

Exercise and antidepressants improve fibromyalgia

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Practice recommendations

- Fibromyalgia is diagnosed based on a patient's report of widespread pain of 3 months' duration or longer, and identification of 11 of 18 possible tender points (C).
- Fibromyalgia is functionally disabling and diminishes well-being; therefore, supportive care and evidence-based interventions should be offered (C).
- Aerobic exercise and antidepressants have been shown to moderately relieve symptoms of fibromyalgia in the short term (A).

When a patient complains of pain "all over," consider fibromyalgia, which typically causes a well-documented pattern of pain and characteristic points of tenderness observable on physical exam. Once alternative diagnoses have been ruled out, offer the patient a 2-pronged therapeutic regimen that has proven successful at moderately relieving symptoms.

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FIRST RULE OUT CONCOMITANT OR MIMICKING DISORDERS

Consider the differential diagnosis carefully.¹ A person who meets the criteria for fibromyalgia may have yet another cause of chronic pain, such as rheumatoid arthritis, or may instead have a different treatable condition that mimics fibromyalgia.

Drug-induced myopathy. Pain suggestive of fibromyalgia should prompt a review of the patient's medicines. Drug-induced myopathy may occur in persons taking colchicine, statins, corticosteroids, or antimalarial drugs.

Connective tissue, autoimmune, and rheumatologic disorders. Consider this group of disorders next. In 1 study, one fourth of persons referred to a rheumatology clinic with presumed fibromyalgia instead had a spondyloarthropathy.²

Dermatomyositis and polymyositis may present with muscle pain and tenderness but, unlike fibromyalgia, cause proximal muscle weakness.

Systemic lupus erythematosus, rheumatoid arthritis, and polymyalgia rheumatica can also lead to widespread pain.

Blood tests such as antinuclear antibody (ANA), C-reactive protein, or erythrocyte sedimentation rate (ESR) may prove helpful when a patient has a history of unexplained rashes, fever, weight loss, joint swelling, iritis, hepatitis,

nephritis, or inflammatory back pain (onset before age 40, insidious onset, present for more than 3 months, associated with morning stiffness, improvement with exercise).³ In the absence of these signs, ANA, rheumatoid factor, and ESR testing in persons with fatigue and diffuse musculoskeletal pain have low positive predictive value.⁴ The rate of false-positive ANA results may be as high as 8% to 11%, especially at low titers.^{5,6}

Hypothyroidism. Widespread musculoskeletal pain has also been associated with hypothyroidism (level of evidence [LOE]: **2**, case-control design),^{7,8} supporting the inclusion of a thyroid-stimulating hormone in the work-up of fibromyalgia (strength of recommendation [SOR]: **B**). More recent research suggests that musculoskeletal pain is more related to thyroid microsomal antibodies than to hypothyroidism,⁹ but there has been no further evaluation of antithyroid antibodies in persons with fibromyalgia.

■ DIAGNOSIS: MOSTLY BY CLINICAL JUDGMENT

Persons with fibromyalgia have widespread pain, often worst in the neck and trunk.¹ Additional symptoms include fatigue, morning stiffness, waking unrefreshed, paresthesias, and headache.^{1,10-15} (See "The toll of fibromyalgia.")

Accepted criteria

The diagnosis of fibromyalgia is based on 2 criteria:

1. A patient's report of widespread pain (right and left sides of the body, above and below the waist, and including the axial skeleton) persisting for at least 3 months
2. The clinician's identification of at least 11 of 18 potential tender points as specified in the American College of Rheumatology (ACR) 1990 Criteria for the Classification of Fibromyalgia (**Figure**) (LOE: **3**, case-control design, nonindependent reference standard).¹

These criteria do not exclude persons with rheumatic diseases or other chronic pain conditions.^{1,37-39}

The toll of fibromyalgia

In community-based studies, 2% of adults¹⁶ and 1.2% to 6.2% of school-age children screened positive for fibromyalgia.¹⁷⁻¹⁹ Females are at higher risk than males, and risk increases with age, peaking between 55 and 79 years.

Morbidity associated with fibromyalgia is considerable.^{16,20,21} In one report, persons with fibromyalgia scored lower on a well-being scale than persons with rheumatoid arthritis or advanced cancer.²²

Persons with fibromyalgia use an average of 2.7 drugs at any one time for related symptoms, and they make an average of 10 outpatient visits per year and are hospitalized once every 3 years.²³

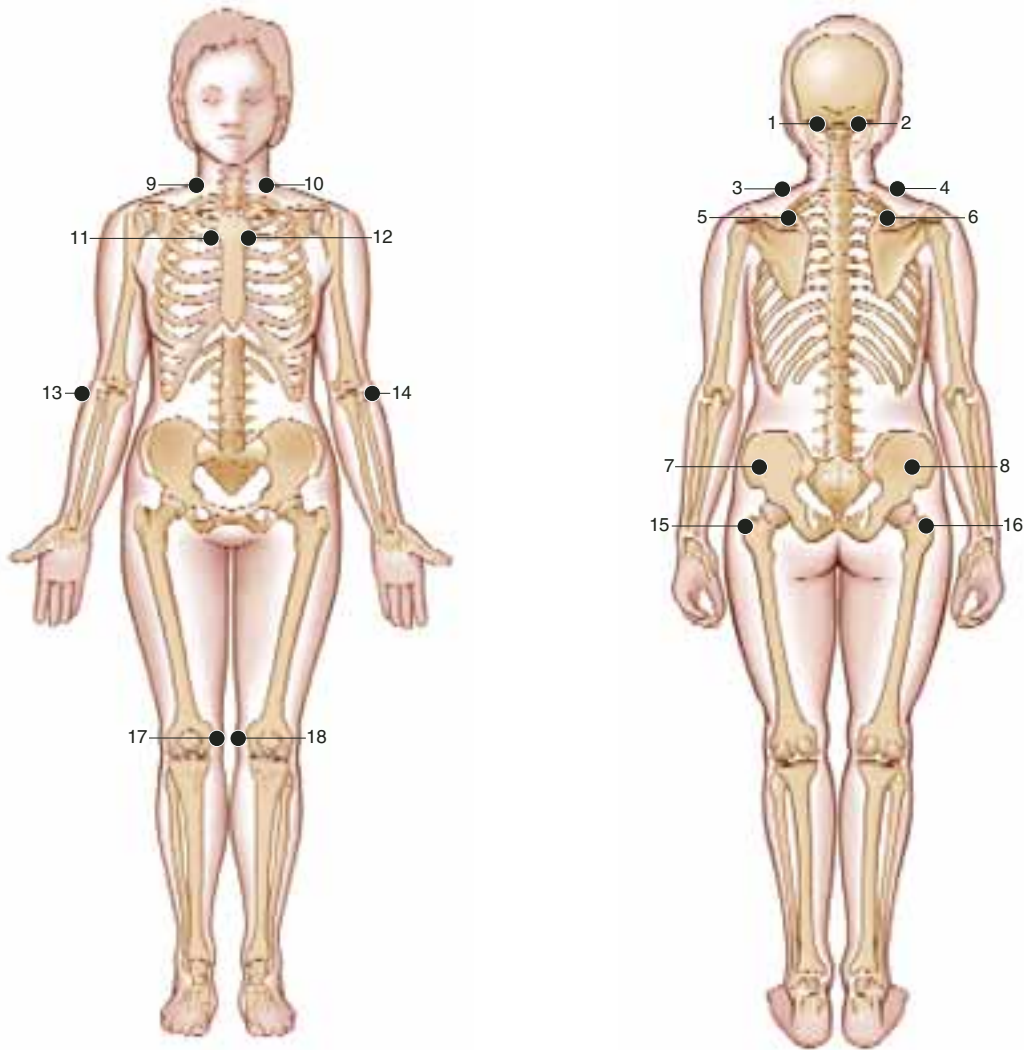
Fibromyalgia has been associated with osteoporosis.²⁴ Compared with other rheumatic diseases, fibromyalgia results in a high rate of surgery, including hysterectomies, appendectomies, back and neck surgery, and carpal tunnel surgery.^{23,25} Among adults who seek medical attention, fewer than 30% have been reported to recover from fibromyalgia within 10 years of onset.²⁶⁻²⁹

However, symptoms tend to remain stable²⁷ or lessen over time,^{28,30-32} with no increase in 10-year mortality.³³ Children appear much more likely to recover from fibromyalgia, with complete resolution in more than 50% by 2 to 3 years in several studies.^{13,18,34,35}

Cormorbid conditions

Compared with other rheumatologic conditions, persons with fibromyalgia more often suffer from comorbid conditions,²³ including chronic fatigue syndrome, migraine headaches, irritable bowel syndrome, irritable bladder symptoms, temporomandibular joint syndrome, myofascial pain syndrome, restless legs syndrome, and affective disorders.^{23,36,37}

FIGURE Manual tender point survey for fibromyalgia



Apply 4 kg of pressure, at a rate of 1 kg/sec, using the thumb pad of the dominant hand. Palpate each site only once without probing. Instruct the patient to rate pain after each palpation, from 0 (no pain) to 10 (worst pain ever experienced). A rating of 2 or more identifies a tender point.

Patient seated

	L	R
Occiput: Suboccipital muscle insertions	1 <input type="checkbox"/>	2 <input type="checkbox"/>
Trapezius: Midpoint of upper border	3 <input type="checkbox"/>	4 <input type="checkbox"/>
Supraspinatus: Above scapular spine near medial border	5 <input type="checkbox"/>	6 <input type="checkbox"/>
Gluteal: Upper outer quadrant of buttocks at anterior edge of gluteus maximus	7 <input type="checkbox"/>	8 <input type="checkbox"/>
Low cervical: Anterior aspect of the interspaces between the transverse processes of C5-7	9 <input type="checkbox"/>	10 <input type="checkbox"/>
Second rib: Just lateral to second costochondral junction	11 <input type="checkbox"/>	12 <input type="checkbox"/>
Lateral epicondyle: 2 cm distal to lateral epicondyle	13 <input type="checkbox"/>	14 <input type="checkbox"/>

Patient on side

Greater trochanter: 2 cm posterior to the greater trochanteric prominence	15 <input type="checkbox"/>	16 <input type="checkbox"/>
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Patient supine

Knee: Medial fat pad proximal to the joint line	17 <input type="checkbox"/>	18 <input type="checkbox"/>
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Adapted from Okifuji et al, 1997.⁴⁶



Caveats with the criteria

Despite these well-defined criteria, the diagnosis is not as clear-cut as it may appear. In 1990, the ACR convened a panel of 24 experts to define and standardize the diagnosis of fibromyalgia. The basis for this consensus was a group of 293 patients with fibromyalgia, each of whom had been assessed by one of the expert investigators according to “his or her usual method of diagnosis.”¹

The investigators determined the unique characteristics of fibromyalgia by comparing the 293 cases to 265 controls who had other chronic pain conditions (eg, low back pain syndromes, neck pain syndromes, regional tendonitis, possible systemic lupus erythematosus, rheumatoid arthritis). The investigators considered a multitude of symptoms and signs including sleep disturbance, morning stiffness, paresthesias, irritable bowel syndrome, fatigue, and anxiety. Their conclusion was that widespread pain and tender points were the most sensitive (88.4%) and specific (81.1%) distinguishing criteria for fibromyalgia.¹

No reference standard. However, these calculations of sensitivity and specificity are less meaningful than in studies where an independent reference standard or gold standard is available. The ACR expert panel derived the criteria in a circular way using a nonindependent reference standard—ie, patients thought to have fibromyalgia compared with control patients thought not to have fibromyalgia. The expert panel essentially set the specificity of the criteria at 100%, since the specificity is based on the rate of false positives.

Furthermore, because there was no objective gold standard for determining who truly had fibromyalgia (and we do not yet have an independent biologic “test” for this condition), this panel could not determine whether additional symptoms or signs that should be considered in the diagnosis of fibromyalgia.

Biases, dubious representation? Unknown elements in this analysis are 1) how closely the

Until a firm biologic diagnosis for fibromyalgia is discovered, it will remain a matter of clinical judgment

reference population used to develop these criteria represents the true population of persons with fibromyalgia, and 2) the biases of the ACR experts. Finally, the positive and negative predictive values of these criteria will depend on the prevalence of fibromyalgia and other similar conditions.

Morbidity not predicted by criteria. In addition, the 1990 ACR criteria assume the number of tender points and degree of pain are directly proportional to overall morbidity; however, a person with fewer than 11 tender points may experience significant morbidity, indicating that the sensitivity of the criteria may be low.⁴⁰⁻⁴² As suggested by Wolfe in 1997, “the tender point count functions as a sedimentation rate for distress” in persons with chronic pain.⁴² Thus, the authors of the 1990 ACR study stated that ACR criteria should not be applied rigidly in diagnosing and treating fibromyalgia,⁴² leaving a large role for clinical judgment.

Subjective factors. A final difficulty with the diagnosis of fibromyalgia is its dependence on patient report and examiner technique.¹ In the 1990 ACR criteria, tender points were defined as a complaint of pain (or any more dramatic response) when an examiner applied 4 kg of pressure with the pulp of the thumb or first two or three fingers, calibrated with a dolorimeter (a device that can measure the amount and rate of pressure applied over a specified surface area).¹ It has been shown that practitioners require training to apply 4 kg of force with regularity.⁴³

However, applying exactly 4 kg of pressure may not be clinically important. Other studies have shown that finger palpation or dolorimetry identifies tender points with equal accuracy (LOE: 3, case-control design with non-independent reference standard).^{44,45}

Persons who exercised improved in global well-being, physical function, and aerobic fitness by about 17%

Manual palpation

A controlled study of manual palpation was conducted to standardize the tender point survey described in the **Figure**.⁴⁶ This method compares well with the ACR 1990 method, with a sensitivity of 88.6% and a specificity of 71.4%.⁴⁶

To speed up the examination, a particular sequence of palpating survey points was established, with the patient positioned as outlined in the **Figure**. Using the thumb pad of his/her dominant hand, each examiner applied 4 kg of pressure, at a rate of 1 kg per second, just once at each survey point. Examiners learned to apply the proper amount of pressure by standing a patient on a scale and watching the scale while pressing down perpendicularly on the trapezius survey point.

The examinee was seated throughout the exam, except when lying on the side for palpation of the trochanter and lying supine for palpation of the knee. A tender point was identified when the patient rated the pain resulting from palpation at least 2 out of 10 (0, no pain; 10 worst pain) (LOE: 3, case-control design, nonindependent reference standard).⁴⁶

Until a firm biologic basis for fibromyalgia is discovered and a true gold standard for testing is developed, the diagnosis of fibromyalgia will remain a matter of clinical judgment and convention (SOR: C).

TREATMENT

A diagnosis of fibromyalgia alone may result in health benefits. In a year-long study published in 1986, Cathey et al reported that among 81 persons diagnosed with fibromyalgia, hospitalization rates decreased in the year following diagnosis (LOE: 2, case-control design).⁴⁷

Treatments for fibromyalgia are numerous, ranging from balneotherapy (bathing) to low-

energy laser therapy, and studies of interventions are often poorly designed, based on small numbers of patients, report nonstandardized outcomes, and yield conflicting results.⁴⁸

Two interventions— aerobic exercise and antidepressant therapy—appear to improve fibromyalgia.

Aerobic exercise

Though pain relief is insignificant with aerobic exercise, other positive effects are significant (SOR: A). A 2003 Cochrane review identified 7 high-quality studies of aerobic training, defined as: 1) frequency of 2 days per week; 2) intensity sufficient to achieve 40% to 85% of heart rate reserve, or 55% to 90% of predicted maximum heart rate; 3) duration of sessions 20 to 60 minutes, either continuously or intermittently throughout the day, using any mode of aerobic exercise; and 4) a total exercise period of at least 6 weeks (Table 1).⁴⁹

Improved functioning, tender-point threshold.

Study subjects engaged in aerobic dancing, whole-body aerobics, stationary cycling, and walking. Persons who exercised improved in global well-being, physical function, and aerobic fitness (by about 17%), and raised the pain threshold of tender points (by about 35%).⁴⁹ Four of the studies were similar enough to be combined for meta-analysis, showing a statistically robust but modest reduction in tender-point threshold (LOE: 1).

Although it seems likely that pain or fatigue might increase at least initially with exercise, participants in the exercise groups were not deterred; the researchers pointed out that reporting of adverse effects of aerobic exercise appeared incomplete, but there was no significant difference in drop-out rates between the exercise (25.1%) and control groups (12.5%).⁴⁹

In the long-term studies (>6 months), improvements were noted up to 1 year after treatment ended but not after 4.5 years.⁴⁹ This Cochrane review further supports aerobic

TABLE 1

Aerobic exercise for fibromyalgia: the evidence

Aerobic exercise (SOR: A)			
Study (LOE)	Treatment specifics	Results	Comments
Busch et al⁴⁹ (1)	Supervised aerobic training—eg, aerobic dancing, stationary cycling, walking: 1) frequency of 2 days per week, 2) intensity sufficient to achieve 40%–85% of heart rate reserve or 55%–90% predicted maximum heart rate, 3) duration of sessions of 20–60 minutes duration, either continuously or intermittently throughout the day, and using any mode of aerobic exercise, 4) total time period of at least 6 weeks, maximum 1 year in these studies.	<i>Benefits over controls:</i> improvements in aerobic performance, tender points, and global well-being. <i>Adverse effects:</i> poorly reported.	4 high-quality aerobic training studies included in meta-analysis. No significant improvements in pain intensity, fatigue, sleep, and psychological function.
Sim et al⁵⁰ (2)	Not standardized, but 3 studies set exercise intensity at 60%–75% of max. heart rate. Duration 6 weeks to 20 weeks.	<i>Benefits over controls:</i> preliminary evidence for improvements in symptoms. <i>Adverse effects:</i> not reported.	Heterogeneous studies.
Rosy et al⁵¹ (2)	Loosely defined and heterogeneous, including “exercise, strengthening, walking, stretching, pool therapy, cycling, swimming, and aerobics.”	<i>Benefits over controls:</i> improvement in physical status, fibromyalgia symptoms, and psychological status with effectiveness comparable with pharmacologic treatment for arthritis pain. <i>Adverse effects:</i> not reported.	Heterogeneous studies. No improvement in daily functioning.

SOR, strength of recommendation; LOE, level of evidence. For an explanation of these ratings, see page 268.

exercise as bring beneficial for persons with fibromyalgia.^{50,51}

Additional improvement measures. A similar systematic review concluded that although studies were too heterogeneous to draw final conclusions, preliminary data supported aerobic exercise (LOE: 2, with

heterogeneous studies).⁵⁰ In another comprehensive meta-analysis of all treatments for fibromyalgia, heterogeneous treatment studies ranging from exercise to physical therapy were identified as physically-based treatments. The analysis revealed a positive effect on physical status (including tender-point index,

TABLE 2

Alternative nonpharmacologic therapies for fibromyalgia: the evidence

Multidisciplinary rehabilitation (physician and psychological, social, or vocational interventions) (SOR: C)

Study (LOE)	Treatment specifics	Results	Comments
Karjalainen et al ⁵² (2)	Education plus physical training vs education; education plus cognitive treatment vs education and group discussion; behavioral therapy vs education; stress management vs aerobic exercise.	<i>Benefits over controls:</i> not significant. <i>Adverse effects:</i> not reported.	Heterogeneous studies. No high-quality randomized controlled trials identified.
Acupuncture (SOR: B)			
Berman et al ⁵³ (2)	Systematic review.	<i>Benefits over placebo:</i> improvements in pain, stiffness, global improvement. <i>Adverse effects:</i> pain with needle insertion.	Only 1 randomized controlled trial. No long-term results.

SOR, strength of recommendation; LOE, level of evidence. For an explanation of these ratings, see page 268.

grip strength, and physician global rating of pain symptoms), fibromyalgia symptoms (including self-reported fatigue and pain using visual analog scales), and psychological status (including measurements of the Hamilton Depression and Anxiety Scales), with no effect on daily functioning (including outcome measures such as the Fibromyalgia Impact Questionnaire [FIQ]) (LOE: 2, with heterogeneous studies).⁵¹

The authors noted that the magnitude of the positive effects of physically-based treatments on fibromyalgia were comparable with drug treatment judged effective for arthritis.⁵¹

Less certain nonpharmacologic therapies

Other nonpharmacologic treatments for fibromyalgia are educational interventions, relaxation therapy, cognitive-behavioral therapy, and acupuncture. These therapies have undergone rigorous analysis, but studies have been too

heterogeneous to allow for strong conclusions across the studies.⁵⁰

A recent Cochrane review concluded that although physical training plus education had a positive effect at long-term follow up, evidence is insufficient to recommend multidisciplinary rehabilitation, defined as the care of a physician plus psychological, social, and vocational interventions (SOR: C).⁵²

In contrast, other investigators have concluded that multidisciplinary treatment incorporating physically and psychologically based treatments was more successful than treatment with a single modality.⁵¹ A systematic review of acupuncture identified only 1 high-quality randomized controlled trial (Table 2), which did show some improvement in symptoms (SOR: C).⁵³

Therapy with antidepressants

Of all pharmacologic treatments, antidepressants have undergone the most thorough study.

TABLE 3

Antidepressant therapy for fibromyalgia: the evidence

Antidepressants (SOR: A)			
Study (LOE)	Treatment specifics	Results	Comments
Arnold et al⁵⁵ (1)	Tricyclic antidepressants: Amitriptyline 25–50 mg daily (n=4 trials) Dothiepin 75 mg daily (n=1) Cyclobenzaprine 10–40 mg daily (n=4) Clomipramine 75 mg daily (n=1) Maprotiline 75 mg daily (n=1)	<i>Benefits over placebo:</i> significant response in 25%–37% of patients with moderate improvements in sleep, pain, and global assessment by patient and physician, and modest improvements in fatigue tenderness and stiffness.	Studies short-term, most less than 6 weeks. In the only trial of 26 weeks, by the end of the study, the effectiveness of amitriptyline and cyclobenzaprine were no greater than placebo.
O'Malley et al⁵⁴ (2)	Amitriptyline 50 mg daily (n=8 trials) S-adenosylmethionine 200–800 mg daily (n=2) Cyclobenzaprine 20 mg daily (PM), 10 mg daily (PM) (n=1) Fluoxetine 20 mg daily (n=2) Citalopram 20 mg daily (n=1) Clomipramine 75 mg once daily (n=1)	<i>Benefits over placebo:</i> number needed to treat of 4 with moderate improvements in sleep, overall well-being, and pain severity. Mild improvements in fatigue and number of tender points.	Combined effects from heterogeneous classes of antidepressants.
Rossy et al⁵¹ (2)	Amitriptyline (n=7 trials) Dothiepin (n=1) Fluoxetine (n=2) Citalopram (n=1) 5-hydroxytryptophan (n=1)	<i>Benefits over placebo:</i> improvement in physical status and fibromyalgia symptoms with effectiveness comparable with pharmacologic treatment for arthritis pain. <i>Adverse effects:</i> not reported.	Heterogeneous studies. No effect on daily functioning or psychological status.

SOR, strength of recommendation; LOE, level of evidence. For an explanation of these ratings, see page 268.

Although the optimal role of medications in fibromyalgia has not been delineated, 3 meta-analyses have reported that antidepressants, most commonly amitriptyline, reduce symptoms during treatment of a few months duration (SOR: A) (Table 3).^{54,55}

Any antidepressants. Pooled results from 13 studies (8 of tricyclics, 3 of selective serotonin reuptake inhibitors, 2 of s-adenosylmethionine) revealed a moderate effect on pain, sleep, and global well-being, and a mild effect on fatigue and number of trigger points.⁵⁴

The authors calculated that persons with fibromyalgia treated with antidepressants were 4 times more likely to improve than persons treated with placebo (number need to treat [NNT]=4). Adverse effects appeared insignificant but were poorly reported in the individual studies.

Tricyclics only. In another meta-analysis, 9 high-quality studies of tricyclic antidepressants (amitriptyline, dothiepin, clomipramine, maprotiline and cyclobenzaprine—classified by the authors as a tricyclic antidepressant) were analyzed for 7 outcomes (patient self-rating of pain, fatigue, stiffness, and sleep; the patient and physician global assessment of improvement; and tenderness of tender points). Significant responses were observed in 25% to 37% of patients. On meta-analysis, outcome measures improved moderately overall with tricyclic treatment, mostly in sleep and global assessment, least in stiffness and tenderness. Long-term safety (more than 8 weeks) and efficacy of tricyclic therapy for fibromyalgia have not been demonstrated.⁵⁵

Combined trials. A third meta-analysis demonstrated improvement when trials of different antidepressants were combined.⁵¹ By pooling studies of antidepressants (amitriptyline, dothiepin, fluoxetine, citalopram, and S-adenosylmethionine) improvements in physical status, fibromyalgia symptoms, and psychological status were found, with no improvement in daily functioning.⁵¹ Although the effect was smaller than physically-based treatments, the effect size was still comparable to drug treatment for arthritis.⁵¹

Muscle relaxants (primarily cyclobenzaprine) and nonsteroidal anti-inflammatories have been studied, with no evidence of a positive effect.⁵¹ Thus, the best evidence currently supports the use of aerobic exercise and antidepressants, particularly tricyclics, for the treatment of fibromyalgia.

Assessing treatment efficacy: Outcome tools online

The Fibromyalgia Impact Questionnaire:

myalgia.com/Paintools/fibromyalgia_impact_questionnaire1.htm

Visual analogue pain scale:

www.outcomesassessment.org/QVAS%20Form.pdf

Arthritis Self-Efficacy Questionnaire:

patienteducation.stanford.edu/research/searthritis.pdf

■ INSTRUCTIONS TO PATIENTS, MANAGEMENT FOLLOW-UP

Persons with fibromyalgia should know that although specific symptoms, particularly pain, may be not be dramatically reduced with treatment, aerobic exercise and tricyclic antidepressants alleviate some symptoms with minimal adverse effects (SOR: **A**). Emphasize that these treatments have been shown to improve one's ability to cope with fibromyalgia symptoms. The best-studied antidepressant for treating fibromyalgia is amitriptyline, usually given at 25 to 50 mg, nightly.

Exercise. Prescribe aerobic exercise, at least twice per week for 20 to 60 minutes, targeting a heart rate of 55% to 90% of the predicted maximum (180 beats per minute-age) (SOR: **A**). One caveat: aerobic exercise in the literature was usually supervised, so the ideal exercise regimen might be a fibromyalgia-specific program.

Medication. Consider a trial of amitriptyline, 25 to 50 mg every night, for up to 6 weeks (SOR **A**). A caveat: tricyclic antidepressants may also have significant side effects, which could outweigh moderate benefits. Moreover, treatment effectiveness beyond 2 months has not been proven. Therefore, longitudinal measurement of outcomes should be part of ongoing care.

Follow-up. Studies have not determined which measures are best to follow (see "Assessing treatment efficacy"), but they might include the following (SOR: **C**):

1. Pain (eg, visual analogue scale, pain drawings)

2. Number of tender points, and tenderness
3. Physical function (eg, cardiorespiratory fitness, self-reported physical function measured by the physical-impairment subscale of the FIQ,⁵⁶ strength)
4. Global well-being or perceived improvement (eg, physician-rated change, FIQ total score)
5. Self-efficacy (eg, Arthritis Self-efficacy Questionnaire)
6. Fatigue and sleep (eg, FIQ fatigsubscale, sleep visual analogue scale)
7. Psychological function (eg, FIQ subscales for depression and anxiety)
8. Ability to work
9. Health care consumption and costs.^{47,50}

Education or psychological coping strategies may also contribute positively to overall patient and family well-being. Consider education/psychological counseling (SOR: **C**) and acupuncture (SOR: **B**).

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DRUG BRAND NAMES

Amitriptyline • Elavil
 Citalopram • Celexa
 Clomipramine • Anafranil
 Cyclobenzaprine • Flexeril
 Dothiepin • Prothiaden
 Fluoxetine • Prozac
 Maprotiline • Ludoimil