Update on Fibromyalgia Therapy
Micha Abeles, MD,a Bruce M. Solitar, MD,b,c Michael H. Pillinger, MD,b,c Aryeh M. Abelesa,b,c

aDivision of Rheumatology, Department of Medicine, The University of Connecticut School of Medicine, Farmington; bDivision of Rheumatology, Department of Medicine, New York University School of Medicine/NYU Hospital for Joint Diseases, New York; cNew York Harbor VA Healthcare System, New York Campus; New York.

ABSTRACT
Primary fibromyalgia, a poorly-understood chronic pain syndrome, is characterized by widespread musculoskeletal pain, nonrestorative sleep, fatigue, psychological distress, and specific regions of localized tenderness, all in the absence of otherwise apparent organic disease. While the etiology of fibromyalgia is unclear, accumulating data suggest that disordered central pain processing likely plays a role in its pathogenesis. Although various pharmacological treatments have been studied and espoused for treating fibromyalgia, no single drug or group of drugs has proved to be particularly useful in treating fibromyalgia patients as a whole, and only one drug has earned U.S. Food and Drug Administration approval for treating the syndrome in the United States. This review critically and systematically evaluates clinical investigations of medicinal and nonmedicinal treatments for fibromyalgia dating from 1970 to 2007.

© 2008 Elsevier Inc. All rights reserved.

KEYWORDS: Complementary therapy; Fibromyalgia; Fibrositis; Pharmacotherapy

Fibromyalgia is characterized by widespread musculoskeletal pain, nonrestorative sleep, fatigue, psychological distress, and specific regions of localized tenderness, all in the absence of otherwise apparent organic disease. The etiology of fibromyalgia is unclear, although accumulating data suggest that disordered central pain processing plays a role in its pathogenesis. While numerous controversies surround the cause and nature of fibromyalgia, few clinicians would disagree that fibromyalgia patients are in need of effective treatment.

Despite the various pharmacotherapies studied and espoused for treating fibromyalgia, only one drug has earned US Food and Drug Administration (FDA) approval for treating the syndrome (pregabalin, in June 2007). Nevertheless, scores of drugs are used for the treatment of fibromyalgia, with varying success. One 5-year prospective survey of 214 patients with fibromyalgia from 114 rheumatology practices revealed a total of 74 different medications being used for treatment, suggesting that no specific drug or class of drugs is particularly useful for fibromyalgia patients as a group.

Given the controversial nature of fibromyalgia, it is not surprising that physicians continue to debate which treatments are useful. While several recent reviews conclude that there is “strong evidence” to support the use of a variety of medications and nonpharmacologic approaches to fibromyalgia, and that “symptoms can be controlled to a moderate degree with various treatments,” a long-term, multicenter outcomes study has refuted these conclusions, noting that despite treatment, individuals followed for up to 7 years demonstrated no change in symptoms. That study might itself have been skewed, because its data were culled from tertiary care rather than a community setting, and community fibromyalgia patients appear to have better prognoses than those seen in specialty clinics. However, as both the fibromyalgia criteria and many therapeutic trials to date have been based on patients in tertiary centers, we are left with conflicting data sets on the value of fibromyalgia treatment. In addition, many therapeutic trials for fibromyalgia have been small or not well controlled, with results that can be of limited use.

One difficulty of assessing therapeutic options for an individual patient is that many clinical trials have not accounted for the heterogeneity of fibromyalgia. The presence of co-morbidities, such as depression, may independently predict a poor response to treatment. In addition, nondrug treatment approaches, considered by many physi-
cians to be among the most useful fibromyalgia treatments, are frequently discordant with patient preferences.11\(^{11}\) Adding to the confusion of how to appropriately manage the syndrome, the Outcome Measures in Rheumatology 7 workshop concluded that when it comes to fibromyalgia therapy, there is “little standardization of an approach to trials or of outcome measures used.”12\(^{12}\) In this article, we attempt to create a modicum of clarity in the current landscape, by providing a critical review of the evidence for various treatments of fibromyalgia.

The authors reviewed the treatments of fibromyalgia by searching the PubMed database for English-language reports of clinical trials and meta-analyses addressing fibromyalgia treatment, published between 1970 and 2007. The main search terms were fibromyalgia and fibrositis, in combination with treatment, clinical trials, and pharmacotherapy. Secondary search terms included exercise, alternative therapy, and cognitive-behavioral therapy. These search terms resulted in the identification of 409 reports for possible inclusion. After an initial triage by one of the authors (AMA), selecting for studies conducted as randomized control trials investigating specific interventions and their effects on improved outcomes, 131 articles remained and were scored semiquantitatively by each of the 4 authors. Each author scored each report on a scale of 0-3 in 2 overarching domains: 1) the quality of methodology (authors were instructed to consider whether studies were randomized double-blind control trial vs randomized open label control trials, large vs small enrollment, independent vs industry-supported, length of study, and appropriateness of outcomes measures); and 2) the relevance of the study to the illness of fibromyalgia (authors were instructed to consider parameters such as the degree of efficacy reported, degree to which the drug is currently used in practice, degree to which the study was unique in examining a particular agent, and level of attention that the study has subsequently received among practitioners). The maximum score any article could receive from a single evaluator was 6, and the maximum total score any article could receive from all authors combined was 24. All manuscripts receiving total scores of >16 were considered for inclusion by the authors in consensus discussions; a total of 55 manuscripts were discussed. Of these, 10 additional manuscripts were excluded, based on a high degree of author discrepancy with regard to study quality or relevance. The remaining 45 research articles were included in the analysis. Our review was not funded.

**PHARMACOLOGICAL TREATMENTS**

### Tricyclic Agents

The tricyclic antidepressants were the first drugs to be intensively studied in fibromyalgia. Tricyclic antidepressants increase synaptic concentrations of both serotonin and norepinephrine in the central nervous system; increased availability of these neurotransmitters reduces pain signaling. Amitriptyline is the tricyclic antidepressant most extensively studied. Short-term studies indicate benefit in up to one third of patients,\(^{13-15}\) if effective, benefit is usually evident within the first 2 weeks of therapy.16 Long-term studies have been less promising, however, and prospective studies have not shown any prolonged beneficial effect.17 In one study, initial improvement noted at 6 to 12 weeks was lost at 26 weeks.17 When employed, amitriptyline dosing should start at 10 mg, because anticholinergic side effects are more likely at higher doses. Studies suggest that increasing the dose to 25-50 mg can be effective in short-term trials.13,14\(^{14}\) The tricyclic antidepressant nortriptyline has a better side-effect profile than amitriptyline and also might be useful, although it requires slightly higher dosing.18

Cyclobenzaprine shares its tricyclic structure with amitriptyline and nortriptyline but does not function as an antidepressant. Instead, cyclobenzaprine acts at the brain stem to induce skeletal muscle relaxation.\(^ {19}\) The idea that muscle spasm may play a role in fibromyalgia pain (despite electromyographic studies showing no evidence of spasm) led to investigations of cyclobenzaprine.\(^ {20,22}\) Short-term (12-week) studies suggest that 10-40 mg per day of cyclobenzaprine reduces fibromyalgia pain and sleep disturbance,\(^ {20,22}\) although in one cross-over study, there was no effect on pain.\(^ {23}\) Moreover, long-term studies have not shown any advantage of cyclobenzaprine over placebo.17 A meta-analysis of cyclobenzaprine treatment of fibromyalgia found only 5 articles of adequate quality to include in the study,\(^ {24}\) and concluded that some short-term benefit may result with cyclobenzaprine use, but that the number needed to treat in order for one patient to experience a benefit was 5. Adding to the difficulty of interpreting cyclobenzaprine studies is the high incidence of side effects (85%), which makes blinding difficult.

<table>
<thead>
<tr>
<th>CLINICAL SIGNIFICANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Fibromyalgia is a heterogeneous pain syndrome of unclear etiology. Review of the literature suggests no single therapy is broadly efficacious.</td>
</tr>
<tr>
<td>- Medications showing some benefit in the treatment of fibromyalgia include antidepressants and voltage-gated Ca++ channel blockers.</td>
</tr>
<tr>
<td>- Evidence suggests that some complementary therapies also might be beneficial.</td>
</tr>
<tr>
<td>- Clinical experience suggests multimodal therapy provides greater benefit than individual interventions, but this hypothesis has yet to be rigorously tested.</td>
</tr>
</tbody>
</table>
Newer Anti-Depressants

Selective serotonin reuptake inhibitors (SSRIs) also might theoretically be useful because of their ability to increase serotonin availability at the neuronal synapse. While initial reports found no improvement in pain symptoms with fluoxetine,25 follow-up studies suggested that this SSRI was as effective as amitriptyline. The 2 medications combined showed greater efficacy than either alone.26 A more recent placebo-controlled 12-week study using a more flexible fluoxetine-dosing regimen (up to 80 mg/day) demonstrated a reduction in pain regardless of effect on depression.27 In addition, both fluoxetine and amitriptyline appear to improve anaerobic, but not aerobic, performance among female fibromyalgia patients.26 Although other SSRIs are regularly used in clinical practice, studies of these various drugs have been limited, lacking, or inconclusive.29,30 For instance, a recent 12-week study investigating the efficacy of extended-release paroxetine (doses ranging from 12.5 mg to 62.5 mg daily) demonstrated that while paroxetine improved Fibromyalgia Impact Questionnaire (FIQ) scores vs placebo, it did not improve pain scores.30 Serotonin-norepinephrine reuptake inhibitors (SNRIs, or dual-reuptake inhibitors) may have greater antinociceptive properties than pure SSRIs. Short-term (12 weeks) studies of SNRIs indicate benefit to their use.31 In one double-blind trial comparing duloxetine with placebo, patients receiving duloxetine had significant overall improvement in their FIQ scores, although not on the FIQ subscales of pain or fatigue. Secondary outcome measures, including Brief Pain Inventory scores, also showed statistically significant improvements. Common side effects included insomnia, dry mouth, constipation, increase in heart rate, and elevated aspartate transaminase, creatine phosphokinase, and cholesterol. Effective doses ranged from 60 mg daily to 60 mg twice a day.31

Milnacipran (unavailable in the US), a SNRI that is somewhat selective for norepinephrine reuptake inhibition, has also been studied. A 12-week study found that milnacipran significantly improved both global assessment and FIQ pain visual analogue scale scores. Despite randomization, mood disorders were much more common in the placebo group. Side effects were similar to those seen with duloxetine. Milnacipran 100 mg twice daily was more effective than at 200 mg once a day.32

Other Central Nervous System-Acting Agents

Pregabalin was originally FDA-approved for diabetic neuropathy and postherpetic neuralgia, but in June 2007 also was approved for the treatment of fibromyalgia. It disrupts neuronal signaling by binding to the α-2δ subunit of voltage-gated calcium channels in the central nervous system. An 8-week double-blind placebo-controlled trial studied 3 fixed doses of pregabalin (150 mg/day, 300 mg/day, and 450 mg/day).33 The highest dose (450 mg/day) was significantly more effective than placebo in reducing pain score (48.4% vs 27.1% response, respectively) at 8 weeks. Pregabalin also was associated with decreased fatigue, improved sleep and health-related quality of life. Common side effects included dizziness (49.2%) and somnolence (28%). No long-term data are yet available, although an as-yet unpublished study demonstrated that, over 6 months, pregabalin retained its effectiveness in pregabalin-responders. The study was unusual in that it randomized patients who had been pregabalin-responders (>50% improvement on visual analogue scale) in an open-label phase to receive either pregabalin or placebo in the double-blinded portion of the study; the primary endpoint of the double-blinded study was time to loss of efficacy. By study’s end, 61% of placebo patients had lost their therapeutic response, compared with 32% of those who continued with pregabalin.34

Gabapentin is FDA-approved as an anticonvulsant and for postherpetic neuralgia, and is frequently prescribed for diabetic neuropathy and other chronic pain conditions. Although structurally related to gamma-aminobutyric acid, gabapentin does not, in fact, bind to gamma-aminobutyric acid receptors, but instead appears to inhibit the same voltage-gated calcium channels as pregabalin. In a 12-week randomized controlled trial, gabapentin was statistically more effective than placebo in improving pain scores (51% vs 31%, clinically significant improvement defined as >30% improvement in pain severity), sleep quality, and fibromyalgia impact questionnaire scores. The dose range was between 1200 and 2400 mg per day, with an average of 1800 mg. No serious adverse events were noted in the gabapentin-treated groups. The most common side effects were dizziness, sedation, and lightheadedness.35

Anti-Inflammatories

While the use of nonsteroidal anti-inflammatory drugs for fibromyalgia is a fairly common practice,5 little objective evidence is available upon which to assess the efficacy of these agents. In one double-blind, placebo-controlled trial, ibuprofen was no better than placebo.36 Similarly, naproxen led to minor but insignificant improvement in symptoms.14 One trial of corticosteroid use in fibromyalgia found steroids to be inefficacious.37

Pure Analgesics

Despite their employment in clinical practice, no short- or long-term data are available to inform the use of pure opiates in fibromyalgia. In contrast, some studies support the use of the mixed opiate agonist tramadol. Tramadol is a centrally acting synthetic opioid analgesic that binds to the μ-opioid receptors and also weakly inhibits norepinephrine and serotonin reuptake.38 In a 91-day, multicenter, randomized controlled trial evaluating tramadol plus acetaminophen in fibromyalgia, the primary endpoint was cumulative time to discontinuation of drug. A large number of dropouts occurred in both treatment arms, but fewer in the active treatment group (48% in the active treatment vs 62% in the placebo arm). Tramadol/acetaminophen combination-treated patients experienced reduced pain, as measured on a
visual analogue scale, compared with patients in a placebo arm, but it is questionable whether the reported reduction was clinically significant. However, another tramadol/acetaminophen study investigating health-related quality-of-life measures in moderate-to-severe fibromyalgia also showed improvement in the active treatment group, compared with controls.

**Miscellaneous Oral Medications**

Despite its continuing prominence on Internet websites, guaifenesin was no more effective than placebo in a formal study. A reported benefit of combining alprazolam and ibuprofen was based on a response in 7 of 15 patients using this combination, compared with 4 of 14 patients responding to placebo (in a study underwritten by the manufacturer of those products); no large studies of benzodiazepines have been performed. The hypnotic zolpidem improved sleep but not pain in fibromyalgia patients. Studies of malic acid and chloropramine have a number of shortcomings, including small subject numbers and lack of confirmatory studies.

**Nonpharmacological Interventions**

A recent review by Goldenberg suggested “strong evidence for efficacy” for a variety of nonmedicinal interventions, including cardiovascular exercise, cognitive behavioral therapy, patient education in group format, and multidisciplinary therapy, as well as “moderate evidence for efficacy” for a number of other adjunctive treatments. In contrast to the Goldenberg review, 2 other systematic reviews came to less sanguine conclusions about the value of nonpharmacological interventions. Karjalainen et al analyzed studies of multidisciplinary rehabilitation for fibromyalgia. Seven studies met the authors’ inclusion criteria, although none were considered “high quality.” Karjalainen concluded that there was little evidence for the effectiveness of a multidisciplinary approach but that high-quality prospective trials are needed. Sim and Adams reviewed all randomized controlled trials of nonpharmacologic fibromyalgia interventions from 1980 to 2000. Most had small sample size, leading to low statistical power and a high probability of type II error. The authors concluded that most interventions showed marginal efficacy but that, owing to the poor quality of the studies, no meaningful conclusions could be derived. Nevertheless, the authors felt that combination approaches seemed to result in better outcomes than single-approach interventions.

Presently, aerobic exercise is widely recommended for fibromyalgia, based on the belief that patients with fibromyalgia are not aerobically fit, and that lack of aerobic fitness contributes to pain. The concept that fibromyalgia and poor physical fitness are intertwined was originally based on the resistance of 3 aerobically fit male volunteers to developing fibromyalgia-like symptoms despite stage IV sleep deprivation. From this finding, a hypothesis evolved asserting that sedentary lifestyle results in muscle deconditioning and a greater risk of muscle microtrauma, in turn leading to increased pain. The hypothesis was tested in a study that compared a flexibility exercise program with cardiovascular training; no significant differences were found between groups with regard to pain intensity scores. Other studies also suggest that physical training does not significantly contribute to the reduction of pain, improvement of psychological symptoms, or functional disability. On the other hand, a combined cardiovascular fitness training and flexibility program provided significantly greater improvement than a psychologically based muscle relaxation technique. Recent studies indicate that isometric exercise reduces mechanical pain thresholds (ie, induces pain) in fibromyalgia patients, in contradistinction to normal controls. Some clinicians suggest that this observation reflects a “transition problem”—that is, fibromyalgia patients may not benefit from exercise unless they can first be brought to a level of minimal exercise capacity without exacerbating their symptoms. Water-based exercise is better tolerated by fibromyalgia patients and may therefore be of particular benefit as an initial regimen. Short-term studies of aquatherapy with small numbers of subjects note improvement in quality-of-life measures and pain.

In one study of behavioral insomnia therapy for fibromyalgia patients, 8 of 14 participants demonstrated sleep improvement. The effect on pain was modest.

**Complementary and Alternative Therapies for Fibromyalgia**

Assessment of complementary and alternative approaches to fibromyalgia treatment is limited by a paucity of clinical trials, with the few completed trials sharing the drawbacks that afflict other fibromyalgia studies.

Meditation-based stress reduction showed benefit in one study that lacked a control group. Dehydroepiandrosterone provided no benefit in pain, fatigue, mood, or functional abilities. Melatonin has not been studied in a blinded fashion.

Acupuncture is commonly tried by fibromyalgia patients, but the evidence for acupuncture in fibromyalgia is conflicting. One randomized sham-controlled study demonstrated no subjective improvement in pain between acupuncture and sham acupuncture. Acupuncture (vs sham acupuncture) had significantly greater improvements in FIQ scores at 1 and 7 months after treatment. An earlier study suggested that electroacupuncture was more effective than sham therapy for fibromyalgia, but the study may not have been adequately blinded.

The alternative therapies purposed to treat fibromyalgia are numerous, unregulated, unstudied, and easily found in advertisements in lay fibromyalgia publications. Examples abound in a recent issue of Fibromyalgia Aware magazine. An advertisement for infrared therapy, for instance, makes various claims for relief of pain and stiffness, improved energy, and a better sense of well-being. Another ad
promotes a mattress claiming to relieve “the pressure points” that will allow for “REM sleep.” Yet another advertisement purports a simple solution for the abnormal foot structure that, the ad claims, perpetuates fibromyalgia pain. In an advertisement for bottled water, aches, pains, and even fatigue are apparently magnified by the slightest hint of dehydration. A brand of moistened towelette claims it has been “clinically shown to relieve pain associated with fibromyalgia.” While such alternative therapies can range from sensible to bizarre, none have been adequately validated.

**APPROACH TO THE PATIENT WITH FIBROMYALGIA: PRACTICE-BASED EVIDENCE IN THE ABSENCE OF EVIDENCE-BASED PRACTICE**

Despite a paucity of solid data in support of many fibromyalgia therapies, the physician caring for a fibromyalgia patient is confronted with an individual whose discomfort is significant, and whose need for melioration is unquestionable. A number of treatments have shown clinical benefit when compared with placebo (see Table), although fre-

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Dose</th>
<th>Positive Effect(s) in Fibromyalgia</th>
<th>Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Increases synaptic availability of both serotonin and norepinephrine in the central nervous system by decreasing their uptake</td>
<td>10 mg qhs/25-50 mg qhs</td>
<td>Several clinical trials have demonstrated short-term improvement in pain and sleep</td>
<td>Has anticholinergic, antihistaminic, and anti-adrenergic side effects</td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
<td>Reduces tonic activity of alpha and gamma motor neurons, leading to muscle relaxation; structurally similar to tricyclic antidepressants</td>
<td>10 mg qhs/10 mg qhs-20 mg bid 10 mg qhs/10 mg bid</td>
<td>One placebo-controlled trial has demonstrated improvement in pain and fatigue; subsequent studies have not shown a difference between placebo and cyclobenzaprine treatment</td>
<td>High incidence of side-effects</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Inhibits reuptake of serotonin in the central nervous system, increasing its synaptic availability</td>
<td>20 mg qd/20-80 mg qd</td>
<td>2 RCTs have demonstrated short-term improvement in sleep and pain (the latter at &gt;20 mg/day)</td>
<td>High incidence of side effects often lead to drug discontinuation</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Inhibits reuptake of serotonin and norepinephrine in the central nervous system; weak inhibitor of central nervous system dopamine reuptake</td>
<td>30 mg qd/60 mg qd-60 mg bid</td>
<td>2 RCTs have demonstrated short-term improvement in pain and most secondary outcome fibromyalgia measures</td>
<td></td>
</tr>
<tr>
<td>Milnacipran</td>
<td>Inhibits reuptake of serotonin and norepinephrine in the central nervous system</td>
<td>25 mg qd/100 mg bid</td>
<td>One RCT showed significant improvement in pain and secondary outcome measures</td>
<td>Not available in the US</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Blocks ascending pain pathways by weakly binding to μ-opiate receptors in the central nervous system; weak reuptake inhibitor of norepinephrine and serotonin in the central nervous system</td>
<td>50 mg/50 mg tid-100 mg tid</td>
<td>One of 2 RCTs has shown very modest short-term improvement in pain</td>
<td>Has abuse potential and may cause dependence</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>In the central nervous system, binds to α2-δ subunit of voltage-gated calcium channels, thus inhibiting excitatory neurotransmitter release</td>
<td>50 mg tid/100 mg tid-150 mg tid</td>
<td>One RCT showed improvement in pain only with 450 mg/day; improved sleep quality and fatigue at ≥300 mg/day</td>
<td>Can be used in combination with any of the above therapies</td>
</tr>
</tbody>
</table>

**Abbreviations:** qhs = at bedtime; bid = twice a day; qd = every day; tid = 3 times a day; RCT = randomized controlled trial.
quent not in a majority of the patients studied. Indeed, the heterogeneity of fibromyalgia patients renders a “one-size-fits-all” approach unlikely to be broadly efficacious, and controlled trials that fail to account for heterogeneity also might fail to tease out useful effects in subsets of patients. Additionally, most fibromyalgia patients exhibit multiple symptoms in addition to pain and tenderness, and therefore require simultaneous treatment for multiple aspects of their illness. While the use of combination therapy may offer the best hope for fibromyalgia management, almost all clinical trials for fibromyalgia have tested only single therapies.

Clinical experience suggests that particular treatments work in some patients, sometimes despite failure in clinical trials. Thus, fibromyalgia treatment choices must be made on an empirical basis, informed wherever possible by evidence. For most patients, the agent of first choice probably remains amitriptyline or nortriptyline at bedtime, initiated at 10 mg and increased incrementally as needed to maximum benefit. If these are not tolerated, low-dose cyclobenzaprine at bedtime may be initiated; other muscle relaxants also might be efficacious. A patient who presents with isolated generalized pain without other associated symptoms may respond to a simple analgesic such as tramadol. Patients with depression may particularly benefit from SSRIs or SNRIs. Patients who fail analgesics, muscle relaxants, or antidepressants may benefit from the use of pregabalin or gabapentin. For most of these therapies, patients need to be reminded that at least several weeks may be required to derive benefit. A failure to respond to one therapy indicates a need for a trial (or addition) of another agent. Because therapeutic responses are rarely durable, clinicians should not be disheartened when a medication loses its initial efficacy. Successful treatment of fibromyalgia may require regular reassessment and possible rotation of medications.

Although no particular physical therapies have definitively proven to be of benefit in fibromyalgia, we encourage all our fibromyalgia patients to participate in some form of low-impact exercise, such as aquatherapy. Patients need to be reminded to not be discouraged by limited exercise capacity at the outset. Moreover, fibromyalgia patients should be encouraged to increase their exercise very gradually; an overly aggressive regimen may lead to significant postexercise discomfort and future noncompliance.

Finally, it is of paramount importance to provide fibromyalgia patients with education, emotional support, and reassurance. Patients should be reassured that, despite the severity of their pain, fibromyalgia is an otherwise benign condition that does not lead to bodily damage or death. The treating physician needs to acknowledge the patient’s experience of pain, because fibromyalgia patients frequently have had their symptoms ignored or dismissed. The challenge is to produce a compassionate and comprehensive treatment program for all aspects of the fibromyalgia patient’s illness.

References


24. Tofteri JK, Jackson JL, O’Malley PG. Treatment of fibromyalgia with

25. Wolfe F, Cathey MA, Hawley DJ. A double-blind placebo controlled
trial of fluoxetine in fibromyalgia. * scand J Rheumatol.* 1994;23(5):
255-259.

blind crossover trial of fluoxetine and amitriptyline in the treat-

controlled, double-blind, flexible-dose study of fluoxetine in the treat-

28. Ozerbiil O, Okudan N, Gokkeli H, Levendoglu F. Comparison of the
effects of two antidepressants on exercise performance of the female

29. Anderberg UM, Marteinsdottir I, von Knorring L. Citalopram in pa-
tients with fibrositis/fibromyalgia syndrome with ibuprofen and alprazolam. A


34. Crofford LJ, Simpson S, Young JP, et al. A six-month, double-blind,

35. Patkar AA, Masand PS, Krulewicz S, et al. A randomized, controlled,

comparing duloxetine with placebo in the treatment of fibromyalgia
patients with or without major depressive disorder. *Arthritis Rheum.*
2004;50(9):2974-2984.


fibromyalgia syndrome: results of a randomized, double-
blind, placebo-controlled trial. *Arthritis Rheum.* 2005;52(4):1264-
1273.

placebo-controlled, durability of effect study of pregabalin for pain

treatment of fibromyalgia: a randomized, double-blind, placebo-
controlled, multicenter trial. *Arthritis Rheum.* 2007;56(4):1336-
1344.

41. Yunus MB, Masi AT, Aldag JC. Short term effects of ibuprofen in
primary fibromyalgia syndrome: a double blind, placebo controlled

42. Clark S, Tindall E, Bennett RM. A double blind crossover trial of
prednisone versus placebo in the treatment of fibrositis. *J Rheumatol.*

43. Bennett RM, Kamin M, Karim R, Rosenthal N. Tramadol and acet-
aminophen combination tablets in the treatment of fibromyalgia pain:
a double-blind, randomized, placebo-controlled study. *Clin Rheumatol.*

44. Russell JJ, Michalek JE, Flechas JD, Abraham GE. Treatment of
fibromyalgia syndrome with Super Malic: a randomized, double blind,
953-958.

symptoms and non-REM sleep disturbance in patients with “fibrositis
syndrome” and healthy subjects. *Psychosom Med.* 1975;37(4):341-
351.

46. Bennett RM. Physical fitness and muscle metabolism in the fibro-

47. McCuin GA, Bell DA, Mai FM, Halliday PD. A controlled study of the
effects of a supervised cardiovascular fitness training program on the
manifestations of primary fibromyalgia. *Arthritis Rheum.* 1988;31(9):
1135-1141.

48. Burckhardt CS, Mannerkorpi K, Hedenberg L, Bjelle A. A random-
ized, controlled clinical trial of education and physical training for

49. Martin L, Nutting A, MacIntosh BR, et al. An exercise program in

50. Staud R, Robinson ME, Price DD. Isometric exercise has opposite
effects on central pain mechanisms in fibromyalgia patients compared

warm water decreases pain and improves health-related quality of life
and strength in the lower extremities in women with fibromyalgia.

52. Assis MR, Silva LE, Alves AM, et al. A randomized controlled trial of
deep water running: clinical effectiveness of aquatic exercise to treat

53. Edinger JD, Wohlgemuth WK, Krystal AD, Rice JR. Behavioral in-
somnia therapy for fibromyalgia patients: a randomized clinical trial.

meditation-based stress reduction program on fibromyalgia. *Gen Hosp

55. Finckh A, Berner IC, Aubry-Rozier B, So AK. A randomized con-
trolled trial of dehydroepiandrosterone in postmenopausal women with

56. Citera G, Arias MA, Maldonado-Cocco JA, et al. The effect of mel-


58. Martin DP, Sletten CD, Williams BA, Berger IH. Improvement in
fibromyalgia symptoms with acupuncture: results of a randomized