Initial treatment of fibromyalgia in adults

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Disclosures: Don L Goldenberg, MD Grant/Research/Clinical Trial Support: Pfizer [Fibromyalgia (pregabalin)]. Peter H Schur, MD Nothing to disclose. Paul L Romain, MD Employee of UpToDate, Inc.

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INTRODUCTION — Fibromyalgia is a chronic pain disorder that is challenging to treat. Effective interventions include a number of nonpharmacologic and pharmacologic therapies that are often provided in combination. Patients with fibromyalgia generally respond best to a multidisciplinary, individualized treatment program that incorporates both clinician and non-clinician providers, including physical medicine, rehabilitation, and mental health specialists [1]. The initial steps in the treatment of fibromyalgia in adults will be reviewed here. The treatment of fibromyalgia in adults who do not respond to initial therapies; the pathogenesis, clinical manifestations, diagnosis, and differential diagnosis of fibromyalgia; and fibromyalgia in children and adolescents are discussed separately. (See "Treatment of fibromyalgia in adults not responsive to initial therapies" and "Pathogenesis of fibromyalgia" and "Clinical manifestations and diagnosis of fibromyalgia in adults" and "Differential diagnosis of fibromyalgia" and "Fibromyalgia in children and adolescents: Clinical manifestations and diagnosis".)

OVERVIEW OF TREATMENT — Treatment of fibromyalgia is directed at reducing the major symptoms of this disorder, including chronic widespread pain, fatigue, insomnia, and cognitive dysfunction [2-5]. A variety of modalities are employed, using a stepwise approach (table 1). (See "Clinical manifestations and diagnosis of fibromyalgia in adults".) The issue of who should be in charge of the treatment of patients with fibromyalgia has been controversial. Most specialty groups recommend that the initial management of patients with fibromyalgia can and should be carried out in the primary care setting [6,7]. Ideally, treatment should include an integrated, multidisciplinary nonpharmacologic and pharmacologic approach, but there have been relatively few trials that have formally evaluated such a combined approach to therapy. (See "Treatment of fibromyalgia in adults not responsive to initial therapies", section on 'Multidisciplinary treatment programs'.)
The initial approach to all patients with fibromyalgia should include:

- Patient education regarding the disease, treatment approaches, good sleep hygiene, and the importance of treating comorbidities that may contribute to symptoms, including mood or sleep disorders (see 'Patient education' below)

- An exercise program, including aerobic conditioning, stretching, and strengthening (see 'Exercise' below)

- Drug monotherapy (eg, with amitriptyline, duloxetine, pregabalin, or milnacipran) for treatment of symptoms not relieved by nonpharmacologic measures (see 'Medications' below)

Interventions that we use in patients who do not respond adequately to initial therapies are discussed in detail separately. (See "Treatment of fibromyalgia in adults not responsive to initial therapies"). Briefly, these include:

- Combinations of drugs (see "Treatment of fibromyalgia in adults not responsive to initial therapies", section on 'Combination drug therapy')

- Referral for a supervised physical therapy evaluation and treatment program (see "Treatment of fibromyalgia in adults not responsive to initial therapies", section on 'Exercise and physical therapy')

- Referral for psychological interventions for pain management, including cognitive behavioral therapy and other interventions (see "Treatment of fibromyalgia in adults not responsive to initial therapies", section on 'Psychological therapies')

- Consultation with one or more specialists, such as a rheumatologist, physiatrist, psychiatrist, psychologist, or pain management specialist, depending upon the specific expertise needed (see "Treatment of fibromyalgia in adults not responsive to initial therapies", section on 'Consultation and referral')

- Assessment and care in a specialized multidisciplinary program, particularly for patients with disease refractory to other interventions or for those on chronic opioids (see "Treatment of fibromyalgia in adults not responsive to initial therapies", section on 'Multidisciplinary treatment programs')

- Other treatments, including medications for which there is more limited evidence, and complementary and alternative measures, including “mind-body” therapies such as tai chi and yoga (see "Treatment of fibromyalgia in adults not responsive to initial therapies", section on 'Analgesic and antiinflammatory drugs' and "Treatment of fibromyalgia in adults not responsive to initial therapies", section on 'Complementary and alternative therapies' and "Treatment of fibromyalgia in adults not responsive to initial therapies", section on 'Selective serotonin reuptake inhibitors')

Nonpharmacologic interventions are important in the initial management of fibromyalgia and remain of benefit in patients with disease that does not respond to initial therapies. Some patients respond sufficiently well without drug therapy to avoid the need for medications; this is more common among those presenting in the primary care setting. (See 'Prognosis' below.)

The benefits of nonpharmacologic interventions are supported by systematic reviews and a 2009 meta-analysis, which have found that cardiovascular exercise, cognitive behavioral therapy (CBT), other psychological therapies, patient education, and multidisciplinary interventions may
provide benefit in patients with fibromyalgia, particularly short-term improvements in pain and health-related quality of life [2,3,8-10].

PATIENT EDUCATION — Patients with fibromyalgia need to understand their illness before any medications are prescribed [1,11]. It is important to educate the patient regarding the diagnosis and treatment of fibromyalgia, the uncertainty regarding pathogenesis, and the patient’s role in their own treatment. This approach is supported by systematic reviews of observational studies and randomized trials [2]. When possible, such education should also include family members. (See 'Effectiveness of patient education' below and 'Efficacy of exercise' below and 'Information for patients' below.)

Patient education should include the following elements:

● Reassurance that fibromyalgia is a real illness – The patient must be reassured that fibromyalgia is a real illness and is not imagined or “in your head.” The benign nature of the disorder should also be emphasized. As an example, patients must be told that this is not a deforming or deteriorating condition and that it is neither a life-threatening nor a cosmetic problem. The relationship of neurohormones to pain perception, fatigue, abnormal sleep, and mood disturbances should be discussed; this will help the patient to understand the rationale of therapy with medications such as tricyclic and other antidepressants and antiseizure medications.

● Lack of evidence of persistent infection – Patients should be assured that, although infections may be important precipitating factors, there is no evidence that these syndromes are related to persistent infection. Diagnostic criteria for the classification of chronic fatigue syndrome (CFS) are similar to those for fibromyalgia, and the majority of patients with CFS meet tender point criteria for fibromyalgia [12]. Similarly, approximately 70 percent of patients with fibromyalgia meet the criteria for CFS [13]. Some patients with fibromyalgia, particularly those who also meet the criteria for chronic fatigue syndrome, may believe that their illness is caused by an undiagnosed infection. In our experience, patients generally have a better response to treatment when they understand that they are not harboring some infectious agent over which they have no control. (See "Clinical features and diagnosis of chronic fatigue syndrome".)

● Role of stress and mood disorders – A review of the role of stress and mood disturbances in fibromyalgia will encourage the patient to learn simple relaxation techniques and to consider formal stress-reduction programs. Physical or emotional stress may precipitate or aggravate fibromyalgia. Additionally, approximately 30 percent of patients with fibromyalgia have major depression at the time of diagnosis. The lifetime prevalence of depression is 74 percent, and that of an anxiety disorder is 60 percent [1,14,15]. Patients with mood disorders should be strongly encouraged to obtain treatment for these conditions, which may be provided by primary care clinicians or by experts in psychiatric care.

● Role of sleep disorders and sleep hygiene – Patients should be educated regarding good sleep hygiene and the potential benefit of correcting poor sleep habits and of recognizing and obtaining treatment for sleep disorders that may contribute to symptoms of fibromyalgia. Relatively common sleep disorders that may require intervention include obstructive sleep apnea and restless legs syndrome. (See "Overview of obstructive sleep apnea in adults" and "Clinical manifestations and diagnosis of restless legs syndrome in adults".)

● Role of exercise – We counsel patients regarding the importance of exercise for reconditioning and for functional capacity, and caution that a temporary increase in myalgias may occur upon initiating an exercise program. It has been suggested that blood flow to muscle and skin may be
sluggish in fibromyalgia. In our experience, a discussion of the role of muscle “spasm” and deficient muscle blood flow is useful when prescribing exercise and physical therapy.

●Prognosis – Patients need to appreciate that their symptoms will wax and wane but that the pain and fatigue generally persist. Despite the presence of these chronic symptoms, it is reassuring to emphasize that the great majority of patients live normal and active lives.

●Education about maladaptive chronic illness behavior should be provided, either by the primary care provider or in conjunction with a more formal cognitive behavior therapy (CBT) program. CBT can be done individually or in group sessions. (See "Treatment of fibromyalgia in adults not responsive to initial therapies", section on 'Psychological therapies'.)

Effectiveness of patient education — Patient education, including making or confirming the diagnosis, and education regarding the nature of the disorder and the rationale for the treatment approach have a beneficial effect. Most patients have had fibromyalgia for years before the diagnosis is finally made. They often have undergone multiple diagnostic evaluations and have consulted with many different specialists. Some patients may feel rejected by the medical profession, while others may fear that a life-threatening illness will eventually be found.

Evidence of benefit for patients and society from making the diagnosis includes:

●A study from the United Kingdom, which found that there were fewer referrals and less diagnostic testing after a fibromyalgia diagnosis was made [16]

●Another study in which, following a diagnosis of fibromyalgia, patients underwent less diagnostic testing and imaging and in which there were fewer specialty referrals, fewer primary care visits, and fewer drug prescriptions than prior to the diagnosis being made [17]

Evidence of benefit from education is illustrated by the following:

●The benefits of educational interventions are supported by a 2004 systematic review of treatment of fibromyalgia that assessed the effectiveness of educational interventions in patients receiving those interventions, compared with controls either waiting for care or receiving training in gentle stretching exercises [2]. The studies reviewed were typically unblinded. Small group sessions, printed materials, lectures, and demonstrations were used to inform patients of the nature of fibromyalgia. Numbers of sessions ranged from 6 to 17. Those receiving the educational intervention had significantly more improvement than the controls in one or more of several outcomes used, including pain, sleep, fatigue, self-efficacy, quality of life, and the six-minute walk, and beneficial effects lasted from 3 to 12 months after the sessions ended.

●A single intensive educational intervention may also be beneficial, as was the case in a study in which patients received education from a multidisciplinary team over 1.5 days [18]. One month later, there was significantly less pain, as well as more improvement in self-reported function, fatigue, stiffness, anxiety, and depressed mood, in those who received the educational intervention.

●Trials demonstrating the benefit of multidisciplinary nonpharmacologic treatment programs have frequently included a significant patient education component [19,20]. Additionally, education focusing on self-management, combined with exercise, enhances the benefits of exercise in fibromyalgia [21]. (See 'Exercise' below and 'Efficacy of exercise' below.)

EXERCISE — Exercise can be of significant benefit for pain and function, and we recommend cardiovascular fitness training for patients with fibromyalgia based upon the data from
randomized trials and observational studies [8,22-26]. In practice, it has been difficult to start and maintain fibromyalgia patients in a structured cardiovascular exercise program, because patients generally perceive that their pain and fatigue worsen as they begin to exercise. Thus, it is important to instruct patients in the principles and methods of gradual incremental cardiovascular fitness programs.

Low-impact aerobic activities such as fast walking, biking, swimming, or water aerobics are most successful among the interventions that have been studied and in our experience [2,8,26,27]. The type and intensity of the program should be individualized and should be based upon patient preference and the presence of any other cardiovascular, pulmonary, or musculoskeletal comorbidities. Physical therapists or exercise physiologists familiar with fibromyalgia can provide helpful instruction.

Optimal cardiovascular fitness training generally requires a minimum of 30 minutes of aerobic exercise three times per week in a range near target heart rate. However, even with gradual increases in exercise, some patients may not achieve this goal, and patients should be encouraged to continue exercising regularly. (See "Overview of the benefits and risks of exercise", section on 'Exercise prescription' and "Exercise and fitness in the prevention of cardiovascular disease", section on 'The exercise prescription'.)

Additional forms of exercise that have shown some benefit in fibromyalgia but which are not primarily directed at developing aerobic fitness include “mind-body” interventions such as tai chi and yoga. (See "Treatment of fibromyalgia in adults not responsive to initial therapies", section on 'Tai chi' and "Treatment of fibromyalgia in adults not responsive to initial therapies", section on 'Yoga'.)

Efficacy of exercise — A 2008 systematic review of randomized trials of aerobic exercise for fibromyalgia, involving 2276 subjects across 34 studies, found beneficial effects on aerobic performance, pain, and pressure thresholds over tender points in those subjects who received aerobic exercise training [8]. Improvement was seen in pain, global wellbeing, and physical function.

Strength training and flexibility exercises have not been extensively studied; however, there is some evidence of benefit from strength training in some small trials that used several different types of resistance training programs [28]. Some reports have found that the benefits of a muscle strength training program, including reduced pain severity, are comparable to those of an aerobic exercise program [22,29]. Reports also suggest that water exercises may be an effective form of therapy [24,25].

A Canadian panel that reviewed the evidence for exercise in 2008 created a practice guideline that makes similar recommendations to ours for aerobic fitness exercises and strength training in the management of fibromyalgia [23,30,31]. This approach is also supported by the findings of a three-year trial examining the benefits of a six-month exercise training program in women with fibromyalgia, which resulted in improvements in a number of key health domains that were maintained over 30 months [32].

MEDICATIONS — In most patients, we recommend the use of medications for the treatment of the symptoms associated with fibromyalgia together with continued nonpharmacologic measures. However, some patients respond adequately to nonpharmacologic measures alone; such responses are more common among patients presenting initially to primary care clinicians,
compared with those initially seen by specialists or referred to specialty treatment centers. (See 'Patient education' above and 'Exercise' above.)

The medications that are the best studied and that have been most consistently effective in the treatment of fibromyalgia are certain antidepressants and selected anticonvulsants. The antidepressants include widely available tricyclic medications, such as amitriptyline, and several selective serotonin and norepinephrine reuptake inhibitors (SNRI), including duloxetine and milnacipran. Another related tricyclic medication, cyclobenzaprine, is also effective in patients with fibromyalgia, but it is not used to treat depression. The anticonvulsants that are beneficial include gabapentin and pregabalin.

Studies to define the mechanisms of action for these central nervous system acting drugs in fibromyalgia are ongoing. For example, functional magnetic resonance imaging (MRI) was used to show that pregabalin influenced aspects of the whole pain matrix, inducing longitudinal changes in neuronal activity during the pain state, which correlated with less pain and improved other symptoms [33].

The efficacy of these drugs compared with placebo has been demonstrated in randomized trials and meta-analyses, but there have been few direct comparisons of one with another, particularly with the older drugs [34-36]. We base the choice between these medications in an individual patient upon our clinical experience, patient preference, and symptoms. Factors we consider include the relative prominence of particular symptoms, including fatigue, insomnia, and depression; potential adverse effects; patient tolerance of individual medications; and patient cost and regulatory limitations on prescription choice [4,5].

We take a stepwise approach to treatment, most often initiating therapy with a tricyclic (table 1). In patients with an inadequate response or with intolerance of a tricyclic, we use a SNRI (one of the dual reuptake inhibitors) or one of the anticonvulsants. An alternative initial therapy in patients with more severe fatigue or depression or with more severe sleep disturbance is a SNRI or an anticonvulsant, respectively. In general, drugs should be started at low doses and should be built up slowly. (See 'Tricyclic antidepressants as initial drug therapy' below and 'Inadequate response to tricyclics' below.)

Although all of these agents, including amitriptyline, duloxetine, and milnacipran, are considered as first-line medications by experts on fibromyalgia, a 2012 meta-analysis of antidepressants used for fibromyalgia found that only a minority of patients experienced substantial improvement with these drugs and that adverse side effects were common [37]. Moderate degrees of benefit were seen in pain and sleep, but effects on fatigue and quality of life were small [37].

Despite the clinical trial efficacy, in “real-world experience” the majority of fibromyalgia patients do not achieve great benefit from any single medication. Many patients do not stay on the prescribed medication and never achieve the recommended dose. In a very large database evaluation of more than 13,000 patients with a diagnosis of fibromyalgia, the mean daily dose at the start of follow-up was 25 mg for amitriptyline, 60 mg for duloxetine, 300 mg for gabapentin, and 75 mg for pregabalin [38]. More than 60 percent of patients remained on the same dose throughout the follow-up period, and only one-fifth of patients continued the treatment started for at least one year. Patients had multiple comorbidities, and the mean number of different prescription drugs at baseline ranged from 8 to 10 across the groups. Opioids were used by more
than half of the patients, and benzodiazepines, sleep disorder drugs, and muscle relaxants were used by a third of the patients.

Tricyclic antidepressants as initial drug therapy — Tricyclic antidepressants and related agents are often effective as initial treatment for patients with fibromyalgia. We suggest initiating therapy with a low dose of a tricyclic medication (eg, amitriptyline 10 mg) at night time, especially since these drugs are effective, widely available, and far less costly for most patients than some of the newer agents. The dose may be limited by adverse side effects, especially in older adults. In patients with mild to moderate symptoms, cyclobenzaprine is an alternative to amitriptyline.

Individual randomized trials have demonstrated that clinically important improvement occurs in 25 to 45 percent of patients treated with these medications, compared with 0 to 20 percent of those treated with placebo [39-46]. However, their use is limited by a lack of uniform effectiveness and by a relatively high frequency of side effects. In addition, the efficacy of the tricyclic drugs may decrease over time in some patients [43,47].

The doses of amitriptyline studied have been 25 to 50 mg, usually given as a single bedtime dose. These doses are usually lower than those required to treat depression. Nevertheless, even at low doses, dry mouth, constipation, fluid retention, weight gain, grogginess, and difficulty concentrating are common. Such side effects and possible cardiotoxicity limit use in older patients.

Desipramine is a tricyclic antidepressant that has been less well-studied for fibromyalgia but that remains a possible alternative because it generally has fewer anticholinergic side effects.

Regardless of the agent chosen, patients with fibromyalgia should be started on very low doses; a typical starting dose of amitriptyline or desipramine is 5 to 10 mg one to three hours before bedtime. The dose may be increased by 5 mg at two-week intervals. The final dose should be set by the patient, based upon efficacy and side effects, always keeping the dose as low as possible. A dose of 20 to 30 mg is adequate in many patients, and we do not exceed a dose of 75 mg in most patients.

Comparative efficacy of amitriptyline — The comparative efficacy and side effects of amitriptyline and the other available agents that are also used as antidepressants are illustrated by the following:

● A 2010 systematic review and meta-analysis provided an indirect comparison that suggested greater efficacy of amitriptyline compared with duloxetine and milnacipran in reducing pain, sleep disturbance, and fatigue, without differences in acceptability [35]. The strength of the conclusions was limited, to some degree, by the lower methodologic quality of the amitriptyline trials.

● A 2009 meta-analysis comparing antidepressants for the treatment of fibromyalgia included 18 randomized trials of a variety of agents, finding evidence for efficacy of antidepressants for pain relief, fatigue, depressed mood, sleep disturbance, and improvement in health-related quality of life [36]. The effect sizes for tricyclic antidepressants were larger than those for selective serotonin reuptake inhibitors (SSRIs) (eg, fluoxetine) and for dual serotonin and norepinephrine reuptake inhibitors (SNRIs) (eg, duloxetine or milnacipran). However, the comparisons were largely indirect, and authors of the meta-analysis concluded that the data did not allow for “a definitive conclusion regarding the superiority of one class of antidepressants over another.” This meta-analysis did not include two additional placebo-controlled randomized trials also
suggesting benefit with use of the SNRI, milnacipran, which were published subsequently [48,49]. (See 'Milnacipran' below.)

Cyclobenzaprine as alternative initial drug — In patients with mild to moderate symptoms, cyclobenzaprine is an alternative to amitriptyline. The medications have a similar tricyclic structure and presumed mode of action in fibromyalgia, although cyclobenzaprine is thought to have minimal antidepressant effect [5,41].

Various doses of cyclobenzaprine have been used in placebo-controlled trials, including 10 mg in the morning and 20 mg at night [42], 10 mg three times daily [50], 10 mg in the morning and 30 mg in the evening [51], and 10 to 40 mg daily as needed [41]. We usually start with doses of 10 mg near bedtime and increase as tolerated to the larger doses. In patients who find an initial dose of 10 mg too sedating, we reduce the dose to 5 mg before bedtime.

The efficacy of cyclobenzaprine is illustrated by the following:

● A 2004 meta-analysis of five randomized trials included 312 patients [43]. Self-reported improvement (measured in three studies) was more likely in subjects receiving cyclobenzaprine than placebo (odds ratio 3.0, 95% CI 1.6-5.6); the absolute difference in the rate of improvement was 21 percent, suggesting that approximately five patients would need to be treated with cyclobenzaprine for one to improve. The degree of benefit relative to placebo was similar to that observed with amitriptyline in trials comparing the latter drug with placebo [44,45]. Pain decreased more in those who received cyclobenzaprine than placebo for four weeks, but the change in pain was not significantly different in active or placebo groups after 8 or 12 weeks. Changes in pain and in the number of tender points were not significantly different between the groups at any time.

● A randomized eight-week trial performed subsequent to the meta-analysis above and involving 36 patients found that use of very low-dose cyclobenzaprine (1 to 4 mg at bedtime) statistically significantly improved the symptoms of fibromyalgia, including pain, fatigue, and depression, compared with symptoms at baseline and with use of placebo, which did not result in significant improvement [52]. Significantly more patients who received the low-dose cyclobenzaprine had improved restorative sleep, based upon analysis of cyclic alternating pattern sleep by electroencephalography; the increase in nights with improved sleep by this measure correlated with improvements in fatigue and depression. The authors proposed that improvement in cyclic alternating sleep may be a biomarker for treatment efficacy.

Inadequate response to tricyclics — In patients who do not respond to trials of low-dose tricyclics or who have intolerable side effects, we advise a trial of pregabalin, duloxetine, or milnacipran, depending upon the patient’s symptoms. These medications may also be used as an alternative to amitriptyline for initial therapy.

● In patients who have more severe problems due to fatigue, we use a dual uptake inhibitor (eg, duloxetine or milnacipran) at breakfast. Duloxetine may be preferred in patients with depression requiring drug therapy, but, in such cases, care should be coordinated with a clinician with expertise in psychopharmacology of depression. In addition, regulatory factors may limit availability of one or the other agent (eg, there are differences between the US and Europe regarding which of these medications has regulatory approval for the treatment of mood disorders). (See 'Dual reuptake inhibitors' below and 'Duloxetine' below and 'Milnacipran' below.)
● In those patients with more severe problems with sleep, we use pregabalin taken at bedtime. Gabapentin is an acceptable alternative for patients for whom cost or regulatory constraints limit the availability of pregabalin. (See 'Anticonvulsants (alpha2-ligands)' below and 'Pregabalin' below and 'Gabapentin' below.)

Dual reuptake inhibitors — The serotonin and norepinephrine reuptake inhibitors (SNRIs or dual reuptake inhibitors), duloxetine, milnacipran, and venlafaxine, inhibit both norepinephrine and serotonin reuptake and have been evaluated in patients with fibromyalgia. Duloxetine and milnacipran, which are both available for the treatment of fibromyalgia in the United States, have shown benefit in multiple randomized trials, while venlafaxine has received more limited study [48,49,53-59]. These drugs have been compared indirectly with amitriptyline and other agents. (See 'Comparative efficacy of amitriptyline' above and 'Comparison of dual reuptake inhibitors and other agents' below.)

Duloxetine — In patients unresponsive to or intolerant of amitriptyline and in patients who have severe fatigue or who require concomitant drug therapy for depression in addition to pain, we suggest treatment with duloxetine in place of amitriptyline. It is also available in many countries for the treatment of depression and of diabetic neuropathy. Duloxetine should be used in the morning at breakfast. The usual starting dose in patients with fibromyalgia is 20 to 30 mg/day, which is gradually increased to the recommended dose of 60 mg/day. In one 12-week trial, a dose of duloxetine of only 30 mg daily did not result in significant pain reduction in fibromyalgia patients when compared with placebo [60].

The benefits of duloxetine in fibromyalgia have been shown in a 2014 systematic review that identified six randomized trials involving 2249 patients in which duloxetine was compared with placebo [61]. On meta-analysis of the data, duloxetine (60 mg daily) was significantly more likely than placebo to reduce pain by at least 50 percent at 12 weeks (RR 1.57, 95% CI 1.20-2.06) and at 28 weeks (RR 1.58, 95% CI 1.10-2.27). The number needed to benefit at 12 weeks was 8 (95% CI 4-21).

The efficacy of duloxetine in patients with fibromyalgia was initially demonstrated in two multicenter trials of 12 weeks’ duration [53,54]. As an example, in one trial, pain was reduced by at least 30 percent in a significantly greater proportion of patients receiving duloxetine (60 mg once or twice daily) compared with those taking placebo (55 and 54 versus 33 percent, respectively) [54]. Longer-term benefit was demonstrated in a subsequent six-month, multicenter, randomized, double-blind, placebo-controlled trial of 520 patients who were assigned to a single daily dose of either 60 mg or 120 mg of duloxetine or to placebo [55]. Duloxetine statistically significantly reduced pain severity (measured on a 0 to 10 scale) in patients receiving duloxetine at three and six months (-2.0 and -2.3 versus -1.4 at both time points). The reductions in pain were seen in the first week of therapy and occurred in patients with and without major depression. Mental fatigue improved, but general fatigue did not. The most common side effects were nausea, headache, and dry mouth. They usually occurred within the first three months of therapy.

In our experience, sustained responses are seen in most patients receiving duloxetine who initially benefit from treatment, when such patients are followed for more than one year on continued therapy.

Milnacipran — Milnacipran is an alternative to duloxetine in patients with severe fatigue in addition to pain. We initiate therapy with 12.5 mg each morning, gradually titrating as tolerated.
to 50 mg twice daily. Some patients will require a higher dose; up to 100 mg twice daily may be needed.

In randomized trials, it improved pain and global wellbeing more than placebo [48,49,56-59]. As an example, in one trial, 1196 patients were randomly assigned to treatment with one of two doses of milnacipran or to placebo [48]. Primary outcomes were improvement in a composite of pain, patient-reported global status, and self-reported physical function after 15 weeks of treatment. A greater than 30 percent improvement in the composite measure was significantly more likely among those receiving milnacipran at either dose (100 mg/day or 200 mg/day) than among the placebo group (OR 1.79, 95% CI 1.14-2.8, and 1.75, 95% CI 1.11-2.75, respectively). Greater improvements in individual component scores (ie, pain, global status, and physical function) were also noted in the milnacipran-treated patients compared with the placebo group. As an example, patient-reported pain (on a 100 point scale) improved from baseline levels by a statistically greater degree in the patients receiving milnacipran than those receiving placebo (-15.7 and -17.4 versus -13).

Adverse effects leading to discontinuation of study drug were more common in the milnacipran-treated subjects than in the placebo group (19 to 24 percent versus 9.5 percent, respectively). Commonly reported adverse effects were nausea, headache, and constipation.

The other major trial randomly assigned 888 patients, followed similar efficacy measures, and also noted greater efficacy for milnacipran than placebo for pain relief, improvement in global wellbeing, and physical function [49]. Nausea and headache were the most frequent adverse effects.

Responses to milnacipran were sustained among patients responding initially in randomized trials during follow-up with continued treatment for periods of up to one year [62,63].

The evidence available indicates that milnacipran 100 mg or 200 mg is effective for a minority of patients in the treatment of pain due to fibromyalgia, providing moderate levels of pain relief (at least 30 percent) to about 40 percent of patients receiving the active drug, compared with about 30 percent of those receiving placebo who achieved the same level of pain relief [64,65].

Venlafaxine — We generally do not use venlafaxine, although, as a selective SNRI, it might be expected to provide similar benefit to that observed with other SNRIs. Additionally, it may be available to some patients at lower cost than the other SNRIs. However, there are more limited data regarding the efficacy of venlafaxine for fibromyalgia, compared with duloxetine or milnacipran, and withdrawal symptoms may more readily occur because of the short half-life of this medication if a dose is missed. A small study using a flexible dose design in which the final mean dose of venlafaxine was 167 mg per day suggested that this agent may also be effective [66].

Comparison of dual reuptake inhibitors and other agents — The dual reuptake inhibitors have been compared indirectly with each other and with other antidepressants and pregabalin in several studies. The medications differed from one another in efficacy for particular symptoms and in their side effect profiles. A 2010 meta-analysis of the relative efficacy of duloxetine, pregabalin, and milnacipran, involving 7739 patients in 17 studies, found that all three were superior to placebo for pain relief, although duloxetine and pregabalin were superior to milnacipran [34]. The drugs also differed in their effects on sleep disturbance and depression and in alleviating fatigue. Headaches and nausea were more likely with duloxetine and milnacipran;
diarrhea was more likely with duloxetine and milnacipran; and cognitive defects and weight gain were more likely with pregabalin.

In a 2013 systematic review and meta-analysis involving 6038 patients in 10 randomized trials that compared dual reuptake inhibitors with placebo, both duloxetine and milnacipran provided a small incremental benefit over placebo in pain reduction. The most common symptoms leading to stopping these medications were nausea, dry mouth, constipation, headache, somnolence, dizziness, and insomnia [64].

The medications have also been compared with amitriptyline and other antidepressant agents. (See 'Comparative efficacy of amitriptyline' above.)

Anticonvulsants (alpha2-ligands) — The alpha-2/delta (α2δ) calcium channel modulators, also termed alpha2-ligands, including the anticonvulsants pregabalin and gabapentin, are beneficial for the treatment of fibromyalgia and other conditions causing chronic pain. These two agents are the only anticonvulsants for which there is convincing evidence of benefit in fibromyalgia [67,68]. Pregabalin and gabapentin have similar effects on cellular calcium channels and may exert their analgesic effects by blocking the release of various neurotransmitters. Imaging studies demonstrate the analgesic proof of principle for pregabalin in fibromyalgia [33,69]. As an example, in one study, pregabalin, but not placebo, reduced combined glutamate and glutamine levels within the posterior insula and was associated with reduction of the increased functional connectivity between pain regions.

The efficacy of these agents was best described in a meta-analysis of five placebo-controlled randomized trials (four with pregabalin and one with gabapentin) consisting of 2918 patients with fibromyalgia [70]. Compared with placebo, active therapy significantly reduced pain and improved sleep and quality of life. Evidence in support of the efficacy of each agent is described separately below. (See 'Pregabalin' below and 'Gabapentin' below.)

The pharmacologic properties of these medications are discussed in detail elsewhere. (See "Pharmacology of antiepileptic drugs", section on 'Drugs with other mechanisms of action'.)

Pregabalin — In patients unresponsive to or intolerant of amitriptyline and in patients with more severe sleep disturbance in addition to pain, we suggest the use of pregabalin. We begin with a dose of 25 to 50 mg at bedtime before adjusting the dose upwards as tolerated to the recommended dose of 300 to 450 mg/day. Some patients may respond to lower doses, such as 100 to 300 mg/day, and do not require further dose escalation.

The efficacy and safety of pregabalin has been evaluated in randomized trials and in systematic reviews and meta-analyses [71-76]. In a 2010 meta-analysis involving three randomized trials and a total of 1890 patients, those allocated to receive pregabalin in any one of three doses (600, 450, and 300 mg daily) were significantly more likely to respond to treatment, defined as a ≥30 percent reduction in pain score, compared with patients receiving placebo (odds ratios 1.7, 95% CI 1.27-2.29, 1.92, 95% CI 1.49-2.12, and 1.53, 95% CI 1.18-1.98, respectively). Some trials also documented improvements in sleep, fatigue, health-related quality of life, and global wellbeing compared with placebo [71,72]. Adverse events led to withdrawal from treatment in 25 percent of patients; these side effects included dizziness, somnolence, dry mouth, weight gain, and peripheral edema, and occurred with all three doses.

A 2013 meta-analysis, involving five randomized trials with 3256 patients, used a higher threshold to define benefit; a ≥50 percent reduction in pain was achieved significantly more often in the pregabalin-treated patients, compared with those receiving placebo (22 versus 14 percent,
relative risk 1.59, 95% CI 1.33-1.90) [76]. A small benefit was also seen in reducing problems with sleep, but in this analysis pregabalin did not significantly reduce fatigue.

The durability of pregabalin was studied in a six-month trial during which patients initially were treated with increasing doses of pregabalin for six weeks [73]. Among patients randomly assigned to pregabalin or placebo after initially responding to pregabalin, more of the patients continuing pregabalin maintained their response (68 versus 39 percent). Another report found that the efficacy of pregabalin at doses of 75 to 300 mg twice daily persisted for one year without changes in safety or tolerability [77].

Pregabalin has also been compared indirectly with the dual reuptake inhibitors. (See ‘Comparison of dual reuptake inhibitors and other agents’ above.)

Gabapentin — We use gabapentin, for which evidence is more limited, as an alternative to pregabalin in patients for whom cost of the medication or regulatory requirements limit the use of pregabalin. We begin with a dose of 100 mg at bedtime before titrating the dose upwards as tolerated and as required. The recommended dose is 1200 to 2400 mg/day, based upon the study described below. As with pregabalin, some patients may respond to lower doses.

The efficacy and safety of gabapentin were assessed in a trial that randomly assigned 150 patients to receive gabapentin (1200 to 2400 mg/day) or placebo for 12 weeks [78]. A response was defined as at least a 30 percent decrease in the Brief Pain Inventory (BPI) score. A significantly greater proportion of patients receiving gabapentin were responders than were those in the placebo group (51 versus 31 percent, respectively), and the difference in the mean BPI scores between the two groups also favored gabapentin treatment. Gabapentin was generally well-tolerated, although dizziness, sedation, lightheadedness, and weight gain were reported significantly more often by those in the gabapentin group. There was no significant difference in the incidence of serious adverse events.

TREATMENT FOR PERSISTENT SYMPTOMS — Many patients experience continued symptoms despite initial nonpharmacologic measures and treatment with a single pharmacologic agent at the maximum tolerated dose. There are several approaches we advise in such patients, depending upon patient preference and upon available resources and expertise. These interventions are discussed in detail separately. (See "Treatment of fibromyalgia in adults not responsive to initial therapies").

PROGNOSIS — Most patients with fibromyalgia continue to have chronic pain and fatigue, although most longitudinal long-term studies of outcome in fibromyalgia have been from tertiary referral centers. One study of 538 patients followed at six referral centers found that pain, fatigue, sleep disturbances, anxiety, and depression were essentially unchanged over a follow-up period of approximately eight years [79]. Similarly, in the author’s experience at a referral rheumatology center, there has been little change in the patients’ symptoms. However, two-thirds of patients reported that they were working full-time and that fibromyalgia interfered only modestly with their lives.

In an observational study involving 1555 patients with fibromyalgia followed for up to 11 years by American rheumatologists, there was little clinically meaningful change in mean symptom severity, with patients reporting generally continuing high levels of symptoms and distress [80]. There was a slight trend toward improvement, with approximately 25 percent of patients experiencing at least moderate improvement of pain over time.
In contrast with the patient population studied from tertiary referral centers, patients treated by primary care clinicians in the community have a much better prognosis. In one community survey of 141 fibromyalgia subjects, only 35 percent of those with chronic widespread pain at the initial assessment still had widespread pain two years later [81].

Approximately 10 to 30 percent of patients with fibromyalgia report that they are work disabled, a higher incidence than some other groups with chronic pain. In a Canadian study, for example, the incidence of disability was evaluated in 100 patients with fibromyalgia, 76 patients with widespread musculoskeletal pain, and 135 control individuals [82]. The proportions reporting being work disabled were 31, 11, and 2 percent, respectively. Fibromyalgia patients were also much more likely to be receiving a disability pension (26, 9, and 3 percent, respectively).

Certain psychological factors may be associated with a better prognosis. This was illustrated in a study of 198 patients among whom the following were beliefs or sentiments that were more often shared by those with better outcomes [83]:
- An increased sense of control over pain
- A belief that one is not disabled
- A belief that pain is not a sign of damage

Behaviors that were associated with better outcomes included:
- Seeking help from others
- Decreased guarding during examination
- Exercising more
- Pacing activities

Conversely, “catastrophizing” about the pain of fibromyalgia is associated with increased awareness of pain (as indicated by increased brain activation in response to painful stimuli in functional magnetic resonance images) and also is associated with worsening of, rather than improvement in, symptoms [84].

Overall mortality rates do not appear to be increased in patients with fibromyalgia, but an increased risk of suicide may be present among such patients, as shown in other studies of non-cancer related chronic pain [85-87]. In a study of 1361 Danish patients with fibromyalgia referred over a 16-year period, using the Danish Mortality Register, the standardized mortality ratios (SMR) for an increased risk of death from suicide was significantly increased (SMR 10.5, 95% CI 4.5-20.7) [85].

GUIDELINES OF PROFESSIONAL ORGANIZATIONS — Our approach is generally consistent with the recommendations of various expert panels and with the guidelines from professional organizations that have been proposed for treatment of adults with fibromyalgia [2,3,88,89]. Most of these guidelines preceded the regulatory approval of pregabalin, duloxetine, and milnacipran for fibromyalgia treatment.

As an example of such guidelines, a Canadian task force recommended that fibromyalgia care be initiated in the primary care setting, incorporating nonpharmacologic and pharmacologic strategies in a multimodal approach with active patient participation [88]. The proposed treatment objectives were reduction of symptoms, as well as improved function using a patient-tailored treatment approach that is symptom-based. Self-management strategies combining good
lifestyle habits and fostering a strong locus of control were considered imperative. It was noted that medications afford only modest relief, with doses often lower than suggested.

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient information: Fibromyalgia (The Basics)"
- Beyond the Basics topics (see "Patient information: Fibromyalgia (Beyond the Basics)"

SUMMARY AND RECOMMENDATIONS

- Treatment of fibromyalgia is directed at reducing the major symptoms of this disorder, including chronic widespread pain, fatigue, insomnia, and cognitive dysfunction. Treatment should be individualized and multidisciplinary, involving both nonpharmacologic measures and, in most patients, drug therapy. Some patients, particularly among those presenting initially to primary care clinicians, may respond adequately to nonpharmacologic measures alone. (See 'Introduction' above and 'Overview of treatment' above.)

- Patients should be educated regarding the diagnosis and treatment of fibromyalgia, the uncertainty regarding pathogenesis, and the patient’s role in their own treatment. (See 'Patient education' above and 'Effectiveness of patient education' above.)

- Exercise can be of significant benefit for pain and function, and we recommend cardiovascular fitness training for patients with fibromyalgia (Grade 1A). Low-impact aerobic activities such as fast walking, biking, swimming, or water aerobics are most successful. The type and intensity of the program should be individualized and should be based upon patient preference and the presence of any other comorbidities. (See 'Exercise' above and 'Efficacy of exercise' above.)

- In patients who do not have mild disease that responds to educational measures and exercise alone, we recommend the addition of medications (eg, amitriptyline, duloxetine, milnacipran, or pregabalin) as the next step for the treatment of the symptoms associated with fibromyalgia, rather than nonpharmacologic measures alone (Grade 1A). In general, drugs should be started at low doses and should be built up slowly. (See 'Medications' above.)

- We suggest initiating therapy with a low dose of a tricyclic medication at nighttime (eg, amitriptyline) (Grade 2B). The initial amitriptyline dose is usually 10 mg one to three hours before bedtime, increased by 5 mg at two-week intervals to the minimal dose required (eg, 25 to 50 mg). The dose may be limited by adverse side effects, especially in older adults. In patients with mild to moderate symptoms, cyclobenzaprine is an alternative to amitriptyline. (See 'Medications' above and 'Tricyclic antidepressants as initial drug therapy' above and 'Cyclobenzaprine as alternative initial drug' above.)
In patients who do not respond to trials of low-dose tricyclics or who have intolerable side effects, the choice of medications is guided by patient preference, by the patient’s symptoms, and by comorbidities. (See 'Medications' above.)

In those patients who have more severe problems due to fatigue, we suggest use of a dual uptake inhibitor (Grade 2C). Examples include duloxetine 20 to 30 mg at breakfast, gradually increased to 60 mg/day, or milnacipran 12.5 mg each morning, gradually increased as tolerated to 50 mg twice daily. (See 'Dual reuptake inhibitors' above and 'Duloxetine' above and 'Milnacipran' above.)

In patients with more severe problems with sleep, we suggest treatment with pregabalin taken at bedtime (Grade 2C). Treatment is initiated at a dose of 25 to 50 mg at bedtime and is adjusted upwards as tolerated to 300 to 450 mg/day. Gabapentin is an acceptable alternative for patients for whom cost or regulatory constraints limit the availability of pregabalin. (See 'Anticonvulsants (alpha2-ligands)' above and 'Pregabalin' above and 'Gabapentin' above.)

In patients unresponsive to a program including education, exercise, and drug monotherapy, we use additional interventions, such as drug combinations, psychological interventions, and supervised physical therapy, and may obtain additional consultation with other specialists. (See 'Overview of treatment' above and "Treatment of fibromyalgia in adults not responsive to initial therapies".)

The prognosis of fibromyalgia varies. Patients treated by primary care clinicians in the community have a better prognosis than the population of patients seen in tertiary referral centers. Despite continued chronic pain and fatigue in the latter population, the majority of patients are not disabled from working. A better prognosis is associated with certain psychological factors and behaviors. (See 'Prognosis' above.)

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REFERENCES


