Pharmacotherapy for Patients With Fibromyalgia

Daniel J. Clauw, M.D.

Fibromyalgia is a common and disabling syndrome. Despite research detailing the efficacy of a variety of medicinal treatments, most notably, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and $\alpha_2\delta$ ligands, there is still widespread, routine use of agents that are mostly ineffective in treating the central nature of fibromyalgic pain. This article discusses pharmacotherapeutic options for fibromyalgia, including those with high-level evidence for efficacy, moderate-level evidence, and little or no evidence for efficacy. The importance of an integrated treatment approach that includes pharmacotherapy and at least one, but preferably more, of the most effective nonmedicinal treatment options available (e.g., education, aerobic exercise, and cognitive-behavioral therapy) is also discussed. *(J Clin Psychiatry 2008;69[suppl 2]:25–29)*

Fibromyalgia is a central pain disorder associated with increased disability and morbidity. The disorder affects approximately 2% of the U.S. population, with the majority of the sufferers being women.[1] The presence of fibromyalgia is indicated by chronic widespread pain and by tenderness at 11 or more of 18 muscle-tendon sites.[2] Primary characteristics of the disorder include abnormal pain processing, fatigue, and sleep abnormalities.[2] Fibromyalgic symptoms overlap with those of irritable bowel syndrome, chronic fatigue syndrome, and other disorders.[2,3] Individuals with fibromyalgia often suffer from concurrent chronic illnesses or pain syndromes, as well as anxiety or depression. Pharmacotherapy plays an integral role in the management of fibromyalgia, but the most effective treatment approach combines pharmacotherapy with adjunctive nonpharmacologic programs.

PHARMACOTHERAPY IN FIBROMYALGIA

As shown in Table 1, pharmacotherapeutic options for fibromyalgia are supported by varying levels of evidence. Three classes of drugs have strong evidence supporting their efficacy in fibromyalgia: tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and $\alpha_2\delta$ ligands. Other classes of drugs that may be efficacious, although the evidence is less compelling, include medications such as tramadol, the older selective serotonin reuptake inhibitors (SSRIs), γ-hydroxybutyrate (GHB), and dopamine agonists. Nonsteroidal antiinflammatory drugs (NSAIDs) and opioids are probably not effective in the treatment of fibromyalgia, despite being routinely used in that setting. Benzodiazepines, hypnotics, and sedatives also have not been shown to be efficacious in treating fibromyalgia.

Drugs With Strong Evidence of Efficacy

Tricyclic antidepressants. Meta-analyses[4,5] of randomized controlled trials of antidepressant treatment for fibromyalgia found evidence of efficacy of TCAs in addressing fibromyalgic pain, fatigue, and sleep disturbances. Amitriptyline[4,6–8] and cyclobenzaprine[4,8–10] are the most thoroughly studied of the tricyclic compounds for patients with fibromyalgia. However, TCAs are associated with some safety concerns. Adverse events including dry mouth, sedation, weight gain, urinary retention, constipation, and tachycardia may be reported with TCAs.[11] Patients with cardiac problems or narrow-angle glaucoma should not take TCAs. Elderly patients should not take amitriptyline due to the agent's elevated risk of anticholinergic side effects.

To minimize the incidence of side effects associated with TCAs, a low dose should be used at the beginning of therapy, and the dose should be titrated up slowly.[12] For example, amitriptyline will often work best if started at a dose of 10 mg/day taken several hours before bedtime, with the dose being slowly escalated upward (by about 10 to 25 mg per week) to a maximum of 70 or 80 mg/day or the highest therapeutic dose that the patient will tolerate.[11] Cyclobenzaprine should usually be started at 5 mg several

From the Division of Rheumatology, Department of Internal Medicine, and the Michigan Institute for Clinical and Health Research, University of Michigan Medical School, Ann Arbor.

This article is derived from the planning teleconference series "Understanding Fibromyalgia and Its Related Disorders" that was held in October and November 2007 and supported by an educational grant from Eli Lilly and Company.

Dr. Clauw is a consultant for and a member of the speakers/advisory boards for Cypress Bioscience, Forest, Wyeth, Pfizer, and Eli Lilly and has received grant/research support from Cypress Bioscience.

Corresponding author and reprints: Daniel J. Clauw, M.D., Domino's Farms, 24 Frank Lloyd Wright Dr., Room Lobby M, Ann Arbor, MI 48106 (e-mail: dclauw@umich.edu).

Table 1. Pharmacologic Treatments Used for Fibromyalgia

Drug	Dosage	Side Effects/Safety Concerns
Strong Evidence of Efficacy		
Tricyclic antidepressants (TCAs)		Dry mouth, sedation, weight gain, urinary retention, constipation, and tachycardia Do not prescribe to patients with cardiac problems and narrow-angle glaucoma
Amitriptyline[4,6–8]	10 mg/d several hours before bedtime; titrate up by 10–25 mg/wk until 70–80 mg/d or maximally tolerated dose is reached	Elevated risk of anticholinergic side effects and should not be prescribed to the elderly
Cyclobenzaprine[4,8–10]	5 mg several hours before bedtime; titrated up to 20 mg/d or maximally tolerated dose	
Serotonin-norepinephrine reuptake inhibitors		Constipation, nausea, dizziness, insomnia, and dry mouth
Duloxetine[15]	60–120 mg/d	
Milnacipran[16,17]	100–200 mg/d	
$\alpha_2\delta$ Ligands		Fatigue, sedation, nausea, drowsiness, dizziness, and weight gain
Gabapentin[18]	1200–2400 mg/d with a higher percentage of the dose taken at bedtime, eg, 500 mg in the morning and 1000 mg at night	
Pregabalin[19,a]	Up to 450 mg/d with a higher percentage of the dose taken at bedtime, eg, 150 mg in the morning and 300 mg at night	
Moderate Evidence of Efficacy		
Selective serotonin reuptake inhibitors	May need higher than antidepressant dose	Nausea, sedation, headache, weight gain, decreased libido, and sexual dysfunction
Fluoxetine[21,27,28]	10–80 mg/d	
Fluoxetine and TCA[21,28]	No evidence available	Not available
Paroxetine[12,29,30]	10–80 mg/d	
Tramadol[20,24–26]	50–100 mg every 6 hours	Nausea, dizziness, headache, pruritus, constipation, sinusitis, somnolence, and upper respiratory infection
Tramadol and acetaminophen[25,26]	No evidence available	
γ-Hydroxybutyrate[22]	No evidence available	Abuse potential
Dopamine agonists		
Pramipexole[23]	No evidence available	Weight loss and transient anxiety
Weak Evidence of Efficacy		
Nonsteroidal antiinflammatory drugs[12]	No evidence available	Not available
Opioids	No evidence available	Abuse potential
No Evidence of Efficacy		
Benzodiazepines		
Hypnotics		
Sedatives		

[a]Pregabalin is approved by the U.S. Food and Drug Administration for treatment of fibromyalgia.

hours before bedtime and escalated up to 20 mg/day or the maximally tolerated dose[13]; a double-blind crossover study[14] found no significant difference in efficacy between dosages of 10 mg/day and 30 mg/day but a greater incidence of side effects at the higher dose. Doses used in studies of TCAs for the treatment of fibromyalgia or other chronic pain conditions are not nearly as high as those used for treating depression, so some of the most dangerous side effects of TCAs (e.g., cardiac toxicity) are not typically seen in this setting.[4]

Serotonin-norepinephrine reuptake inhibitors. Concerns about the tolerability of tricyclic compounds have created interest in using SNRIs to increase norepinephrine and serotonin without producing the cardiac side effects associated with tricyclic drugs.[12] In randomized controlled trials, duloxetine[15] and milnacipran[16,17] have demonstrated efficacy in patients with fibromyalgia. Both substances were shown to diminish fibromyalgic pain as well as some of the other symptoms and domains present in fibromyalgia, such as fatigue, stiffness, tenderness, and decreased quality of life. In contrast with TCAs, duloxetine and milnacipran have been used at or above the doses recommended for depression when tested in patients with fibromyalgia (60–120 mg/day for duloxetine[15] and 100–200 mg/day for milnacipran[16,17]), giving these dual reuptake inhibitors the added advantage of treating the comorbid depression that sometimes exists in individuals with fibromyalgia. However, the effect of these drugs on symptoms of fibromyalgia was distinct from the effect on mood. Side effects associated with duloxetine include constipation, nausea, dizziness, insomnia, and dry mouth.[11] These side effects are often most pronounced when the drug is first administered and with dose escalation, so starting at a low dose and increasing slowly, as

well as taking this class of drugs with food, will help improve tolerability.

$\alpha_2\delta$ Ligands. The $\alpha_2\delta$ ligands gabapentin[18] and pregabalin[19] have similar, if not identical, mechanisms of action, and both drugs have demonstrated efficacy in fibromyalgia treatment. Gabapentin was effective when used with a dosage range of 1200 to 2400 mg per day.[18] Up to 450 mg per day of pregabalin is approved for use in fibromyalgia. These drugs are better tolerated if a higher percentage of the daily dose is taken at bedtime. For example, when using gabapentin to treat fibromyalgia or other chronic pain conditions, the patient can be directed to take 500 mg in the morning and 1000 mg at night. Similarly, pregabalin could be administered at a dose of 100 mg in the morning and 200 mg at night or 150 mg in the morning and 300 mg at night. Patients taking gabapentin or pregabalin may experience fatigue, sedation, nausea, drowsiness, dizziness, and weight gain.[11]

Possibly Effective Treatment Options

Other drugs appear to be beneficial in fibromyalgia, although the evidence supporting their efficacy is less compelling than that of the previously discussed medications. These potentially helpful drugs include the atypical opioid tramadol,[20] older SSRIs such as fluoxetine,[21] GHB,[22] and the dopamine agonist pramipexole.[23]

Tramadol, a compound exhibiting serotonin-norepinephrine reuptake inhibition and some opioid activity, has been studied both as monotherapy[20,24] and in combination with acetaminophen[25,26] in randomized controlled trials for fibromyalgia. One study,[20] a randomized, double-blind, placebo-controlled clinical trial, evaluated the efficacy of tramadol in 100 patients with fibromyalgia. Initially, all study participants were treated with tramadol. Of those 100 subjects, 69 tolerated the agent and perceived it to be beneficial. These subjects entered the 6-week placebo-controlled, double-blind phase of the trial and were randomly assigned to either tramadol (N = 35) or placebo (N = 34). Of the tramadol group, 15 subjects dropped out owing to inadequate pain relief prior to study completion compared with 25 subjects from the placebo group. Approximately 57% of patients in the tramadol group tolerated the medication and perceived a benefit, but this was only 20% of the total group of patients with fibromyalgia at study initiation. A monotherapy trial[24] performed 2 years earlier found no significant difference in pain reduction when comparing tramadol with placebo. A study[25] of 315 subjects comparing a tramadol/acetaminophen combination with placebo found the treatment to be effective and safe for most participants. Treatment discontinuation for any reason occurred in 48% of the tramadol/acetaminophen group compared with 62% of the placebo group ($p = .004$). Bennett et al.[26] stated that the side effect profile for combination tramadol/acetaminophen includes nausea, dizziness, headache, pruritus, constipation, sinusitis, somnolence, and upper respiratory infection, which is similar to that of tramadol as monotherapy.

Older SSRIs such as fluoxetine[21,27,28] and paroxetine[12,29,30] have been found effective in some patients with fibromyalgia either as monotherapy[12,27,29,30] or in combination with TCAs.[21,28] In 1994, Wolfe and colleagues[31] found no significant improvement in fibromyalgic symptoms for fluoxetine. However, a randomized, placebo-controlled, double-blind, flexible-dose study[27] performed in 2002 found fluoxetine to be efficacious in several outcome measures for fibromyalgia. A study[28] that compared combination fluoxetine and cyclobenzaprine with cyclobenzaprine monotherapy found significant effectiveness for both groups, although superior results were demonstrated by the combination treatment. Likewise, Goldenberg and colleagues[21] found that fluoxetine and amitriptyline were effective as monotherapy, and that a combination of the 2 was more effective in alleviating the symptoms of fibromyalgia than either medication on its own. A 2007 study[29] found that paroxetine provided moderate pain relief in fibromyalgia. While neither fluoxetine nor paroxetine have been approved in the United States for the treatment of fibromyalgia, they can both be effective for some patients when dosed at 10 to 20 mg per day and as high as 80 mg per day.[11] In contrast to TCAs, where lower doses are needed to treat pain than depression, it appears that the higher doses of the SSRIs are more useful as analgesics, most likely because of the enhanced noradrenergic properties seen at higher doses. The most common side effects for these SSRIs include nausea, sedation, headache, weight gain, decreased libido, and sexual dysfunction. The newer SSRI, citalopram, appears to be less effective in the fibromyalgic population,[32–34] perhaps because it is a more selective serotonin reuptake inhibitor while the older drugs have noradrenergic activity, especially at higher doses.[34]

GHB may be efficacious in patients with fibromyalgia. A study[22] of 24 female patients found that the substance reduced pain and fatigue, but was most effective in reducing sleep abnormalities associated with fibromyalgia. GHB is a scheduled substance because of its abuse potential.

Pramipexole has been shown to be moderately effective in some patients with fibromyalgia. One study[23] found that pramipexole reduced pain and fatigue while improving function and global status for patients with fibromyalgia who were disabled and/or required narcotic analgesia. Pramipexole was associated with weight loss and transient anxiety.

Drugs to Avoid

A common problem in clinical practice is the routine use of NSAIDs and opioids for fibromyalgia treatment. These analgesics can be quite helpful in alleviating acute pain and so-called peripheral or nociceptive pain, such as that which occurs with osteoarthritis or tendonitis, but

they are not nearly as efficacious for central or neuropathic pain, such as that which occurs in fibromyalgia.[12,35,36] An additional risk with opioid therapy is the development of a substance use disorder.[37] So, these analgesic compounds can and should be used if an individual is experiencing a concurrent or comorbid peripheral pain syndrome, but opioids, in particular, should be reserved for patients refractory to other of the more efficacious therapies noted above.[12] Likewise, benzodiazepines, hypnotics, and sedatives should be avoided, as they have not been shown to be efficacious in the treatment of fibromyalgia. Hooten and colleagues[38] found that a multidisciplinary pain rehabilitation program based on a cognitive-behavioral model helped patients with fibromyalgia to withdraw from analgesic medication. The number of patients using NSAIDs, opioid analgesics, benzodiazepines, and muscle relaxants significantly decreased from baseline to endpoint.

Mechanism of Action of Effective Treatments

Evidence[11] suggests that the descending analgesic systems that use serotonin and norepinephrine are attenuated or reduced in individuals with fibromyalgia. The dual reuptake inhibitors may work by increasing serotonergic and noradrenergic activity down these descending analgesic pathways, thus inhibiting the upward transmission of pain. In contrast, it appears that compounds such as pregabalin and gabapentin work by decreasing the release of certain neurotransmitters, including the neuropeptide substance P, glutamate, and other excitory amino acids, that have a tendency to facilitate pain transmission.[39]

In the future, other compounds that are antagonists for neurotransmitters that facilitate pain transmission (e.g., neurotensin, nerve growth factor, and cholecystokinin) and compounds that increase the levels of inhibitory neurotransmitters (e.g., γ-aminobutyric acid, cannabinoids, and adenosine) may likely have utility in treating subsets of fibromyalgia patients. But physicians will probably need an even broader pharmacologic armamentarium addressing the various transmitters involved in pain transmission if fibromyalgia is ever to be completely managed.

INTEGRATED TREATMENT APPROACH

It is extremely important that health care providers understand that fibromyalgia and other chronic pain syndromes should be approached with more of a rehabilitation model than a classic biomedical model. Pharmacologic treatment should be integrated with nonpharmacologic therapies. Clinicians need to appreciate that pharmacologic therapies primarily address pain or pain processing, whereas nonpharmacologic therapies address the functional consequences of the pain, such as the fatigue and the other symptoms that individuals with fibromyalgia experience. A number of nonpharmacologic therapies have repeatedly been shown to be effective. Strong evidence supports education, aerobic exercise, and cognitive-behavioral therapy (CBT) as effective treatments for patients with fibromyalgia.[40] Weaker evidence suggests that therapies including strength training[41] and hypnotherapy[42] can provide some benefit for individuals suffering from fibromyalgia. Tender point injections, despite routine clinical use, have not been shown to be effective in the treatment of fibromyalgia.[12]

A typical individual who has had fibromyalgia for several years will, as a result of having dealt with the pain, fatigue, and other symptoms for that period of time, often develop high levels of distress because he or she cannot function normally in societal roles. This inability usually leads to decreased activity and to social isolation, especially if the individual has gotten involved in litigation or is disabled. Additionally, the individual will likely have problems sleeping and will have developed maladaptive illness behaviors. Each of these problems that can result from the suffering brought about by fibromyalgic symptoms are independently capable of in turn causing more pain, more fatigue, and other symptoms. Clinicians should use nonpharmacologic therapies to address the functional consequences of symptoms, such as distress, decreased activity, poor sleep, and maladaptive illness behaviors, and focus pharmacologic therapies on actually managing the pain.

CONCLUSION

The first step for treating fibromyalgia is to establish the diagnosis and determine whether individuals have any comorbid peripheral pain syndromes that might need to be independently addressed. Once the diagnosis is established, an appropriate pharmacologic treatment should be selected. Tricyclic drugs are typically considered the first-line drugs for this condition, because in the individuals for whom these drugs work, TCAs often can lead to global improvements in pain, fatigue, sleep, and other symptoms. If tricyclic monotherapy is ineffective or intolerable, it should be augmented or replaced with the dual reuptake inhibitors and/or the $\alpha_2\delta$ ligands. In many cases, all 3 of these classes of drugs can be used together, with clear salutary effects from each. And then, perhaps most importantly, once the patient is on a regimen that decreases his or her pain and fatigue and improves other symptoms, some combination of the effective nonpharmacologic therapies (e.g., education, aerobic exercise, and CBT) should be aggressively implemented. Effective use of an integrated treatment plan will have a significant, positive impact on the lives of many of those suffering from fibromyalgia.

Drug names: acetaminophen/tramadol (Ultracet and others), citalopram (Celexa and others), cyclobenzaprine (Amrix, Flexeril, and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), gabapentin (Neurontin and others), paroxetine (Paxil, Pexeva, and

others), pramipexole (Mirapex), pregabalin (Lyrica), tramadol (Ultram and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, acetaminophen/tramadol, citalopram, cyclobenzaprine, duloxetine, fluoxetine, gabapentin, paroxetine, pramipexole, and tramadol are not approved by the U.S. Food and Drug Administration for the treatment of fibromyalgia.

REFERENCES

1. Wolfe F, Ross K, Anderson J, et al. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995;38:19–28
2. Mease PJ, Clauw DJ, Arnold LM, et al. Fibromyalgia syndrome. J Rheumatol 2005;32:2270–2277
3. Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. JAMA 2004;292:2388–2395
4. Arnold LM, Keck PE Jr, Welge JA. Antidepressant treatment of fibromyalgia: a meta-analysis and review. Psychosomatics 2000;41:104–113
5. O'Malley PG, Balden E, Tomkins G, et al. Treatment of fibromyalgia with antidepressants: a meta-analysis. J Gen Intern Med 2000;15: 659–666
6. Carette S, McCain GA, Bell DA, et al. Evaluation of amitriptyline in primary fibrositis: a double-blind, placebo-controlled study. Arthritis Rheum 1986;29:655–659
7. Goldenberg DL, Felson DT, Dinerman H. A randomized, controlled trial of amitriptyline and naproxen in the treatment of patients with fibromyalgia. Arthritis Rheum 1986;29:1371–1377
8. Carette S, Bell MJ, Reynolds WJ, et al. Comparison of amitriptyline, cyclobenzaprine, and placebo in the treatment of fibromyalgia: a randomized, double-blind clinical trial. Arthritis Rheum 1994;37:32–40
9. Tofferi JK, Jackson JL, O'Malley PG, et al. Treatment of fibromyalgia with cyclobenzaprine: a meta-analysis. Arthritis Rheum 2004;51:9–13
10. Bennett RM, Gatter RA, Campbell SM, et al. A comparison of cyclobenzaprine and placebo in the management of fibrositis: a double-blind controlled study. Arthritis Rheum 1988;31:1535–1542
11. Maizels M, McCarberg B. Antidepressants and antiepileptic drugs for chronic non-cancer pain. Am Fam Physician 2005;71:483–490
12. Dadabhoy D, Clauw DJ. Therapy insight: fibromyalgia—a different type of pain needing a different type of treatment. Nat Clin Pract Rheumatol 2006;2:364–372
13. Flexeril (cyclobenzaprine) [package insert]. West Point, Pa: Merck; 2001. Available at: http://www.fda.gov/cder/foi/label/2003/017821s045lbl.pdf. Accessed on Dec 18, 2007
14. Santandrea S, Montrone F, Sarzi-Puttini P, et al. A double-blind crossover study of two cyclobenzaprine regimens in primary fibromyalgia syndrome. J Int Med Res 1993;21:74–80
15. Arnold LM, Lu Y, Crofford LJ, et al, for the Duloxetine Fibromyalgia Trial Group. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. Arthritis Rheum 2004;50:2974–2984
16. Vitton O, Gendreau M, Gendreau J, et al. A double-blind placebo-controlled trial of milnacipran in the treatment of fibromyalgia. Hum Psychopharmacol 2004;19(suppl 1):S27–S35
17. Gendreau RM, Thorn MD, Gendreau JF, et al. Efficacy of milnacipran in patients with fibromyalgia. J Rheumatol 2005;32:1975–1985
18. Arnold LM, Goldenberg DL, Stanford SB, et al. Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. Arthritis Rheum 2007;56:1336–1344
19. Crofford LJ, Rowbotham MC, Mease PJ, et al. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52:1264–1273
20. Russell I, Kamin M, Bennett RM, et al. Efficacy of tramadol in treatment of pain in fibromyalgia. J Clin Rheumatol 2000;6:250–257
21. Goldenberg D, Mayskiy M, Mossey C, et al. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. Athritis Rheum 1996;39:1852–1859
22. Scharf MB, Baumann M, Berkowitz DV. The effects of sodium oxybate on clinical symptoms and sleep patterns in patients with fibromyalgia. J Rheumatol 2003;30:1070–1074
23. Holman AJ, Myers RR. A randomized, double-blind, placebo-controlled trial of pramipexole, a dopamine agonist, in patients with fibromyalgia receiving concomitant medications. Arthritis Rheum 2005;52:2495–2505
24. Biasi G, Manca S, Manganelli S, et al. Tramadol in the fibromyalgia syndrome: a controlled clinical trial versus placebo. Int J Clin Pharmacol 1998;18:13–19
25. Bennett RM, Kamin M, Karim R, et al. Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: a double-blind, randomized, placebo-controlled study. Am J Med 2003;114:537–545
26. Bennett RM, Schein J, Kosinski MR, et al. Impact of fibromyalgia pain on health-related quality of life before and after treatment with tramadol/acetaminophen. Arthritis Rheum 2005;53:519–527
27. Arnold LM, Hess EV, Hudson JI, et al. A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. Am J Med 2002;15:191–197
28. Cantini F, Bellandi F, Niccoli L, et al. Fluoxetine combined with cyclobenzaprine in the treatment of fibromyalgia. Minerva Med 1994;85: 97–100
29. Patkar AA, Masand PS, Krulewicz S, et al. A randomized, controlled, trial of controlled release paroxetine in fibromyalgia. Am J Med 2007;120: 448–454
30. Çapaci K, Hepgüler S. Comparison of the effects of amitriptyline and paroxetine in the treatment of fibromyalgia syndrome. Pain Clinic 2002;14:223–228
31. Wolfe F, Cathey MA, Hawley DJ. A double-blind placebo controlled trial of fluoxetine in fibromyalgia. Scand J Rheumatol 1994;23:255–259
32. Anderberg UM, Marteinsdottir I, von Knorring L. Citalopram in patients with fibromyalgia: a randomized, double-blind, placebo-controlled study. Eur J Pain 2000;4:27–35
33. Norregaard J, Volkmann H, Danneskiold-Samsoe B. A randomized controlled trial of citalopram in the treatment of fibromyalgia. Pain 1995; 61:445–449
34. Fishbain D. Evidence-based data on pain relief with antidepressants. Ann Med 2000;32:305–316
35. Goldenberg DL. Pharmacological treatment of fibromyalgia and other chronic musculoskeletal pain. Best Pract Res Clin Rheumatol 2007;21: 499–511
36. Quijada-Carrera J, Valenzuela-Castaño A, Povedano-Gómez J, et al. Comparison of tenoxicam and bromazepan in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled trial. Pain 1996;65:221–225
37. Fleming MF, Balousek SL, Klessig CL, et al. Substance use disorders in a primary care sample receiving daily opioid therapy. J Pain 2007;8: 573–582
38. Hooten WM, Townsend CO, Sletten CD, et al. Treatment outcomes after multidisciplinary pain rehabilitation with analgesic medication withdrawal for patients with fibromyalgia. Pain Med 2007;8:8–16
39. Dooley DJ, Taylor CP, Donevan S, et al. Ca2+ channel alpha2delta ligands: novel modulators of neurotransmission [published online ahead of print Jan 10, 2007]. Trends Pharmacol Sci 2007;28:75–82. Correction 2007;28:151
40. Staud R. Treatment of fibromyalgia and its symptoms. Expert Opin Pharmacother 2007;8:1629–1642
41. Busch A, Schachter CL, Peloso PM, et al. Exercise for treating fibromyalgia syndrome. Cochrane Database Syst Rev 2002;3:CD003786
42. Haanen HC, Hoenderdos HT, van Romunde LK, et al. Controlled trial of hypnotherapy in the treatment of refractory fibromyalgia. J Rheumatol 1991;18:72–75