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A review of fibromyalgia and its treatment

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Fibromyalgia syndrome (FMS) is a type of rheumatism that affects the muscles and ligaments of the body. It is a widespread condition, estimated to affect 2%-4% of the population. FMS most commonly affects women 30 to 50 years of age. Of the 5.7 million Americans currently suffering from FMS, an estimated 38%, or 2.1 million, actively seek treatment. FMS is second only to osteoarthritis as the most common diagnosis made in rheumatology practice.

Criteria for the diagnosis of FMS were developed by the American College of Rheumatology in 1990. A diagnosis of FMS is made based on widespread pain in combination with pain in 11 of 18 tender points (see Fig. 1). Widespread pain is defined as pain in the left and right sides of the body, pain above and below the waist, and axial skeletal pain. The severity of pain varies tremendously between patients. The range is so wide that some people with FMS are able to carry on with normal activities while managing their pain with over-the-counter analgesics, while others find themselves in such constant, unrelenting pain that they require narcotic therapy simply to function. In addition, FMS pain is inconsistent within the individual patient, i.e., the patient may experience pain in one location one day but not the next.

Although the true cause of FMS is unknown, several theories have been proposed. FMS was first thought to be an

inflammatory condition; however, evidence of inflammation has not been found. Another theory suggests that the pain of FMS is related to micro-trauma in deconditioned muscles. And still another theory suggests that FMS may be due to non-restorative deep sleep.

A number of changes in immune-system function have been found in FMS patients, implying an infectious etiology. An additional theory suggests a link to serotonin, as its serum levels and dietary precursor tryptophan are low in FMS patients. High

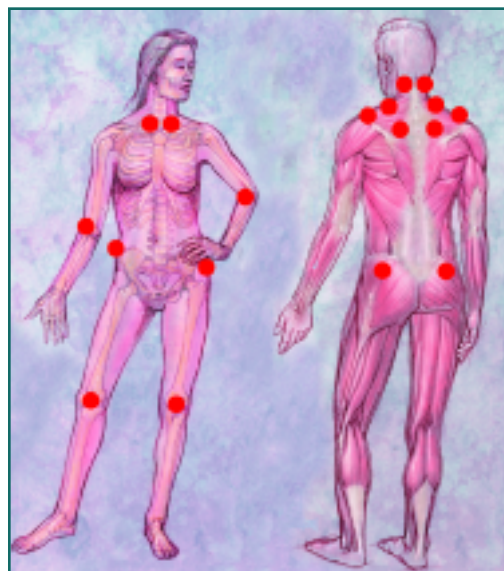


Figure 1. Tender points in the diagnosis of fibromyalgia

Source: Adapted from: <http://www.mckinley.uiuc.edu/Handouts/fibromyalgia/fibromyalgia.html>

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concentrations of substance P (a peptide neurotransmitter) may also play a role. No specific inheritance pattern has been identified; however, an increased incidence in relatives of affected patients has been noted.

The fibromyalgia syndrome, one of the so-called “functional somatic syndromes,” is characterized more by symptoms, suffering, and disability than by consistent tissue abnormality. Functional somatic syndromes (FSS) are a group of chronic pain syndromes that present both physical complaints (e.g., pain) and psychiatric symptoms (e.g., depressed mood). In FSS, the physical symptoms are often exacerbated by stress. Muscular pain, fatigue, insomnia, joint pain, headache, restless leg, paresthesia, impaired memory, leg cramps, impaired concentration, nervousness, and major depression are among the most frequent symptoms of fibromyalgia.

Antidepressants

The antidepressants are perhaps the most widely studied group of drugs for FMS. While the most commonly used are the selective serotonin reuptake inhibitors (SSRIs) and the tricyclic antidepressants (TCAs), other antidepressants affecting the neurotransmitters norepinephrine (NE) and serotonin (5HT) have also been studied.

Fluoxetine (Prozac)

Fluoxetine works by selectively inhibiting the reuptake of serotonin. The most common side effects associated with fluoxetine include insomnia, anxiety, headache, decreased libido, nausea, and diarrhea. Due to the risk of serotonin syndrome, fluoxetine should be avoided or used with caution in patients taking MAO (monoamine oxidase) inhibitors, amphetamines, buspirone, meperidine, nefazodone, serotonin agonists, sibutramine, tramadol, venlafaxine, and other SSRIs. In addition, if administered with a CYP2C8/9 inhibitor, fluoxetine’s effects may become enhanced. In the treatment of FMS, fluoxetine is the most studied antidepressant. It has been compared with placebo in two moderate-sized trials and has been studied in combination with amitriptyline in another small trial.

L. M. Arnold et al. conducted a randomized, placebo-controlled, double-blind, flexible-dose study to assess the efficacy of fluoxetine in the treatment of patients with fibromyalgia. Sixty women were randomly assigned to receive fluoxetine or placebo for 12 weeks. Fluoxetine was started at a dose of 20 mg per day but could be titrated to a maximum of 80 mg per day. The primary outcome measures were the

GOAL:

To provide the pharmacist with the clinical evidence available for treatments used in fibromyalgia patients

CREDIT:

This lesson provides two hours of CE credit and requires a passing grade of 70%.*

OBJECTIVES:

Upon completion of this article, the pharmacist should be able to:

- ✓ Explain fibromyalgia and its diagnosis
- ✓ Identify pharmacologic treatments available for the treatment of fibromyalgia
- ✓ Give two examples of clinical evidence supporting the use of pharmacologic treatments for fibromyalgia

*To receive credit you must score 70% or higher on the quiz and complete the evaluation. Upon successful completion, the University of Florida College of Pharmacy will mail Statements of Credit for written quizzes within 10 working days. Participants completing the program on-line may print a Statement of Credit after successfully completing the program.

Fibromyalgia Impact Questionnaire (FIQ) total score and pain score. The McGill Pain Questionnaire pain-rating index was used as a secondary outcome measure.

Subjects were evaluated at two, four, six, eight, and 12 weeks for medication dose and adverse effects; in addition, they completed the FIQ and McGill Pain Questionnaire at each visit. Patients who received fluoxetine demonstrated a significant improvement in the FIQ total score as well as the McGill Pain Questionnaire compared with placebo. Twenty patients withdrew from the study, 12 of whom because of adverse events. While the most common adverse events reported were headache, insomnia, sedation, and nausea, there was no significant difference between treatment groups. The authors concluded that fluoxetine was effective on most outcome measures and generally well tolerated in women with FMS.

F. Wolfe and colleagues conducted a double-blind controlled trial of fluoxetine in 42 women with FMS. Patients were assigned to receive fluoxetine 20 mg per day or placebo for six weeks. Total tender-point count, dolorimetry scores, and visual analog scales (VAS) for pain, global severity, sleep difficulty, and fatigue were

Table 1
Drugs that inhibit/induce cytochrome P450 enzymes

Inhibitors	Inducers
CYP1A2	Amiodarone, ciprofloxacin, clarithromycin, erythromycin, fluvoxamine, isoniazid, ketoconazole, levofloxacin, norfloxacin, ofloxacin, paroxetine, rofecoxib, carbamazepine, phenobarbital, phenytoin, rifampin, ritonavir
CYP2D6	Amiodarone, cimetidine, chlorpromazine, delavirdine, desipramine, fluoxetine, fluphenazine, haloperidol, miconazole, paroxetine, quinidine, quinine, ritonavir, sertraline, thioridazine, carbamazepine, phenobarbital, phenytoin, rifampin, ritonavir
CYP3A4	Amiodarone, clarithromycin, erythromycin, fluconazole, fluoxetine, fluvoxamine, indinavir, itraconazole, ketoconazole, metronidazole, miconazole, nefazodone, nelfinavir, norfloxacin, quinine, ritonavir, saquinavir, sertraline, zafirlukast, carbamazepine, dexamethasone, ethosuximide, phenobarbital, phenytoin, primidone, rifabutin, rifampin

Source: Adapted from Lacy C, Armstrong L, Ingram N, Lance L. *Drug Information Handbook* 13th edition. Lexicomp Inc; Cleveland: 2005. Michalets EL. Update: clinically significant cytochrome P-450 drug interactions. *Pharmacotherapy* 1998; 18(1): 84-112.

Both the amitriptyline- and fluoxetine-treated groups demonstrated a significant improvement on the FIQ and VAS for pain, global well-being, and sleep. In addition, the combination treatment group produced statistically significant results on all four measures over placebo and either drug given alone. The study investigators stated that, in general, the improvement seen with combination therapy was approximately twice that with either treatment alone. The authors concluded that fluoxetine and amitriptyline in combination improve pain, global well-being, sleep disturbances, and function in patients with FMS.

Amitriptyline (Elavil)

Amitriptyline is a tricyclic antidepressant that exerts its action by inhibiting the reuptake of serotonin and nor-epinephrine. Side effects most commonly associated with amitriptyline use include orthostatic hypotension, changes in AV conduction, dizziness, sedation, weight gain, constipation, blurred vision, and urinary retention. As with fluoxetine, there is a risk of serotonin syndrome with amitriptyline; therefore, its use should be avoided or it should be used cautiously in patients taking MAO inhibitors or ritonavir. Amitriptyline levels, and therefore its effects, may be increased by CYP2D6 inhibitors (see Table 1), cimetidine, fenfluramine, grapefruit juice, indinavir, methylphenidate, diltiazem, valproate, and verapamil. Amitriptyline has been investigated in FMS in several studies in addition to the crossover trial with fluoxetine. Amitriptyline has been compared with cyclobenzaprine and moclobemide (not available in the United States) in separate studies and has been investigated for its usefulness in combination with guided imagery in another study.

S. Carette et al. conducted a randomized, double-blind trial to determine the efficacy and tolerability of amitriptyline, cyclobenzaprine (cyclobenzaprine is reviewed separately on page 43), and placebo in the treatment of FMS. In the trial, 208 patients were randomized to receive amitriptyline, cyclobenzaprine, or placebo in a 2:2:1 ratio. The amitriptyline group started on 10 mg at bedtime for one week, then 25 mg at bedtime from weeks two to 12, then 50 mg at bedtime for weeks 13-24. The cyclobenzaprine group took 10 mg at bedtime for one week, then took 20 mg at bedtime for weeks 2-12, then 10 mg in the morning and 20 mg at bedtime for weeks 13-24.

The amitriptyline group was also given cyclobenzaprine placebo tablets, the cyclobenzaprine group was given amitriptyline placebo tablets, and the placebo group was given both. Patient outcomes were

the primary outcome measures. The study investigators found no statistically significant difference between fluoxetine and placebo in any of the primary outcome measures. The authors concluded that fluoxetine, at a dose of 20 mg per day, does not improve signs or symptoms of FMS. However, the authors did state that perhaps a higher dose and/or a longer treatment period might result in a different outcome.

D. Goldenberg and colleagues conducted a randomized double-blind crossover trial to study the effects of fluoxetine and amitriptyline, alone and in combination, in FMS. Thirty-one patients were randomized to receive fluoxetine 20 mg, amitriptyline 25 mg, fluoxetine and amitriptyline concomitantly, or placebo for four six-week trials. Patients were assessed at the beginning and end of each trial period. Outcome measures included a tender-point score, the FIQ, the Beck Depression Inventory (BDI), and VAS for pain, sleep disturbances, fatigue, feeling refreshed upon waking, and well-being (one physician-administered and one self-administered).

assessed by the McGill Pain Questionnaire; the Sickness Impact Profile (SIP); the Health Assessment Questionnaire (HAQ); the Arthritis Impact Measurement Scales (AIMS); and VAS for pain, fatigue, sleep, feelings on awakening, morning stiffness, and global assessment of fibromyalgia. The McGill score, the SIP score, and the AIMS score showed progressive improvement during the study period; however, there was no statistically significant improvement among the three treatment groups. In addition, the HAQ scores did not differ significantly from baseline throughout the entire study period for any group. Although patients in the active treatment groups appeared to show significant improvement on the VAS after one month, there was at six months of treatment no significant difference between any treatment groups. The investigators concluded that amitriptyline and cyclobenzaprine may be effective in the short term for the treatment of fibromyalgia.

P. Hannonen and colleagues report the results of a randomized, double-blind, placebo-controlled study of amitriptyline and moclobemide (not available in the United States) in the treatment of FMS. After a two-week placebo run-in period, patients were randomized to receive amitriptyline, moclobemide, or placebo for 12 weeks. The percentage of responders (defined as those scoring 3, 2, or 1) to treatment as assessed by the physician using a seven-point clinical impression of change (CIC) scale was the primary efficacy endpoint. In the trial, 74% of patients in the amitriptyline group, 54% of patients in the moclobemide group, and 49% of patients in the placebo group were defined as responders to therapy. The differences in the amitriptyline versus moclobemide group as well as the amitriptyline versus placebo group were statistically significant. There was no statistically significant difference between the moclobemide and placebo groups. The authors concluded that amitriptyline appears to modestly improve FMS symptoms, while moclobemide does not.

A study conducted by E. A. Fors et al. compared the effects of two types of guided imagery on FMS pain. In addition, the study investigators wanted to examine the effect of amitriptyline on FMS pain. In a randomized fashion, 55 women were assigned to a pleasant imagery group ($n = 17$), attention imagery group ($n = 21$), or control group ($n = 17$). The patients then blindly chose amitriptyline or placebo, which were prepared in identical capsules. The slopes of diary pain ratings over the four-week study period were used as the primary outcome measures. The pain slope ratings for the PI group improved significantly over the control group. However, the pain-slope rat-

ings for the AI group did not improve significantly when compared with the control group.

Additionally, there was no significant difference in the pain-slope ratings between the amitriptyline and placebo groups. And there was no interaction between the psychological treatment and amitriptyline. Based on these results, the study investigators concluded that teaching pain distraction techniques such as PI may be beneficial in patients who suffer from FMS.

Mirtazapine (Remeron)

Mirtazapine exerts its action via several mechanisms. Its alpha-2 antagonist action results in increased serotonin and norepinephrine release. In addition, mirtazapine selectively blocks 5-HT₂ and 5-HT₃ receptors. Common side effects associated with mirtazapine include somnolence, increased cholesterol, constipation, xerostomia, increased appetite, and weight gain. Due to its extensive hepatic metabolism, mirtazapine is associated with many drug interactions. The effects of mirtazapine can be increased if administered with CYP1A2, CYP2D6, and CYP3A4 inhibitors. Its effects may be decreased by CYP1A2 inducers (see Table 1).

Mirtazapine has been evaluated in one small study of 29 FMS patients. After a seven-day washout period, patients were started on 15 mg of mirtazapine at bedtime. Therapy with mirtazapine continued for six weeks, and the dose could be increased to 30 mg a day if needed after the first week of therapy. Pain, sleep disturbances, fatigue, cold extremities, dryness of mouth, profuse sweating, dizziness, gastric problems, headache/migraine, irregular breathing, arrhythmia, paresthesia, urinary urgency, duration of morning stiffness, and depressive symptoms were all evaluated during the study.

A responder was defined as one who obtained a reduction of $\geq 40\%$ in clinical symptoms and a score of ≤ 10 on the Hamilton Depression rating scale (HAM-D) and ≤ 12 on the BDI. A patient was considered a partial responder if he/she obtained a reduction in clinical symptoms and intensity of depression of $\geq 20\%$. Of the 26 patients who completed the trial, 14 patients experienced a $\geq 40\%$ reduction in pain, 13 experienced a $\geq 40\%$ reduction in fatigue, and 19 experienced a $\geq 40\%$ reduction in sleep disturbances. Ten patients met the responder criteria; seven met the criteria as partial responders.

A common side effect with mirtazapine treatment is weight gain. In this study, 12% of patients experienced a weight gain of 3 to 4kg; however, no patients discontinued treatment due to this side effect. The

authors concluded that mirtazapine administered at 15-30mg/day appears to be effective in reducing intensity of pain, fatigue, sleep disturbances, and depressive symptoms in FMS patient. However, additional double-blind, placebo-controlled trials should be conducted to confirm the benefits of mirtazapine.

Venlafaxine (Effexor)

Venlafaxine is a serotonin and norepinephrine reuptake inhibitor commonly used in the treatment of depression. It has been proposed that venlafaxine, due to its dual mechanism of action, may be effective for symptom management in patients with FMS. Common side effects associated with venlafaxine include headache, somnolence, dizziness, nausea, and xerostomia.

As with many other antidepressants, the use of venlafaxine with MAO inhibitors may increase the risk of developing serotonin syndrome. This risk can also be increased if venlafaxine is used concomitantly with buspirone, lithium, meperidine, nefazodone, serotonin agonists, and SSRIs. The effects of venlafaxine may be increased by concomitant use with CYP2D6 and CYP3A4 inhibitors (Table 1). Two small studies have been conducted on the use of venlafaxine in FMS, both of which showed a significant improvement in FMS symptoms.

M. M. Dwight et al. conducted a small open-label trial involving 15 patients with FMS. The purpose of the study was to determine the safety and efficacy of venlafaxine in FMS patients. Response to treatment was measured using the HAM-D and Hamilton Anxiety (HAM-A) scales, the McGill Pain Questionnaire, and a VAS. Venlafaxine was started at a dose of 37.5 mg to 75 mg per day and titrated up to a maximum of 375 mg/day. Eleven patients completed the study with a mean final dose of 167 mg/day. Significant improvement was noted at eight weeks on the McGill Pain Questionnaire, VAS, HAM-D, and HAM-A scales. The most common adverse events reported were insomnia, headache, constipation, fatigue, nausea, and dry mouth. The study investigators concluded that venlafaxine may be effective in alleviating symptoms of FMS in some patients; however, controlled trials would need to be conducted in order to confirm their findings.

A trial was conducted by K. Sear and colleagues to determine the efficacy of venlafaxine in FMS patients. Once enrolled in the study, the patients ($n=20$) were given the following assessments at baseline: the Beck Depression and Beck Anxiety Inventories, the HAM-D and HAM-A scales, the FIQ, and the Short Form 36. In addition, patients rated their pain intensity at base-

line on a VAS. All patients were given venlafaxine 75 mg/day, and therapeutic efficacy was assessed at six and 12 weeks. The FIQ and VAS were considered primary outcome measures. Five patients withdrew from the study due to adverse effects, the most common of which were nausea, irritability, insomnia, anorexia, and headache. Pain intensity did not decrease significantly at six weeks; however, there was a significant improvement in pain intensity after 12 weeks of therapy. In addition, the FIQ scores improved significantly during both study periods. The investigators concluded that venlafaxine may be a viable option in decreasing pain intensity and disability in FMS patients. Nonetheless, this finding should be verified by a randomized, double-blind, placebo-controlled trial.

Milnacipran (Ixel)

Milnacipran is a serotonin-norepinephrine reuptake inhibitor. Currently it is approved only for the treatment of depression. It is, however, in phase III clinical development for the treatment of FMS. O. Vitton and colleagues conducted a double-blind, randomized, placebo-controlled trial to determine the safety and efficacy of milnacipran in the treatment of FMS. After a one- to four-week washout period where no medication was taken, patients entered the two-week baseline phase. During this time patients recorded their level of pain in electronic diaries.

Following this two-week period, patients were randomized to receive milnacipran as a single daily dose, milnacipran in two divided doses, or placebo for a four-week dose-escalation period (up to 200 mg/day). After this four-week period, patients entered an eight-week stable dose phase. The primary outcome measure was improvement from baseline of the patients' pain score. Seventy-two percent of patients ($n=125$) completed the study with no significant difference between groups in drop-out rates. Twice-daily milnacipran was significantly more effective than once-daily milnacipran and placebo. Adverse effects leading to early termination of the study included headache, gastrointestinal (GI) complaints, orthostatic dizziness, elevations in blood pressure, depression, lethargy, sweating, and hot flashes. The authors concluded that milnacipran administered twice daily (up to 200 mg day) is an effective analgesic in patients with FMS.

Duloxetine (Cymbalta)

Duloxetine is an antidepressant that exerts its actions by inhibiting the reuptake of serotonin and norepinephrine. Because 5HT and NE are believed to play a

key role in pain pathways, duloxetine has been studied in various animal models of pain. Common side effects associated with the use of duloxetine include nausea, dizziness, and drowsiness. Due to its effects on serotonin, use of duloxetine with other serotonergic agents should be avoided or approached with caution. Duloxetine is both a substrate and a moderate inhibitor of CYP2D6; thus, caution should be exercised when using duloxetine with other drugs metabolized by or that affect CYP2D6 (see Table 1).

The Duloxetine Fibromyalgia Trial Group conducted a study to determine if duloxetine would be safe and efficacious in the treatment of patients with FMS with or without depression.

This study was a randomized, placebo-controlled, double-blind, parallel-group study using 60 mg of duloxetine twice daily in 207 patients. All patients received placebo medication for one week and then randomized to receive duloxetine or placebo for the remaining 12 weeks. Primary outcomes included pain severity as measured on the FIQ pain item, as well as the total FIQ score. The FIQ total score improved significantly in the duloxetine treated group at week 12. The FIQ pain severity score did not differ significantly between the groups at week 12; however, significant differences were seen during earlier visits at weeks 1, 2, and 4.

Although significantly more duloxetine-treated patients reported insomnia, dry mouth, and constipation, there was no statistically significant difference in drop-out rates due to adverse events between groups. The investigators concluded that duloxetine was significantly more efficacious than placebo at improving most outcome measures in patients with FMS.

Cyclobenzaprine (Flexeril)

Cyclobenzaprine is a skeletal muscle relaxant that is pharmacologically related to the tricyclic antidepressants (TCAs). The most common side effects associated with cyclobenzaprine include drowsiness, dizziness, and xerostomia. As with SSRIs and TCAs (and like amitriptyline), cyclobenzaprine should be avoided or used with caution in patients taking MAO inhibitors. CYP1A2 inhibitors may increase the effects of cyclobenzaprine (see Table 1). In addition, additive toxicities may be possible when used with TCAs. Finally, cyclobenzaprine may increase the effects of CNS depressants. In addition to being compared with amitriptyline in a clinical study, cyclobenzaprine has been investigated in three other clinical trials.

W. J. Reynolds and colleagues conducted a double-blind, placebo-controlled, crossover study to determine the effects of cyclobenzaprine on sleep physi-

ology and symptoms of FMS. After a two-week washout period, 12 patients received cyclobenzaprine 10 mg three times a day or placebo. After a second washout period of two weeks, patients received the opposite treatment taken in the first study period. Cyclobenzaprine caused a significant reduction in evening fatigue and a significant increase in total sleep time. No significant differences were found between cyclobenzaprine and placebo on common symptoms associated with FMS (pain scores, mood ratings, etc.). The study investigators concluded that they were unable to demonstrate a beneficial effect of cyclobenzaprine on sleep physiology or symptoms of FMS.

A double-blind crossover study was conducted by S. Santandrea et al. to compare the efficacy and tolerability of cyclobenzaprine 10 mg at bedtime versus cyclobenzaprine 10 mg three times daily in FMS patients. Forty patients were randomized to receive one of the above-mentioned treatments for 15 days. After a 15-day washout period, they then received the other treatment for 15 days. Clinical assessments included: number of tender points, quality of sleep, intensity of pain, and presence/absence of anxiety, stiffness, irritable bowel syndrome (IBS), and fatigue. In addition, routine blood tests and presence of side effects were evaluated. Significant improvement in tender-point count, quality of sleep, anxiety, fatigue, IBS, and stiffness were found in both treatment groups. The percentage of side effects reported by patients in each treatment group was significantly higher in the 30-mg-per-day group. The authors concluded that cyclobenzaprine 10 mg per day was sufficient in reducing symptoms of FMS and was well tolerated.

Cyclobenzaprine has also been evaluated in combination with ibuprofen in patients with FMS. V. Fossaluzza and S. DeVita conducted an open randomized trial to compare cyclobenzaprine alone and in combination with ibuprofen in patients suffering from FMS. After a one-week washout period, 15 patients received cyclobenzaprine 10 mg, and 17 patients received cyclobenzaprine 10 mg plus ibuprofen 600 mg for 10 days. Efficacy was assessed utilizing tender-point count, pain intensity on VAS, and duration of morning stiffness. Both groups showed significant improvement for all symptoms; however, the cyclobenzaprine plus ibuprofen group demonstrated a significantly reduced duration of morning stiffness when compared with cyclobenzaprine alone. The authors concluded that cyclobenzaprine and ibuprofen given together are well tolerated and appear to reduce symptoms in patients with FMS in the short

Table 2
Randomization regimens for ibuprofen and alprazolam trial

Ibuprofen	Alprazolam	Placebo
600 mg QID	0.5 mg HS	None
600 mg QID	None	0.5 mg (alprazolam) placebo HS
None	0.5 mg HS	600 mg (ibuprofen) placebo QID
None	None	600 mg (ibuprofen) placebo QID +0.5 mg (alprazolam) placebo HS

Source: Adapted from Russell IJ, Fletcher EM, Michalek JE, et al. Treatment of primary fibrositis/fibromyalgia syndrome with ibuprofen and alprazolam. *Arthritis and Rheumatism* 1991; 34(5): 552-560.

Recommended reading: Gilliland P. *What is Fibromyalgia Syndrome?* *emedicine Instant Access to The Minds of Medicine Web Site*. Available at: <http://www.emedicine.com/pmr/topic47.htm>. Accessed April 15, 2005

exception of morning fatigue at week 3 in favor of ibuprofen, no other significant differences were found between groups. Based on these results, the authors concluded that short-term treatment with ibuprofen was no more beneficial than placebo in improving symptoms in patients with FMS.

Ibuprofen has also been investigated in combination with and against alprazolam in a double-blind, placebo-controlled study. Seventy-eight patients were randomized to receive one of the **four** regimens outlined in Table 2 for seven weeks, after which patients then received no active treatment for one week. Finally, all patients completing the study participated in a 24-week open-label period during which they received combination therapy of ibuprofen and alprazolam. Four clinical measures were assessed: Dolorimeter Score (DOL), Tender Point Index (TPI), VAS to quantitate the perception of pain (completed by patient), and VAS for overall fibromyalgia severity (completed by physician). Clinical improvement was most apparent in the groups receiving ibuprofen plus alprazolam. This finding was further confirmed during the open-label portion of the study. Based on these results, the authors concluded that the combination of ibuprofen plus alprazolam may be beneficial in some patients suffering from FMS.

Tramadol (Ultram). Tramadol is a non-narcotic analgesic that exerts its action by binding to μ opiate receptors in the central nervous system. In addition, tramadol inhibits the reuptake of norepinephrine and serotonin, thereby modifying the ascending pain pathway. Side effects most commonly reported with tramadol include dizziness, headache, somnolence, constipation, and nausea. The effects of tramadol may be increased with concomitant use of amphetamines, cimetidine, SSRIs, TCAs, linezolid, MAO inhibitors, naloxone, opioids, and quinidine. CYP2D6 inhibitors may decrease the effects of tramadol (Table 1).

Due to tramadol's unique mechanism of action and the ability of acetaminophen to enhance the therapeutic efficacy of other pain relievers, a combination tablet has been evaluated for patients with FMS. R. M. Bennett and colleagues conducted a randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of a combination tramadol/acetaminophen tablet in the treatment of patients with FMS. After a three-week washout period, 315 patients were randomized to receive tramadol 37.5 mg/acetaminophen 325 mg or placebo for 91 days. The primary efficacy outcome was defined as the cumulative time to discontinuation due

term. However, the advantage of combination therapy over cyclobenzaprine alone is limited.

Pain relievers

Ibuprofen. Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) that works by inhibiting prostaglandin synthesis. Side effects most common with ibuprofen therapy are often gastrointestinal in nature and include dyspepsia, nausea, and heartburn. Ibuprofen should be used with caution in patients with congestive heart failure (CHF), hypertension, dehydration, impaired renal/hepatic function, history of GI disease, and those taking anticoagulants. Cyclosporine, digoxin, lithium, and methotrexate levels may be increased with ibuprofen, and the renal effects of ACE inhibitors may be exacerbated by concomitant ibuprofen use. Finally, corticosteroids may increase the risk of GI ulceration when used with ibuprofen. In addition to being studied in combination with cyclobenzaprine, ibuprofen has been compared with placebo and with alprazolam in two additional studies.

M. B. Yunus et al. conducted a double-blind, placebo-controlled trial to determine the short-term effects of ibuprofen in primary fibromyalgia syndrome. Forty-six patients were randomized to receive ibuprofen 600 mg four times daily or matching placebo for the first three weeks of the study. Then both groups entered a three-week open phase during which all patients received ibuprofen 600 mg four times daily. Outcome assessment included pain rating, sleep difficulty, morning fatigue, stiffness, swelling, paresthesia, total pain sites, and total tender points. With the

to lack of efficacy. Twenty-nine percent of patients, compared with 51% of patients, respectively, discontinued treatment due to lack of efficacy from the tramadol/acetaminophen and placebo groups. The difference between groups was found to be statistically significant. No serious adverse events due to study medication were reported. The most commonly reported side effects in the tramadol/acetaminophen group were nausea, dizziness, somnolence, and constipation. Based on the study results, the investigators concluded that the combination of tramadol/acetaminophen provided moderate benefits to patients with FMS for a 13-week period. Further studies should be conducted, however, to determine the long-term efficacy of such treatment.

S-adenosyl-L-methionine

S-adenosyl-L-methionine (SAME) is a dietary supplement proposed to be useful in a variety of conditions, including fibromyalgia. Although the mechanism of action of SAME is largely unknown, it is believed that when administered directly into a joint or muscle, it appears to increase proteoglycan synthesis. Proteoglycans are important in the synthesis of cartilage. In addition, SAME is believed to exhibit anti-inflammatory and analgesic effects. Because SAME is a dietary supplement and is therefore not subject to the rigorous evaluation by the Food & Drug Administration, as are prescription medications, drug interactions and adverse effects are not completely known. Some reported drug interactions include those with antacids, ethanol, levodopa, lithium, MAO inhibitors, and TCAs. Side effects that have been reported with SAME use include dyspepsia, mania, nausea, vomiting, and pseudoparkinsonism.

SAME has been evaluated against placebo in four small studies; in three of these studies, SAME was shown to provide significant benefit over placebo. SAME has also been evaluated against a TENS (Transcutaneous Electric Nerve Stimulation) unit in FMS patients. In this study SAME was found to provide significant improvement on the tender-point score and the HAM-D when compared with the group using the TENS unit.

Of the many available dietary supplements on the market today, SAME is the best studied in the treatment of FMS patients. However, it is difficult at this time to definitively conclude whether SAME should be considered a safe and effective treatment for FMS patients. It appears that at this time, it would be wiser to attempt treatment with more well-known therapies, such as the antidepressants, when treating patients with FMS.

Other pharmacologic treatments

While antidepressants and pain relievers are the best-studied treatments for fibromyalgia, numerous other treatments have been used. Often, patients become frustrated and discouraged when traditional treatments are not successful. They and their physicians then often turn to some of these lesser-known treatments.

One study looked at the effects of intravenous morphine, lidocaine, and ketamine in patients with FMS. A total of 31 patients participated in three separate studies (nine in the morphine study, 11 in the lidocaine study, and 11 in the ketamine study). Results from the morphine study showed no significant changes in pain intensity, tender points, muscle strength, or endurance. The lidocaine test revealed a significant reduction in pain intensity when compared with placebo; however, improvements in tender points, muscle strength, and endurance were not significantly different between lidocaine and placebo. The results of the ketamine test showed a significant difference in pressure pain threshold and pain tolerance at tender points, control points, and muscle endurance. No statistically significant difference was observed between ketamine and placebo on muscle strength.

From these results, the study investigators concluded that ketamine and lidocaine may be useful in patients with FMS, but additional studies should be conducted to confirm these findings.

FMS patients often experience, in addition to pain, disturbed sleep and fatigue. Sedative effects and improvement of fatigue have been reported following the administration of melatonin. Therefore, melatonin was evaluated in an open pilot. Twenty-one patients took a 3-mg melatonin capsule 30 minutes before bedtime for four weeks. Of the primary outcome measures, significant improvement from baseline was observed for tender-point count and severity of pain at selected points, for patient and physician global assessments, and on VAS for sleep. The authors concluded that melatonin may be useful for the treatment of FMS. However, the authors did recognize that an open study such as this one has limited usefulness and that larger, randomized, placebo-controlled trials should be conducted.

Because Bennett and colleagues believed that growth hormone deficiency contributes to the symptoms of fibromyalgia, they conducted a randomized, double-blind, placebo-controlled study of growth hormone in FMS patients. Fifty women were enrolled and were randomized to receive daily subcutaneous injections of growth hormone or placebo. Outcomes

CONTINUING EDUCATION

measures included the FIQ and tender-point assessment. Significant results were seen at nine months in the growth hormone group when compared with placebo. Despite these positive results, the utility of growth hormone in FMS is limited by the cost associated with growth hormone treatment.

In addition to understanding the medications commonly used to treat FMS, it is important for the pharmacist to be able to provide basic education to FMS patients. Some basic educational points include:

Avoid changes in diet, exercise (as prescribed by one's physician), avoid major changes in activity, treat changes in mood or sleep promptly, start new medications at the lowest possible dose, and attempt to identify (and avoid) situations that have previously triggered flare-ups. By becoming educated about FMS and its treatments, pharmacist will be better able to counsel their patients and develop a trusting relationship with the patients they serve.

References are available upon request.

TEST QUESTIONS

Write your answers on the answer form appearing on page 47 (photocopies of the answer form are acceptable) or on a separate sheet of paper. Mark the most appropriate answer.

- FMS affects which age group most often?
 - Women aged 20-30
 - Men aged 20-30
 - Women aged 30-50
 - Men aged 30-50
- Out of 18 tender points, how many must be present for an official diagnosis of FMS?
 - Nine
 - 11
 - 13
 - 15
- Which neurotransmitter is thought to play a significant role in the pathophysiology of fibromyalgia?
 - Dopamine
 - Norepinephrine
 - Histamine
 - Serotonin
- Frequent symptoms of FMS include all of the following except:
 - Joint pain
 - Headache
 - Insomnia
 - Sexual dysfunction
- Of the following, which one is not a common side effect of fluoxetine?
 - Sedation
 - Anxiety
 - Headache
 - Decreased libido
- Its effects may be altered when fluoxetine is administered with which one of the following?
 - CYP2C9 inhibitor
 - CYP3A4 inhibitor
 - CYP2D6 inducer
 - CYP3A4 inducer
- Fluoxetine has been studied for the treatment of fibromyalgia in combination with which antidepressant?
 - Venlafaxine
 - Milnacipran
 - Amitriptyline
 - Duloxetine
- In the trial comparing amitriptyline and moclobemide, what was the authors' conclusion?
 - Amitriptyline shows benefit while moclobemide does not.
 - Moclobemide shows benefit while amitriptyline does not.
 - Amitriptyline and moclobemide are both beneficial.
 - Neither amitriptyline nor moclobemide is beneficial.
- Which receptor does mirtazapine not affect?
 - Alpha-1
 - Alpha-2
 - 5HT-2
 - 5HT-3
- Which dose of mirtazapine has been studied in the treatment of fibromyalgia?
 - 5-10 mg
 - 10-20 mg
 - 15-30 mg
 - 40-50 mg
- Milnacipran, at which one of the following doses, appears to be an effective analgesic in fibromyalgia?
 - Up to 50mg/day
 - Up to 100mg/day
 - Up to 150mg/day
 - Up to 200mg/day
- Duloxetine is an inhibitor of which enzyme?
 - CYP2D6
 - CYP3A4
 - CYP2C19
 - CYP1A2
- Cyclobenzaprine is pharmacologically related to which antidepressant?
 - Fluoxetine
 - Venlafaxine
 - Mirtazapine
 - Amitriptyline
- Based on the studies presented, ibuprofen appears to be most beneficial when used:
 - Alone
 - In combination with cyclobenzaprine
 - In combination with alprazolam
 - Ibuprofen has shown no benefit in FMS
- Tramadol in combination with which pain reliever has been studied for FMS?
 - Acetaminophen
 - Ibuprofen
 - Naproxen
 - Hydrocodone
- Reported drug interactions with SAME include all of the following except:
 - Ethanol
 - Lithium
 - Amitriptyline
 - Warfarin
- In the study involving lidocaine, ketamine, and morphine, which treatment showed no benefit?
 - Lidocaine
 - Ketamine
 - Morphine
 - All three showed benefit

18. For which symptom of FMS would melatonin provide the most benefit?
- a. Fatigue c. Depression
b. Pain d. Impaired concentration
19. Why is growth hormone not a feasible option for FMS treatment?
- a. It has not been shown to be effective
b. It is very costly
- c. It requires monitoring of therapeutic levels
d. It is highly toxic
20. Which is not a basic educational point related to FMS?
- a. Avoid exercise
b. Avoid significant changes in activity
c. Start new medications at the lowest possible dose
d. Avoid situations which have triggered past flare-up

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ANSWER FORM

A REVIEW OF FIBROMYALGIA AND ITS TREATMENT

NOVEMBER 21, 2005 012-999-05-227-H01

Test questions start on preceding page

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|----------------|----------------|-----------------|-----------------|-----------------|
| 1. a. b. c. d. | 5. a. b. c. d. | 9. a. b. c. d. | 13. a. b. c. d. | 17. a. b. c. d. |
| 2. a. b. c. d. | 6. a. b. c. d. | 10. a. b. c. d. | 14. a. b. c. d. | 18. a. b. c. d. |
| 3. a. b. c. d. | 7. a. b. c. d. | 11. a. b. c. d. | 15. a. b. c. d. | 19. a. b. c. d. |
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