

Management of Fibromyalgia Syndrome

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AT ANY ONE TIME, 10% TO 12% of the general population report chronic generalized musculoskeletal pain that cannot be traced to a specific structural or inflammatory cause.¹ Such idiopathic widespread pain most often will fit the classification criteria for fibromyalgia syndrome (FMS).²

The diagnosis of FMS is based on a history of widespread pain, defined as bilateral, upper and lower body, as well as spine, and the presence of excessive tenderness on applying pressure to 11 of 18 specific muscle-tendon sites.³ The 1990 American College of Rheumatology classification criteria for the diagnosis of fibromyalgia provide a sensitivity and specificity of nearly 85% in differentiating FMS from other forms of chronic musculoskeletal pain. Surveys using these criteria have found an FMS prevalence of 2% in the United States, including 3.4% of women and 0.5% of men.^{4,5} Fibromyalgia is the second most common disorder observed by rheumatologists (after osteoarthritis), yet rheumatologists in the United States currently provide care for less than 20% of individuals with fibromyalgia.^{6,7}

Chronic pain syndromes, such as FMS, are defined by subjective symptoms and lack unique pathophysiological characteristics. Questions often arise regarding the nature and existence of illnesses like FMS. Indeed, no discrete

Context The optimal management of fibromyalgia syndrome (FMS) is unclear and comprehensive evidence-based guidelines have not been reported.

Objective To provide up-to-date evidence-based guidelines for the optimal treatment of FMS.

Data Sources, Selection, and Extraction A search of all human trials (randomized controlled trials and meta-analyses of randomized controlled trials) of FMS was made using Cochrane Collaboration Reviews (1993-2004), MEDLINE (1966-2004), CINAHL (1982-2004), EMBASE (1988-2004), PubMed (1966-2004), Healthstar (1975-2000), Current Contents (2000-2004), Web of Science (1980-2004), PsychInfo (1887-2004), and Science Citation Indexes (1996-2004). The literature review was performed by an interdisciplinary panel, composed of 13 experts in various pain management disciplines, selected by the American Pain Society (APS), and supplemented by selected literature reviews by APS staff members and the Utah Drug Information Service. A total of 505 articles were reviewed.

Data Synthesis There are major limitations to the FMS literature, with many treatment trials compromised by short duration and lack of masking. There are no medical therapies that have been specifically approved by the US Food and Drug Administration for management of FMS. Nonetheless, current evidence suggests efficacy of low-dose tricyclic antidepressants, cardiovascular exercise, cognitive behavioral therapy, and patient education. A number of other commonly used FMS therapies, such as trigger point injections, have not been adequately evaluated.

Conclusions Despite the chronicity and complexity of FMS, there are pharmacological and nonpharmacological interventions available that have clinical benefit. Based on current evidence, a stepwise program emphasizing education, certain medications, exercise, cognitive therapy, or all 4 should be recommended.

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boundary separates syndromes such as FMS, chronic fatigue syndrome, irritable bowel syndrome, or chronic muscular headaches.⁸ Furthermore, these illnesses are each comorbid with mood disturbances.⁹

Defining pain syndromes like FMS, headaches, or back pain provides a common framework to study the clinical and physiological characteristics.¹⁰ Research during the past decade has demonstrated similar abnormal pain processing in FMS and related chronic pain syndromes. Patients with FMS have lowered mechanical and thermal pain thresholds, high pain ratings for noxious stimuli, and altered temporal

summation of pain stimuli.¹⁰⁻¹³ Physiological evidence of altered pain processing in FMS has been demonstrated by brain imaging¹⁴⁻¹⁶ as well as

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by a 3-fold higher concentration of cerebrospinal fluid substance P compared with that in healthy controls.¹⁷

The familial coaggregation and frequent comorbidity of FMS, irritable bowel syndrome, and chronic fatigue syndrome with mood disorders also suggests a major role for neuroendocrine and stress-response abnormalities.⁹ Specific polymorphisms in the serotonin transporter gene and the catechol-O-methyltransferase enzyme that inactivates catecholamines have been associated with FMS.¹⁸⁻²⁰ Altered patterns of basal and stimulated activity of several neuroendocrine axes and autonomic nervous system dysfunction have also been demonstrated.²¹⁻²³ Psychosocial factors contribute greatly to the clinical expression of FMS and related disorders.²⁴

Despite improved recognition and understanding of FMS, treatment remains challenging. Some believe that no effective treatment exists.²⁵ Nevertheless, approximately 500 peer-reviewed articles on FMS therapy have been published during the past 25 years.²⁶ We summarize the findings of a report commissioned by the American Pain Society (APS) to provide evidence-based guidelines for the optimal treatment of FMS.

METHODS

Data Sources and Study Selection

Under the auspices of the APS, an interdisciplinary panel was selected, that comprised 13 experts in various pain management disciplines. A comprehensive literature review conducted by this panel and staff members and commissioned by the APS, including the Utah Drug Information Service from The University of Utah Health Sciences Drug Information Resource Center, included MEDLINE (1966-2004), CINAHL (1982-2004), EMBASE (1988-2004), PubMed (1966-2004), Healthstar (1975-2000), Current Contents (2000-2004), Web of Science (1980-2004), PsychInfo (1887-2004), Science Citation Indexes (1996-2004), and Cochrane Collaboration Reviews (1993-2004). References were consistently checked electronically for any relevant articles. A total of 505 articles

were reviewed and classified according to their level of evidence.

Evidence for treatment efficacy was ranked as strong (positive results from a meta-analysis or consistently positive results from more than 1 randomized controlled trial [RCT]), moderate (positive results from 1 RCT or largely positive results from multiple RCTs or consistently positive results from multiple non-RCT studies), and weak (positive results from descriptive and case studies, inconsistent results from RCTs, or both). We also discuss therapies that are commonly used in FMS but have not been adequately evaluated.

Outcome Measures

Change in pain was the most common outcome measure and was usually evaluated with 100-mm numerical rating scales or visual analog scales. Similar self-administered instruments were used to evaluate fatigue, sleep, and global well-being in most trials. A manual tender point assessment was usually performed, although some trials also measured pain thresholds with dolorimetry. Function was generally assessed by self-reported, validated instruments, most often the Fibromyalgia Impact Questionnaire (FIQ).^{27,28} The FIQ measures physical functioning, work status, depression, anxiety, morning tiredness, pain, stiffness, fatigue, and well-being during the preceding week.

Psychological function was often evaluated with FIQ subscales for depression and anxiety or validated instruments for depression (Beck Depression Inventory²⁹ and Hamilton Rating Scale³⁰). Most studies that evaluated exercise training also used measures of cardiorespiratory fitness, such as submaximal or maximal treadmill or cycle ergometer tests, 6-minute walk, and measured grip strength or hip and knee extension strength.

TREATMENTS

Diagnosis and Education

Although no study has formally assessed the therapeutic impact of an FMS diagnosis, we believe that establishing the diagnosis, if integrated with patient

education, is an essential component of high-quality management. Nevertheless, some clinicians have speculated that knowledge of the FMS diagnosis has an adverse effect on patient outcome.²⁵ A single study³¹ designed to evaluate whether the fibromyalgia diagnosis alters health status followed previously nonlabeled FMS (prelabeling) patients after they were given the FMS diagnosis (postlabeling). There was significant improvement in health satisfaction and fewer symptoms 3 years postlabeling. No significant increase in the percentage of patients claiming disability occurred postlabeling.

There is strong evidence that intensive patient education is an effective treatment in FMS. Randomized controlled trials compared patient education with wait-listed or untreated controls or with stretching and movement.³²⁻³⁵ Education was usually given in a group format using lectures, written materials, group discussions, and demonstrations. Length of the education ranged from 6 to 17 sessions. Educational groups improved on 1 or more outcomes including pain, sleep, fatigue, self-efficacy, quality of life, and the 6-minute walk. Changes in the treated groups were maintained for 3 to 12 months. A single multidisciplinary education program, conducted over 1½ days with 100 patients, demonstrated significant improvements at 1-month posttreatment in the FIQ total score as well as in pain severity, fatigue, morning tiredness, stiffness, anxiety, and depression.³⁶

Medications

Pharmacotherapy for FMS has been most successful with central nervous system agents (BOX 1). Although they carry labels such as antidepressant, muscle relaxant, or anticonvulsant, these drugs affect various neurochemicals (eg, serotonin, norepinephrine, substance P) that have a broad range of activities in the brain and spinal cord, including modulation of pain sensation and tolerance.

Although likely to change in the future, none of the drugs reviewed here are currently approved by the US Food and

Box 1. Treatment of Fibromyalgia Syndrome**Medications****Strong Evidence for Efficacy**

Amitriptyline: often helps sleep and overall well-being; dose, 25-50 mg at bedtime.^{37-39,42,43}

Cyclobenzaprine: similar response and adverse effects; dose, 10-30 mg at bedtime.³⁹⁻⁴¹

Modest Evidence for Efficacy

Tramadol: long-term efficacy and tolerability unknown; administered with or without acetaminophen; dose, 200-300 mg/d.⁵⁴⁻⁵⁶

Serotonin reuptake inhibitors (SSRIs):

Fluoxetine (only one carefully evaluated at this time): dose, 20-80 mg; may be used with tricyclic given at bedtime; uncontrolled report of efficacy using sertraline.⁴⁵⁻⁴⁷

Dual-reuptake inhibitors (SNRIs):

Venlafaxine: 1 RCT ineffective but 2 case reports found higher dose effective.⁴⁹⁻⁵¹

Milnacipran: effective in single RCT.⁵²

Duloxetine: effective in single RCT.⁵³

Pregabalin: second-generation anticonvulsant; effective in single RCT.⁵⁷

Weak Evidence for Efficacy

Growth hormone: modest improvement in subset of patients with FMS with low growth hormone levels at baseline.⁶³

5-Hydroxytryptamine (serotonin): methodological problems.^{59,60}

Tropisetron: not commercially available.⁵⁸

S-adenosyl-methionine: mixed results.⁶¹

No Evidence for Efficacy

Opioids, corticosteroids, nonsteroidal anti-inflammatory drugs, benzodiazepene and nonbenzodiazepene hypnotics, melatonin, calcitonin, thyroid hormone, guaifenesin, dehydroepiandrosterone, magnesium.

Nonmedicinal Therapies**Strong Evidence for Efficacy (Wait-List or Flexibility Controls But Not Blinded Trials)**

Cardiovascular exercise: efficacy not maintained if exercise stops.⁶⁶⁻⁷⁵

CBT: improvement often sustained for months.⁸³⁻⁸⁷

Patient education: group format using lectures, written materials, demonstrations; improvement sustained for 3 to 12 months.³²⁻³⁶

Multidisciplinary therapy, such as exercise and CBT or education and exercise.^{76-78,91-98}

Moderate Evidence for Efficacy

Strength training,^{75,79} acupuncture,¹⁰⁴⁻¹⁰⁶ hypnotherapy,^{99,100} biofeedback,^{101,103} balneotherapy.^{111,112}

Weak Evidence for Efficacy

Chiropractic, manual, and massage therapy; electrotherapy, ultrasound.¹⁰⁷⁻¹¹⁰

No Evidence for Efficacy

Tender (trigger) point injections, flexibility exercise.

CBT indicates cognitive behavioral therapy; RCT, randomized controlled trial; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor.

Drug Administration for treatment of FMS. Many of these drugs are older agents for which approval is unlikely to be sought. Furthermore, the Food and Drug Administration is just beginning to consider the parameters on which approval of a drug for treatment of FMS could be granted (J. Witter, written communication, June 2003).

Tricyclic Antidepressant Medications. The strongest evidence for medication efficacy in FMS is for tricyclic antidepressant medications, particularly amitriptyline and cyclobenzaprine. In 1986, 2 RCTs demonstrated modest effectiveness of amitriptyline (25-50 mg at bedtime).^{37,38} Other RCTs confirmed these results during the next decade.³⁹ Cyclobenzaprine, usually marketed as a muscle relaxant but structurally a tricyclic compound, has also been effective in RCTs lasting 6 to 12 weeks.³⁹⁻⁴¹ The usual dose of cyclobenzaprine found to be effective in FMS has been 10 to 40 mg/d. A recent meta-analysis confirmed the efficacy of cyclobenzaprine in FMS.⁴¹

Two meta-analyses found that tricyclic antidepressants were better than placebo in the treatment of FMS. Arnold and Keck⁴² found 9 of 16 studies suitable for meta-analysis. Tricyclic agents were more effective than placebo for all clinical outcomes, especially quality of sleep. A significant clinical response was observed in 25% to 37% of patients with FMS and the overall degree of efficacy was modest. A second meta-analysis also found that antidepressants improved sleep, fatigue, pain, and sense of well-being, but there was no improvement in tender-point pain.⁴³ Both meta-analyses found better evidence for the efficacy of tricyclic medications than other classes of antidepressants. Most of these RCTs were of short duration, 6 to 12 weeks. The longest study of tricyclic medications followed up 208 patients treated with amitriptyline, cyclobenzaprine, or placebo for 6 months and reported that the initial improvement at 6 and 12 weeks was lost at 26 weeks.³⁹

Other Antidepressant Medications. There is moderate evidence that the selective serotonin reuptake inhibitor

(SSRI) fluoxetine is effective in FMS. In 1 article of 42 patients with fibromyalgia, there was no significant benefit of fluoxetine (20 mg/d) compared with placebo over a 6-week period.⁴⁴ However, a flexible placebo-controlled dose study of fluoxetine (<80 mg/d) demonstrated significant efficacy in 60 women with fibromyalgia.⁴⁵ Improvement was noted on FIQ total score as well as subscores for pain, fatigue, and depression. Pain in tender points and total myalgic scores were not significantly improved. There was no difference in the measures of mood disturbances in the 2 groups and the effect of fluoxetine on pain was still significant after adjustment for change in depression score.

A crossover trial found that fluoxetine (20 mg/d) as well as amitriptyline (25 mg/d) were better than placebo in a number of outcome measures in patients with FMS.⁴⁶ The combination of the 2 medications was better than either alone. Similar results were noted with fluoxetine (20 mg) combined with cyclobenzaprine (10 mg) over a 12-week period.⁴⁷ In 1 controlled study, sertraline (50 mg) was as effective as amitriptyline (25 mg).⁴⁸

Recent RCTs of dual serotonin and norepinephrine reuptake inhibitors (SNRIs) have been undertaken. An RCT of 90 patients with FMS found that venlafaxine (75 mg/d) was not significantly different from placebo⁴⁹; however, it was found useful in 2 small open-label studies using higher doses.^{50,51} Two new SNRIs, milnacipran and duloxetine, demonstrated efficacy in a number of outcome variables in 2 high-quality multicenter RCTs. Milnacipran, twice daily, improved pain and other outcome measures in 125 patients with FMS over 12 weeks.⁵² Duloxetine (60 mg twice daily) was better than placebo in FIQ scores and a number of other outcomes, independent of its effect on mood, in 207 patients with FMS over 3 months.⁵³

Analgesic Medications. Tramadol, with or without acetaminophen, has been effective in 3 RCTs in patients with FMS.⁵⁴⁻⁵⁶ A small double-blind, placebo-controlled trial initially suggested that tra-

madol is effective and well-tolerated in patients with FMS.⁵⁴ A larger RCT reported decreased visual analog pain scores, improved pain relief, and decreased pain threshold after tramadol treatment.⁵⁵ The most recent article compared a combination of 37.5-mg tramadol/325-mg acetaminophen tablets with placebo in 315 patients with FMS.⁵⁶ Discontinuation rates, pain scores, and the FIQ scores were better in the tramadol/acetaminophen group compared with patients receiving placebo.

There is no evidence that nonsteroidal anti-inflammatory drugs are effective when used alone in FMS, although they may be useful adjuncts for analgesia when combined with tricyclic medications.³⁸ There have been no RCTs of opioids in patients with FMS. Opioids should be considered only after all other medicinal and nonmedicinal therapies have been exhausted.

Anticonvulsant Medications. Although gabapentin is currently undergoing an RCT, no trials have yet been reported in patients with FMS. However, pregabalin, a second-generation anticonvulsant, has been found to be effective in FMS in an RCT.⁵⁷ This multicenter trial compared various doses of pregabalin in 529 patients with FMS. Pregabalin (450 mg/d) significantly reduced the average severity of pain compared with placebo (mean difference, -0.93; $P < .001$) and significantly more patients had a more than 50% improvement in pain. There were also significant improvements in sleep, fatigue, and health-related quality of life.

Other Medications. Tropicisetron, a 5-hydroxytryptamine-3 receptor antagonist, and 5-hydroxytryptophan, an intermediate metabolite of L-tryptophan, were more effective than placebo in RCTs.⁵⁸⁻⁶⁰ S-adenosylmethionine, an agent with both anti-inflammatory and antidepressant effects, was found helpful in one study but performed no better than placebo in a second study in patients with FMS.⁶¹ There has been no evidence that benzodiazepenes or nonbenzodiazepene sedatives are effective in patients with FMS other than their role in sleep disturbances.

Hormones and Supplements. The only controlled study of corticosteroids in patients with FMS reported that 10 mg of prednisone daily was not effective.⁶² Administration of parenteral growth hormone to patients with FMS who had low levels of growth hormone improved function modestly.⁶³ There are no data from RCTs to support the use of thyroid hormone, dehydroepiandrosterone, melatonin, or calcitonin in the treatment of FMS. Dietary modifications, nutritional supplements, magnesium, herbal, and vitamin therapy have not been adequately evaluated in FMS. The only RCT of guaifenesin found no significant effects on pain, other symptoms, or laboratory measures in a 12-month study.⁶⁴

Nonmedicinal Therapy

Exercise. There is strong evidence that cardiovascular exercise is effective treatment in FMS. The therapeutic benefit of exercise for individuals with fibromyalgia was first recognized 20 years ago when patients randomized to 20 weeks of high-intensity exercise had greater improvements in fitness, tender point pain thresholds, and global assessment ratings than did patients randomized to flexibility training.^{65,66} The benefits of aerobic exercise⁶⁷⁻⁷¹ and muscle strengthening⁷² have subsequently been confirmed in FMS clinical trials. Pool exercise has been well-tolerated and especially helpful.^{70,73,74}

Busch et al⁷⁵ performed a systematic review of 16 exercise trials involving a total of 724 participants with FMS and compared exercise intervention groups ($n = 379$), control groups ($n = 277$), or groups receiving an alternate treatment ($n = 68$). The studies were classified by whether they used exercise alone or combined exercise with a nonexercise component (composite intervention). Exercise-only interventions were subdivided according to whether the intervention involved 1 type of exercise (aerobic training, strength training, or flexibility training) or more than 1 type of exercise (mixed exercise). Studies were considered to be high quality if their methods were adequate and also met criteria for

adequate training stimuli, as determined by American College of Sports Medicine guidelines. Seven studies^{65,67,76-80} were high-quality training studies: 4 aerobic training, with 1 a mixture of aerobic, strength, and flexibility training; 1 strength training; and 2 with exercise training as part of a composite treatment. The 4 high-quality aerobic training studies used cycle ergometry, aerobic dance, whole-body aerobics, and walking indoors.^{65,76-78}

Overall, there was greater improvement in the exercise groups vs control groups in aerobic performance (17.1% increase in aerobic performance with exercise vs 0.5% increase in the control groups), tender-point pain pressure threshold (28.1% increase vs 7.0% decrease), and improvements in pain (11.4% decrease in pain vs 1.6% increase). One strength training intervention found significant improvement in pain and function.⁷⁹ One trial using walking, strengthening, and flexibility found significant improvements in tender-point pain pressure threshold and aerobic performance but not in global well-being or self-efficacy.⁸⁰

Two high-quality studies combined exercise with at least 1 other nonexercise intervention. Gowans et al⁶⁷ reported significant improvements in aerobic performance, global well-being, fatigue, and sleep in patients with FMS who received education and aerobic training compared with wait-list controls. Significant improvements were found in tender-point pain, self-reported physical function, and self-efficacy for function in an aerobic training plus biofeedback group compared with the control group.⁷⁶ Stretching has not been adequately tested but aerobic fitness training was better than stretching exercises in pain, depression, and function, as well as physical fitness.^{81,82}

Cognitive Therapies. There is strong evidence that psychological and behavioral therapy, especially cognitive behavioral therapy (CBT), is effective in FMS. Randomized controlled trials of CBT with longitudinal data over 6 to 30 months found decreased pain sever-

ity and improved function in FMS.⁸³⁻⁸⁷ Improvement was also noted in 3 RCTs of meditation, relaxation, and stress management.^{78,88,89} Most control groups were wait-listed or education controls. Systematic reviews have confirmed that CBT improved pain, fatigue, mood, and function in FMS.^{90,91}

Multidisciplinary Treatment. There is strong evidence that multidisciplinary treatment is effective in treating FMS. Five RCTs of multidisciplinary treatment that combined education, CBT, or both with exercise found beneficial effects on patient self-efficacy, overall FMS impact as measured by the FIQ, significant decreases in pain, and improvements on a 6-minute walk.^{33,67,73,74,92,93} Treatment length ranged from 6 to 24 weeks. One RCT studied the effects of a 6-week biofeedback therapy in combination with education, CBT, and exercise and found the combination better than the education attention control group on self-efficacy and tender points.⁷⁶ Significant improvements in pain severity, physical activity, and physician rating of disease severity were also noted in the combination group. Each of these RCTs collected follow-up data between 3 months and 2 years after completion of the experimental treatment. In all of these RCTs, treatment gains were maintained.

Six uncontrolled single-group pretest-posttest clinical trials, using multidisciplinary approaches and ranging in length from 1.5 days to 24 weeks, have found significant positive changes in the FIQ, pain severity, self-efficacy, and the 6-minute walk.^{83,84,86,94-97} Five of these trials had a follow-up component between 2 and 30 months after the end of the trial.^{86,94-96} Improvements in the outcomes were maintained in 3 trials while the other 2 trials did not maintain improvements in the primary outcome of visual analog scale pain but the other outcome measures did improve.

Other Treatments. Although commonly used, there are no RCTs of trigger-point and tender-point injections in patients with FMS. Uncontrolled articles suggest that dry needling or soft-tissue

injections with lidocaine or saline are equally effective. There is some evidence to support the use of relaxation techniques, biofeedback, and hypnosis in patients with FMS. In 1 study,⁹⁸ patients had less pain during deep relaxation and pleasant imagery than the control group did. Eight sessions of hypnotherapy delivered over 12 weeks improved visual analog scale pain ratings, fatigue, sleep, and global assessment.⁹⁹ A third study using hypnotically induced analgesia found that patients experienced less pain during hypnosis than at rest.¹⁰⁰ Subcortical cerebral blood flow increased in the patients who were treated. Electromyogram biofeedback was moderately effective in decreasing pain ratings and tender-point counts.¹⁰¹⁻¹⁰³

There is modest evidence to support the use of acupuncture in patients with FMS. A review of 7 studies reported increased pain thresholds and decreased pain ratings and medication use with acupuncture treatment.¹⁰⁴ One high-quality RCT of electroacupuncture found that along with positive changes in pain perception and sleep quality, pain threshold improved by 70% in the treated group compared with only 4% in the sham acupuncture control group.¹⁰⁵ However, a recent RCT reported equal improvement in sham compared with traditional acupuncture.¹⁰⁶

Chiropractic spinal manipulation and soft-tissue massage decreased tenderness in patients with FMS.^{107,108} The chiropractic manipulation was a pilot uncontrolled trial but the massage trial comprised 16 patients with active treatment compared with 13 controls who received discussion group intervention. Connective tissue manipulation and massage has produced positive results by reducing depression, pain intensity, and amount of analgesics used.^{108,109} Combined ultrasound and inferential current improved pain levels and sleep compared with sham treatment.¹¹⁰ Two Israeli RCTs concluded that medicinal baths (Dead Sea sulfur baths) resulted in relief of FMS-related symptoms of pain, fatigue, stiffness, and tender points.^{111,112}

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE TREATMENT TRIALS

There is strong evidence to support the use of low-dose tricyclic medications, such as amitriptyline and cyclobenzaprine, as well as cardiovascular exercise, CBT, patient education, or a combination of these for the management of FMS. There is moderate evidence that tramadol, SSRIs, SNRIs, and certain anticonvulsants are effective but the complete results of some trials are not available and systematic reviews have not been reported. Moderate evidence exists for the efficacy of strength training exercise, acupuncture, hypnotherapy, biofeedback, massage, and warm water baths. Many of the commonly used FMS therapies have not been carefully evaluated. Based on these reports, a stepwise FMS management guideline can be recommended (BOX 2).

The FMS diagnosis first must be confirmed and the condition explained to the patient and family. Any comorbid illness, such as mood disturbances or primary sleep disturbances, should be identified and treated. Medications to consider initially are low doses of tricyclic antidepressants or cyclobenzaprine. Some SSRIs, SNRIs, or anticonvulsants may become first-line FMS medications as more RCTs are reported. All patients with FMS should begin a cardiovascular exercise program. Most patients will benefit from CBT or stress reduction with relaxation training. A multidisciplinary approach combining each of these modalities may be the most beneficial. Other medications such as tramadol or combinations of medications should be considered. Patients with FMS not responding well to these steps should be referred to a rheumatologist, physiatrist, psychiatrist, or pain management specialist.

There are important shortcomings in the FMS treatment literature. Most medication trials have been short, such as 6 to 12 weeks. Fibromyalgia syndrome is a chronic illness. There is strong evidence for effective FMS treatments in the short-term but more studies need to determine whether the im-

provement is maintained over months or years. Many of the medication trials had methodological problems, including inadequate blinding, small number of patients, and nonstandardized outcome measures. Exercise and CBT trials were of longer duration and their efficacy often persisted for up to 24 weeks. Such interventions cannot be adequately blinded, although appropriate control groups were evaluated. These same issues have been noted in clinical trials of other chronic idiopathic illnesses, such as headaches and irritable bowel syndrome.

Much of the treatment response differences in FMS clinical trials may be related to the heterogeneity of this illness. No therapeutic trials have included patients with FMS who also have a rheumatic disease, such as rheumatoid arthritis or systemic lupus erythematosus. Recent work has identified subgroups of patients with FMS on the basis of psychosocial status and biological response to pain.^{96,113} The ability of patients with FMS to self-manage pain correlated with their functional status.¹¹⁴ In another study, brain imaging and broad psychological profiles were used to identify 4 FMS patient subgroups.¹¹⁵ Such studies suggest that certain treatments may be differentially effective in individual patients. For example, interventions impacting central pain mechanisms may be most effective in those with few neuropsychological symptoms while therapies that affect many central nervous system pathways may be best suited to patients reporting multiple symptom domains.

Evaluation of multidisciplinary management has been especially challenging. Very few trials attempted to combine medication and nonpharmacological treatments.^{98,116} Several non-medicinal trials maintained stable drug doses during the clinical trial but failed to evaluate drug efficacy. Future RCTs in FMS using multidisciplinary therapies should include medications, and future clinical trials should use a core set of outcome measures. International efforts are under way to establish a working definition of optimal

Box 2. Stepwise Fibromyalgia Management

Step 1

Confirm the diagnosis.
Explain the condition.
Evaluate and treat comorbid illness, such as mood disturbances and primary sleep disturbances.

Step 2

Trial with low-dose tricyclic antidepressant or cyclobenzaprine.
Begin cardiovascular fitness exercise program.
Refer for cognitive behavior therapy or combine that with exercise.

Step 3

Specialty referral (eg, rheumatologist, physiatrist, psychiatrist, pain management).
Trials with selective serotonin reuptake inhibitor, serotonin and norepinephrine reuptake inhibitor, or tramadol.
Consider combination medication trial or anticonvulsant.

FMS outcome measures. Complete protocols for all treatments, including both pharmacological and nonmedicinal therapies, should be delineated so that replication can be accomplished with some certainty.

As we learn more about pathophysiologic and genetic mechanisms, there will be enormous opportunities to develop therapies that improve health-related quality of life in patients with FMS. An ongoing challenge will be to define individual patient characteristics and subgroups that will respond best to a specific therapy. Techniques such as individualized patient trials can be widely applied in the clinic and are especially useful in conditions such as FMS.^{117,118} Like any complex chronic pain syndrome, FMS cannot be effectively treated with one approach to intervention. This fits with the heterogeneity of the illness and the complexity of evaluating its outcome. Optimal FMS management requires a combination of

pharmacological and nonmedicinal therapies best arrived at when patients and health care professionals work as a team.

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