals with fibromyalgia and that a supervised exercise program may be preferable. Furthermore, the fractionation of exercise did not enhance exercise adherence or minimize attrition.

By contrast, a 12 week, home-based, moderate intensity exercise program for fibromyalgia that included 4 sessions with an exercise physiologist who provided an individualized exercise prescription based on the ACSM guidelines for developing and maintaining cardiorespiratory fitness was effective in improving health status, especially for women who were more functionally disabled [121]. Notably, cardiovascular fitness levels did not change for patients, despite improvement in functional ability. However, this study did not include an attention-control group, making it difficult to assess the effects of subject expectancy on the results.

The relationship between cardiovascular fitness and symptom change was explored further in a recent, randomized, controlled, 20 week study comparing aerobic fitness training and stretching exercises in 76 sedentary women with fibromyalgia [122]. Sixty women completed the twenty week trial and were included in the analysis. Unlike most previous exercise studies in fibromyalgia, all patients in this trial were newly diagnosed and had never had previous treatment. In addition, only acetaminophen was allowed as rescue medication during the trial. The aerobic group exercise consisted of walking that was monitored with frequency meters and supervised by a physiotherapist 3 times a week for 45 minutes duration. The group stretching program consisted of 3 sessions a week for 45 minutes duration and included 17 exercises using muscles and joints without increasing heart rate. Although aerobic exercise was significantly superior to stretching in improvement of pain, quality of life and psychological status, there was no association between gains in cardiovascular fitness and these improvements.

Exercise in combination with other interventions

Education in combination with exercise was explored in two recent trials. One study was a 6 and 24 month follow up of participants in a previous study that examined the effects of 6 months of pool exercises combined with a 6 session education program in 69 women with fibromyalgia. The program included 35 minutes of exercise in a temperate pool, supervised by a physical therapist, once a week for 6 months in groups of 6 to 10 patients. Patients were encouraged to modify the exercises individually for pain or fatigue, and the exercise was not designed to elicit a training effect. The education program, which consisted of six one-hour sessions led by a physical therapist, included education about factors contributing to chronic pain, strategies to cope with fibromyalgia symptoms and stress, instruction and practice of relaxation techniques, and encouragement to increase physical activity. Only the 58 patients who completed the trial, including 28 in the treatment group and 30 in the no-

treatment control group, were included in the analysis. The total Fibromyalgia Impact Questionnaire score improved significantly more in the treatment group compared with the control group. However, because the control was a no-treatment group, it is difficult to assess the effect of therapist attention or patient expectancy on the results. Furthermore, it is not possible to determine whether the combination of education and exercise was superior to either intervention alone [123]. In the 6 and 24 month uncontrolled follow-up study, 26 members of the original treatment group were assessed and most reported regular physical activity but only a few continued pool exercises. The patients reported that the symptoms of fibromyalgia, including pain and fatigue, were improved 30 months after the baseline, although the scores still indicated moderate to severe symptoms. Furthermore, the total Fibromyalgia Impact Questionnaire score was not significantly improved compared to baseline [124]. Another study that examined the efficacy of a six week program of supervised pool exercises and education compared to a waiting list control found that the patients in the treatment group had significantly more improvement in quality of life, functional consequences of fibromyalgia, and patient satisfaction compared to the waiting list control group [125]. However, as noted above, limitations in the study design, including the no-treatment control group and the lack of comparison groups of exercise or education alone, make it difficult to determine which elements of the intervention contributed to the encouraging results.

The effects of exercise and education were separately evaluated in a 12 week study of a supervised aerobic exercise program, a self-management education program, and the combination of exercise and education in 152 women with fibromyalgia [126]. The exercise, which was a supervised program that met 3 times a week, for an average duration of 20 to 40 minutes, was based on the ACSM recommendations for maintaining and developing cardiorespiratory fitness in healthy adults, monitored with heart rate and ratings of perceived exertion, and included walking, pool exercise or low impact aerobics. However, patients were instructed to begin at a comfortable level and to strive to increase the intensity and duration to meet the ACSM guidelines. The education group, based on principles of self-management, met once a week for one-and-a-half to two hours per session. A control group was given written instructions for basic stretches and general coping strategies, and they were contacted once or twice to ensure that they were completing a logbook that documented the course of fibromyalgia and weekly goals (also given to treatment groups) and answer any questions about their condition. Only when compliance was taken into account did any significant differences arise in the groups. For patients who complied with the protocol (only about half of the total group), the combination of supervised exercise and group education improved self-efficacy for coping with some symptoms compared with the control group, although this significant difference was lost at the six month follow-up evaluation. The high drop out rate indicated that patients with fibromyalgia may have difficulty complying with treatments that involve exercise and behavior modification.

Muscle strengthening exercises

Two recent studies evaluated the effectiveness of muscle strength training in women with fibromyalgia. The first study of 68 women compared a 12 week, twice weekly 60 minute exercise program consisting of either muscle strengthening or stretching [127]. The muscle strengthening group received a supervised, classroom based, progressive non-aerobic training program that minimized eccentric work. The control flexibility training group received a classroom-based supervised program with stretching that targeted the same muscle groups as the strengthening group. Both groups experienced increased strength and flexibility, but there were no significant differences between the treatment and control groups at the end of testing in the 56 patients (28 in each group) who completed the study. Another study examined the effect of a 12 week, twice weekly, 30 minute, strength training program that worked the major muscle groups in 29 women with fibromyalgia [128]. Although there were significant improvements in strength and upper body functionality compared to a waiting list control, tender point sensitivity and fibromyalgia impact did not change. The results were also limited by the small sample size and high attrition rate in the strength group (47% did not complete the study).

Maintenance of exercise

Long-term adherence with exercise programs after completion of studies has been consistently low in the studies of fibromyalgia. Recent studies have attempted to identify predictors of exercise maintenance in patients with fibromyalgia in order to address the problem of adherence. A follow-up study of 39 women with fibromyalgia who had been randomized to an individualized, home-based exercise program of stretching and aerobics found that worse maintenance of stretching at 3 months was associated with high stress at baseline and increase in stress during the treatment. Disability at baseline, increases in barriers to exercise and upper-body pain during treatment were associated with worse maintenance of aerobic exercise. Therefore, maintenance of exercise in this group of women with fibromyalgia was contingent on being able to deal with stress, pain, barriers to exercise, and disability [129]. Another study of 444 patients with fibromyalgia found that having a higher exercise self-efficacy (i.e., confidence in the ability to exercise under adverse conditions), lower depression, and larger social support network predicted continued exercise. Interventions that address exercise self-efficacy, depression, and social support are needed to improve exercise participation [130].

Cognitive-behavioral therapy

The results of the aforementioned systematic reviews suggest that cognitive behavioral therapy (CBT) was no

better than educational or attention controls in improving fibromyalgia. Since 2000, there have been other randomized, controlled studies that further explored the possible use of CBT in fibromyalgia. In the first study, 145 patients with fibromyalgia were randomized to either standard medical care that included pharmacological treatment and suggestions for aerobic fitness or the same standard medical treatment and the addition of six group cognitive behavioral therapy sessions over a four week period that were specifically aimed at improving physical function [131]. The CBT focused on instruction and practice of nine skills, including the relaxation response, visual imagery techniques, pacing skills, pleasant activity scheduling, communication and assertiveness training, cognitive restructuring principles, stress management, and problem solving. Patients in both groups were contacted monthly by phone to track health care use and CBT skills in those assigned to CBT. Significantly more (25%) of the 62 patients who completed the CBT protocol achieved a clinically meaningful and sustained improvement in physical functional status as measured by the physical component summary score of the SF-36 compared with the control group (12% of 60 completers). However, there were no significant differences between the control and CBT groups in change in sensory or affective pain scores as measured by the McGill Pain Questionnaire. Although the study was limited by the lack of monitoring of medication use in the two groups, the lack of an attention-placebo group, and the low level of adherence to CBT treatment (only 15% of patients consistently reached their stated monthly CBT goals), the study provided some evidence that targeted, brief, group CBT, in conjunction with standard medical care, might improve physical function in some patients with fibromyalgia.

A coping skills training (CST) intervention for adolescents with fibromyalgia was developed to include developmentally appropriate explanation and training guidelines as well as a parent training component [132]. The content, similar to adult CBT, included relaxation training, distraction techniques, calming statements, activity pacing, pleasant activity scheduling, and problem solving. Parents were given suggestions for encouraging the adolescent to manage their pain independently, maintain their normal day to day routines and guidance for reducing avoidance of school or social activities. In an 8 week study of this intervention added to standard medical care that was stabilized for at least 4 weeks prior to enrollment, 30 adolescents with fibromyalgia were randomly assigned to either CST or a self-monitoring condition in which patients monitored daily symptoms without instruction about behavioral change. After 8 weeks, patients were crossed over into the opposite treatment arm for an additional 8 weeks. At the end of 8 and 16 weeks, there were no significant differences in function disability or depressive symptoms between the CST and self-monitoring groups. However, the CST group showed significantly greater improvement than the control group for increase in pain-coping efficacy. These results are consistent with adult studies of CBT in which there have been inconsistent effects of CBT on pain reduction, although there have been improvements in function and the perception of control over pain.

Finally, CBT developed for the treatment of insomnia in patients with fibromyalgia was tested in 47 patients who were randomized to receive 6 weekly sessions of CBT, a control behavioral therapy (sleep hygiene education), or usual care (all patients continued any ongoing medical care) [133]. Patients receiving CBT achieved about 50% reduction in nocturnal wake time, compared with the sleep hygiene education group (20%) and the usual care group (3.5%). Both CBT and the sleep hygiene education showed benefits over usual care for reducing global insomnia symptoms, and for improving mental well-being and mood. However, only the sleep hygiene group reported significant improvement in pain compared with the usual care group. Therefore, sleep hygiene education and CBT may benefit fibromyalgia patients with chronic insomnia, but further study is needed with larger samples and greater experimental control through standardization of other medical treatment [133].

Other non-pharmacological therapies

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 multimodal mind-body intervention or a control education support group. At the end of 8, 16, and 24 weeks, there were no significant differences between groups in change in pain, tenderness, walking, mood, or impact of fibromyalgia [134].

Another study evaluated social support as a primary intervention in patients with fibromyalgia [135]. In this study, 600 patients with fibromyalgia were randomized to either a social support group, a social support and education group, or a no-treatment control group that participated in assessment interviews only. The experimental groups met for 10, 2-hour weekly meetings followed by 10 monthly meetings. At the end of one year, there were no significant differences in reductions of health care costs for the groups. There were also no significant differences between groups in improvement in depression, self-efficacy, fibromyalgia impact, or fibromyalgia knowledge. The social support and education group reported significantly less helplessness compared with the other groups. Notably, attendance rates for the interventions were low, with experimental groups attending only about 40% of all meetings.

Complementary and alternative medicine

A 2003 review of studies conducted between 1975 and 2002 evaluating the use of complementary and alternative medicine in fibromyalgia concluded that, across the five classifications of complementary and alternative medicine, including alternative medical systems (e.g., acupuncture, homeopathy), biological-based therapy (e.g., nutritional

supplements), dietary modifications, energy therapies (e.g., magnetic therapy), and manipulative and body-based systems (e.g., chiropractic care, massage), and mind-body interventions (e.g., relaxation, biofeedback, and hypnotherapy), no single modality was consistently effective [136]. Acupuncture had the strongest evidence for effectiveness while there was moderate evidence supporting the use of magnesium supplementation, S-adenosyl-L-methionine, and massage therapy.

However, two recent, randomized, controlled trials found that acupuncture was no better than control interventions in reduction of pain associated with fibromyalgia. The first study randomized 114 patients with fibromyalgia to either traditional needle placement with or without needle stimulation or to control groups of non-traditional needle location with or without needle stimulation [137]. All patients received a total of 18 treatments beginning once weekly, followed by twice weekly, and finally three times weekly. Clinically meaningful treatment response, defined by a 30% improvement in pain, occurred in 25% to 35% of all patients; there were no significant differences between groups on improvement in pain. These results suggest that there are no specific effects of acupuncture on pain reduction in patients with fibromyalgia.

A second study of acupuncture in fibromyalgia randomized 100 patients with fibromyalgia to 12 weeks of twice weekly acupuncture that was specifically designed to treat fibromyalgia, or 1 of 3 sham acupuncture treatments: acupuncture for an unrelated condition; needle insertion at non-acupoint locations; or non-insertive simulated acupuncture using a toothpick to mimic needle insertion [138]. The mean pain ratings among patients receiving acupuncture did not differ from that in the pooled sham acupuncture group. Therefore, consistent with the previous study, acupuncture was no better than sham treatment at relieving pain in fibromyalgia.

Limitations of non-pharmacological treatment studies in fibromyalgia

Non-pharmacological treatment studies of fibromyalgia are limited for several reasons [111,118,139]. First, there was variability in accounting or controlling for other interventions, particularly pharmacological treatment, making it difficult to isolate the effects of the non-pharmacological treatment on fibromyalgia. Second, there was also variability in the treatment intensity, duration, and frequency, making it difficult to identify the best treatment levels for patients with fibromyalgia. Third, diversity of treatment modalities limited comparisons between studies. For example, training modalities in exercise studies have included cycling, pool exercise, walking, muscle strength exercises, stretching, and others. The diversity of treatment elements was also evident in CBT studies, which varied in the skill sets that were taught and format of treatment (e.g., group or individual). Fourth, patient selection criteria in exercise studies have not consistently taken into account the baseline level of physical activity or fitness and the potential impact of these variables on the results. In addition, few studies identified comorbid mood or anxiety disorders, which may have affected the patients' response to treatment. Notably, patients with severe depression may not respond well to some non-pharmacological treatments, such as education and physical training [104]. The studies have not yet clarified which subgroups of patients with fibromyalgia might benefit from a specific mode of non-pharmacological treatment. Fifth, many studies had small sample sizes and high attrition rates in the treatment groups, making it difficult to identify benefits of the treatment. Indeed, adherence to CBT skills over an extended period of time has been problematic in studies of fibromyalgia [131]. Adherence with exercise programs, especially after the completion of the intervention, was also generally low. Furthermore, there was some discrepancy in several exercise studies between the prescribed exercise program and the actual performed exercise because of problems with patient tolerability. Furthermore, there was inconsistent reporting of specific adverse events from exercise such as exacerbation of pain. Sixth, several studies had no-treatment controls, which made it difficult to distinguish the specific effects of the treatment from the non-specific effects of attention or group experience or the role of subject expectancy on the results. Indeed, CBT studies that used attention or education controls found that CBT-supported skills added little to the outcome of the studies [105,108]. Seventh, although some studies followed patients for more than one year after the intervention, most studies focused on short-term benefits of treatment in fibromyalgia, which is a chronic disorder. Eighth, as in pharmacological clinical trials of fibromyalgia, there was a lack of consensus about important symptom domains and outcome measures, making comparisons between studies difficult. Furthermore, it was unclear from some studies whether significant changes were actually clinically meaningful. In exercise studies, there were also multiple approaches to the assessment of aerobic capacity and performance. Furthermore, other health outcomes that might be affected by exercise, such as blood pressure, weight, or metabolic indicators have not been consistently tracked in exercise studies.

Summary of non-pharmacological trials in fibromyalgia

Although more research is needed to address the aforementioned limitations, the available evidence supports the conclusions summarized in Tables 3 and 4.

Conclusions and recommendations for the treatment of fibromyalgia

The rapid growth of trials in fibromyalgia in recent years has resulted in new, evidence-based approaches to treatment. The American Pain Society (APS) developed guidelines for the optimal treatment of fibromyalgia, a summary of which was published in 2004 [140]. With the subsequent publication of new treatment data reviewed above, some updates to these guidelines may be necessary. The first recommended steps of the APS guidelines, which included

Table 3

Summary of findings from exercise studies in fibromyalgia

1. Among exercise interventions, the evidence is most supportive of aerobic exercise in the treatment of fibromyalgia.
2. Aerobic exercise does not consistently improve major symptom domains associated with fibromyalgia, including pain, fatigue, sleep disturbance, or psychological symptoms.
3. Patients who tolerate and comply with a high level of aerobic exercise intensity that meets the American College of Sport Medicine guidelines for cardiovascular endurance demonstrate improvements in cardiovascular fitness, pain pressure thresholds, global well being, and self-reported physical function.
4. Many patients do not tolerate high intensity aerobic exercise with reports of increased pain following this intervention.
5. Low to moderate intensity, graded aerobic exercise (e.g., walking or cycling on a stationary bicycle) may lead to improvements in global assessments, tender points, and quality of life.
6. Improvements in fibromyalgia with exercise may occur without change in cardiovascular fitness levels, and the mechanisms by which exercise improves fibromyalgia are unclear.
7. Although optimal intensity, duration, and frequency of exercise have not clearly been established, studies to date suggest that, for many patients, a gradual increase, as tolerated, in exercise to reach a goal of 30 to 60 minutes of low-moderate intensity aerobic exercise (e.g., walking, pool exercises, stationary bike) at least 2 to 3 times a week for more than 10 weeks appears to be associated with positive short-term benefits. Ongoing exercise is associated with maintenance of improvements in fibromyalgia.
8. Supervised, group exercise interventions may be preferable to home-based exercise regimens, especially at the initiation of an exercise program.
9. Adherence to exercise is problematic for many patients with fibromyalgia. Factors that contribute to low adherence to exercise include 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.

Table 4

Summary of findings from cognitive and behavioral therapies, education, and complementary and alternative medicine

1. Cognitive skills training in general has not shown more benefit than group education or social support in improving fibromyalgia.
2. CBT that is targeted to specific outcomes such as function, sleep, or coping may be beneficial for fibromyalgia.
3. Group education with social support can reduce pain behaviors and feelings of helplessness.
4. Combining education with exercise can improve a sense of control over symptoms and reduce the impact of fibromyalgia.
5. As in exercise studies, adherence to psychological and education programs is problematic, emphasizing the need to identify subgroups of patients who might benefit from these programs. For example, patients with severe depression may not be candidates for this approach until the depression is treated.
6. Traditional acupuncture did not reduce pain associated with fibromyalgia more than sham interventions.
7. Convincing evidence does not exist for complementary and alternative medicine in the treatment of fibromyalgia.

confirmation of the diagnosis, education about fibromyalgia, and evaluation and treatment of comorbid disorders, such as mood and sleep disturbances, are still appropriate. However, the subsequent steps do not take the presence of comorbidity into account when recommending treatment for fibromyalgia. Recent evidence suggests that comorbidity and the presence and severity of symptom domains should be an important consideration when selecting initial treatments for fibromyalgia. In the APS guidelines, the first recommended pharmacological treatment is a trial of low dose tricyclic antidepressants or cyclobenzaprine. However, these medications are often poorly tolerated and, at low doses, are not effective for the treatment of mood or anxiety disorders, two common comorbid conditions. An alternative approach would be to recommend one of the new selective SNRIs as a first line treatment for pain in patients with or without depression or anxiety. One caveat related to the use of SNRIs or other medications with antidepressant effects in fibromyalgia is that they should not be used as monotherapy in patients with bipolar disorder, another frequently reported comorbid condition [141], because of the risk of increased mood instability. An alternative first line medication approach is an alpha 2 delta ligand, which may be particularly helpful in patients with prominent sleep disturbances or anxiety. For those patients who do not respond completely to monotherapy with either an SNRI or an alpha 2 delta ligand, a combination of these medications should be considered, although studies of this and other combination pharmacotherapy is still very limited [142].

In the APS guidelines, exercise was recommended early in treatment of fibromyalgia. However, recent studies indicate that the compliance with exercise is quite low and influenced by factors such as pain severity, stress, disability, depression, self-efficacy, social support, and barriers to exercise. Therefore, these issues should be addressed before recommending exercise. Studies suggest that exercise does not consistently improve major symptom domains such as pain, fatigue, sleep disturbance, or psychological symptoms. Patients with these symptoms may not be able to tolerate exercise and may in fact experience a worsening of pain with exercise. Consequently, these symptoms should be treated with medication (or other therapy as described below) first to increase the likelihood that the patients will be able to participate in exercise and benefit from the positive impact of exercise on cardiovascular fitness, pain pressure thresholds, global well being, and self-reported physical function. The patient's level of fitness should also be considered when suggesting specific exercises. For most patients, a gradual increase, as tolerated, in exercise to reach a goal of 30 to 60 minutes of low-moderate intensity aerobic exercise (e.g., walking, pool exercises, stationary bike) at least 2 to 3 times a week is best tolerated. Furthermore, studies suggest that supervised, group exercise interventions may be preferable to home-based exercise regimens, especially at the initiation of an exercise program.

Table 5

Stepwise treatment of fibromyalgia

Step 1

Confirm diagnosis

- Identify important symptom domains and their severity (e.g., pain, sleep disturbance, fatigue) and level of function
- Evaluate for comorbid medical and psychiatric disorders (e.g., sleep apnea, osteoarthritis, depressive or anxiety disorders); may require referral to specialist
- Assess psychosocial stressors, level of fitness, barriers to treatment
- Provide education about fibromyalgia (individual or group)
- Review treatment options

Step 2

Recommend treatment based on the results of the individual evaluation

- For patients with moderate to severe pain, trial with medication as a first line approach:
  - With or without lifetime depression or anxiety: trial of selective serotonin and norepinephrine reuptake inhibitor (not recommended as monotherapy for patients with comorbid bipolar disorder)
  - Prominent sleep disturbance or anxiety: trial of alpha 2 delta ligand
  - Partial response to monotherapy with either selective serotonin and norepinephrine reuptake inhibitor or alpha 2 delta ligand: trial of combination of these agents
  - Consider other medications if no response to the above approach (e.g., selective serotonin reuptake inhibitor (SSRI); tricyclic antidepressant (TCA); combination of SSRI with low dose TCA (watch for drug interaction between SSRI and TCA); combination of SSRI and alpha 2 delta ligand)
  - Avoid drugs with high likelihood of abuse or dependence

Provide any additional treatment for comorbid conditions (e.g., non-steroidal anti-inflammatory drugs for osteoarthritis, continuous positive airway pressure for sleep apnea)

Step 3

Adjunctive CBT for patients with prominent psychosocial stressors, or difficulty coping or functioning

Exercise prescribed according to fitness level (e.g., goal of 30 to 60 minutes of low-moderate intensity aerobic exercise (e.g., walking, pool exercises, stationary bike) at least 2 to 3 times a week). Encourage participation in supervised or group exercise.

Some patients who do not respond fully to medication alone or have prominent psychosocial problems might benefit from the addition of CBT or group education as an adjunct to their medical treatment. Group education with social support may help to reduce pain behaviors, feelings of helplessness, improve a sense of control over symptoms, and reduce the impact of fibromyalgia. CBT that addresses disability, function, or self-efficacy might also be helpful in overcoming some of the barriers to exercise, improving overall function, and regaining a sense of control in their lives. Combinations of exercise and education or CBT may be an option for patients who do not respond to a single approach, but more study of combination therapies is needed.

Table 5 summarizes the new approach to the stepwise treatment of fibromyalgia.

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Other articles in this series can be found at
http://arthritis-research.com/articles/review-series.asp?series=ar_fibromyalgia

Competing interests

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