FIBROMYALGIA AND DIFFUSE MYALGIA

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PREVALENCE, PRESENTATION, AND PROGRESSION OF THE PATIENT WITH FIBROMYALGIA

Chronic pain is one of the most common complaints encountered by primary care clinicians. Often, patients present not with well localized pain but with diffuse and nonspecific myalgias. Fibromyalgia is the most common etiology for this type of pain. In community-based studies, 2% [1] and 1.2% to 6.2% of school-age children screened positive for fibromyalgia [2–4]. Women and girls are at higher risk than males, and risk increases with age, peaking between 55 and 79 years [1,5].

Persons suffering from fibromyalgia most commonly complain of widespread pain. The pain is usually bilateral and is usually worse in the neck and trunk [6]. Additional symptoms include fatigue, waking unrefreshed, morning stiffness, paresthesias, and headaches [6–12]. Compared with patients with other rheumatologic conditions, persons with fibromyalgia more often suffer from comorbid conditions [13], including chronic fatigue syndrome, migraine headaches, irritable bowel syndrome, irritable bladder symptoms, temporomandibular joint syndrome, myofascial pain syndrome, restless leg syndrome, and affective disorders [13–15].

Fibromyalgia can cause significant morbidity [1,16,17]. Patients with fibromyalgia require an average of 2.7 drugs at any time for fibromyalgia-related symptoms and have an average of 10 outpatient visits per year, with one hospitalization every 3 years [13]. Fibromyalgia has been associated with higher rates of osteoporosis [18]. Patients with fibromyalgia have higher rates of surgery, including hysterectomies, appendectomies, back/neck surgery, and carpal tunnel surgery, compared with patients with other

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rheumatic diseases [13,19]. Although there is significant morbidity related to fibromyalgia, there does not seem to be increased mortality. Studies have found no increase in 10-year mortality in fibromyalgia patients [20].

Among adults who seek medical attention for fibromyalgia, less than one third recover within 10 years of onset [21–24]. Symptoms tend to remain stable [22] or improve over time [23,25–27]. Children seem to be much more likely to recover from fibromyalgia, with complete resolution in more than 50% by 2 to 3 years in several studies [3,10,28,29].

DIAGNOSIS OF FIBROMYALGIA AND DIFFUSE MYALGIAS

The most likely cause of chronic diffuse myalgia is fibromyalgia, but other conditions can cause similar symptoms. Before concluding that a patient's symptoms are entirely caused by fibromyalgia, primary care physicians should consider other conditions [6].

Medication-Induced Myalgias

First, the clinician must consider whether diffuse myalgias might be caused by medications. Drug-induced myopathy may occur in persons taking statins, colchicine, corticosteroids, and antimalarial drugs.

Connective Tissues Diseases

Next, connective tissue diseases should be considered. In one study, one fourth of persons referred to a rheumatology clinic with presumed fibromyalgia had a spondyloarthropathy [30]. 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 lead to widespread pain. Blood tests, such as an antinuclear antibody (ANA) test, C-reactive protein, or erythrocyte sedimentation rate (ESR), may be helpful in evaluating patients with 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) [31]. In the absence of these signs, anti-nuclear antibody, rheumatoid factor and ESR testing in persons with fatigue and diffuse musculoskeletal pain have low positive predictive value [32]. Rates of false-positive ANAs may be as high as 8% to 11%, especially at low titers [33,34].

Hypothyroidism

Widespread musculoskeletal pain has been associated with hypothyroidism (level of evidence: 3) [35,36], supporting the inclusion of a

thyroid-stimulating hormone in the work-up of persons with diffuse myalgias (grade of recommendation: C). More recent research suggests that musculoskeletal pain is more related to thyroid microsomal antibodies than to hypothyroidism [37], but there has been no further evaluation of antithyroid antibodies in persons with diffuse myalgia.

Vitamin D Deficiency and Osteomalacia

Vitamin D deficiency has recently been discovered to be common in the United States, even among persons with lightly pigmented skin [38]. Vitamin D deficiency results in osteomalacia and diffusely aching bones [38]. Persons with fibromyalgia have been found to have high rates of vitamin D deficiency (level of evidence: 3b); therefore, it is reasonable to check these levels in persons with symptoms of fibromyalgia (grade of recommendation: C) [39]. Risk factors include obesity, living at a latitude north of 35 degrees (north of Atlanta and Los Angeles), working indoors year round, advanced age, pigmented skin, and sunblock use [38]. Blood levels of 25-hydroxyvitamin D of <50 ng/mL are considered deficient [38]. Misinterpretation of laboratory results often occurs when clinicians order 1,25-dihydroxyvitamin D levels, which is the active form of the protein found at blood levels that are a thousand-fold less than 25-hydroxyvitamin D. 1,25-dihydroxyvitamin D levels remain normal or elevated in deficient states because increased levels of parathyroid hormone increase renal production of 1,25-dihydroxyvitamin D in response to vitamin D deficiency and decreased intestinal absorption of calcium [38].

DIAGNOSTIC CRITERIA FOR FIBROMYALGIA

The diagnosis of fibromyalgia is based on clinical grounds, as specified in the American College of Rheumatology (ACR) 1990 Criteria for the Classification of Fibromyalgia (Box 1 and Fig. 1) [6]. Fibromyalgia is characterized by widespread pain for at least 3 months, including both sides of the body. The diagnosis of fibromyalgia is based on a combination of the 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 and the clinician's identification of at least 11 of 18 potential tender points (level of evidence: 3b) [6].

Despite these well-defined criteria, the diagnosis is not as clear-cut as it may seem to be. The criteria were based on a study of 293 fibromyalgia patients, each of whom had been diagnosed by one of 24 expert investigators according to "his or her usual method of diagnosis" [6]. The investigators identified unique characteristics of fibromyalgia by comparing the 293 cases with 265 control subjects with other chronic pain conditions (low back pain syndromes, neck pain syndromes, regional tendonitis, possible systemic lupus erythematosus, rheumatoid arthritis, or similar disorders). The investigators considered a multitude of symptoms and signs, including sleep disturbance, morning stiffness, paresthesias,

Box 1. Clinical Evaluation of Fibromyalgia

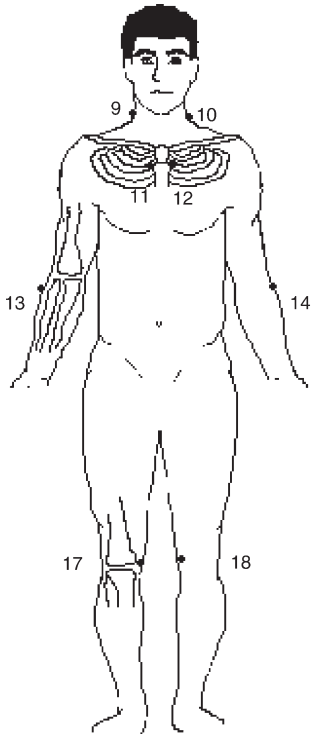
IF:
History: Three months widespread pain defined as pain on the right and left sides of the body (including shoulder and buttock pain) and above and below the waist and including the axial skeleton (cervical spine, anterior chest, thoracic spine, or low back) (grade of recommendation: C)
THEN:
Physical examination: Complaint of pain rated as 2/10 (0 no pain, 10 worst pain) upon palpation with enough pressure to whiten fingernail in 11 of 18 sites as listed in Fig. 1 (grade of recommendation: C)
THEN:
Fibromyalgia diagnosed (grade of recommendation: C)
THEN:
Additional history and examination: Consider other causes of diffuse myalgia, such as medication-induced myalgias, hypothyroidism, osteomalacia, and connective tissue disease (grade of recommendation: D).
THEN:
Testing: Thyroid-stimulating hormone (grade of recommendation: C), 25-hydroxyvitamin D (grade of recommendation: D), and ESR (grade of recommendation: D), with any additional targeted testing (grade of recommendation: D)

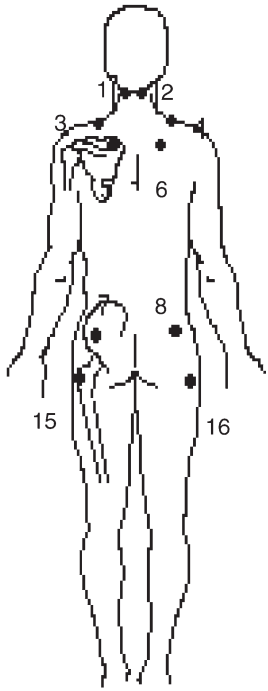
irritable bowel syndrome, fatigue, and anxiety, and determined that widespread pain and tender points were the most "sensitive (88.4%) and specific (81.1%)" distinguishing criteria [6]. In this study, calculations of sensitivity and specificity are less meaningful than in studies where an independent reference standard or gold standard is available.

When the 1990 ACR criteria are applied to the general population, there is a continuum of numbers of tender points and pain that is proportionate to overall morbidity; a person with fewer than 11 tender points may experience significant morbidity, suggesting that strict adherence to the ACR criteria may result in many false negatives [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]. The authors of the 1990 ACR study stated that ACR criteria should not be applied rigidly in diagnosing and treating fibromyalgia [42], leaving the diagnosis largely to clinician judgment.

A final difficulty with the diagnostic criteria for fibromyalgia is the dependence on patient report and examiner technique [6]. In the 1990 ACR criteria, tender points were defined as a complaint of pain (or any more dramatic response) upon application of 4 kg of pressure with the pulp of the thumb or first two or three fingers, calibrated using a dolorimeter (a device that can measure the amount and rate of pressure applied over a specified surface area) [6]. It has been shown that practitioners require training to

FIGURE 1.
Manual tender point survey. (*Adapted from *Okifuji A, Turk DC, Sinclair JD, et al. A standardized manual tender point survey: I. development and determination of a threshold point for the identification of positive tender points in fibromyalgia syndrome. J Rheumatol 1997;24:377–83; with permission.)





4 kg pressure is applied at a rate of 1 kg of force per second, using the thumb pad of the dominant hand. Palpate each site only once without probing. The patient is instructed 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	R	L
Occiput: Suboccipital muscle insertions...	**1.__**	**2.__**
Trapezius: Midpoint of upper border	**3.__**	**4.__**
Supraspinatus: Above scapular spine near medial border	**5.__**	**6.__**
Gluteal: Upper outer quadrant of buttocks at anterior edge of gluteus maximus	**7.__**	**8.__**
Low cervical: Anterior aspect of the interspaces between the transverse processes of C5-7	**9.__**	**10._**
2nd Rib: Just lateral to 2nd costochondral junction	**11.__**	**12.__**
Lateral epicondyle: 2 cm distal to lateral epicondyle	**13.__**	**14.__**
Patient on side		
Greater trochanter: 2cm posterior to the greater trochanteric prominence	**15.__**	**16.__**
Patient supine		
Knee: Medial fat pad proximal to the joint line	**17.__**	**18.__**

apply 4-kg of force with regularity [43]. However, applying exactly 4 kg of pressure may not be clinically important because other studies have demonstrated that the use of finger palpation or dolorimetry identifies tender points with equal accuracy (level of evidence: 3b) [44,45]. Until a more objective test is available, the diagnosis of fibromyalgia will depend mostly on clinical judgment (grade of recommendation: C).

AEROBIC EXERCISE AND OTHER NONPHARMACOLOGIC TREATMENTS

Although aerobic exercise has no significant effect on pain, aerobic exercise exerts other positive effects in persons with fibromyalgia (level of evidence: 1a; grade of recommendation: A). A 2003 Cochrane review identified seven 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% predicted maximum heart rate; (3) duration of sessions of 20 to 60 minutes duration, continuously or intermittently throughout the day, and using any mode of aerobic exercise; and (4) total time period of at least 6 weeks [46]. Study subjects undertook aerobic dancing, whole body aerobics, stationary cycling, and walking. Subjects who exercised improved in measures of global well being, physical function, aerobic fitness (about 17%), and pain threshold of tender points (about 35%) [46]. In long-term studies, improvements were noted at up to 1 year after treatment ended but not as long as 4.5 years [46]. This Cochrane review strengthens the indication from earlier studies [47,48] that aerobic exercise is beneficial for persons with fibromyalgia.

Other nonpharmacologic treatments for fibromyalgia include educational interventions, relaxation therapy, cognitive-behavioral therapy (CBT), and acupuncture. Although these therapies have been tested in rigorous studies, the heterogeneity of the studies makes it difficult to draw strong conclusions across studies [47]. A systematic review of acupuncture identified only one high-quality RCT showing some improvement in symptoms (grade of recommendation: D) [49].

One therapeutic approach that seems more promising is multidisciplinary rehabilitation. One randomized clinical trial found that combining biofeedback, CBT, exercise, and education resulted in better outcomes than education alone [50]. Other studies have found similar results when combining exercise or CBT with education [51,52]. A meta-analysis concluded that multidisciplinary treatment incorporating physically based and psychologically based treatments was more successful than treatment with a single modality [48]. However, a recent Cochrane review found the evidence on multidisciplinary approaches to be less convincing. The authors concluded that although some physical training plus education had a positive effect at long-term follow-up, current evidence is insufficient to recommend multidisciplinary rehabilitation (grade of recommendation: D) [53].

PHARMACOLOGIC TREATMENT

Of all pharmacologic treatments, antidepressant therapies have undergone the most thorough study. Three meta-analyses have reported that antidepressants, most commonly amitriptyline, improve symptoms for up to several months (level of evidence: 1a; grade of recommendation: A) [54,55]. Pooled results from 13 studies of different antidepressant classes (primarily tricyclics, with three studies of selective serotonin reuptake inhibitors and two 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 four times more likely to improve than persons treated with placebo. However, they felt that the evidence was much stronger for tricyclic antidepressants than for other antidepressants [54]. Adverse effects seemed to be insignificant but were poorly reported in the individual studies.

A second meta-analysis found that tricyclic antidepressants (generally in doses lower that that used to treat depression) led to improved outcomes; the most improvements were seen in sleep and global assessment, and the least improvements were seen in stiffness and tenderness [55]. The evidence was stronger for tricyclic antidepressants than for other antidepressants. A third meta-analysis of trials using different antidepressants (amitriptyline, dothiepin, fluoxetine, citalopram, and S-adenosyl-methionine) demonstrated improvements in physical status, fibromyalgia symptoms, and psychologic status with no improvement in daily functioning [48].

Another medication that has been found to be beneficial is cyclobenzaprine (level of evidence: 1a; grade of recommendation: A). A recent meta-analysis concluded that cyclobenzaprine was beneficial for patients with fibromyalgia in doses of 10 to 40 mg/d [56] One reason for the benefit of cyclobenzaprine is that, although it is most commonly used as a muscle relaxant, it is structurally similar to the tricyclic antidepressants [57]. Studies have found that the general category of muscle relaxants have no significant benefit [48,55].

The analgesic tramadol has been found to benefit patients with fibromyalgia (level of evidence: 1b; grade of recommendation: A). Several randomized controlled trials showed that the use of tramadol resulted in decreased pain scores [58,59]. This was true when tramadol was used with [58] or without [59] acetaminophen. There is no evidence of benefit for nonsteroidal anti-inflammatory drugs (NSAIDs) [48,55].

In summary, the best evidence supports the use of aerobic exercise and antidepressants in the treatment of fibromyalgia. Regarding antidepressants, the evidence is much stronger for tricyclic antidepressants (particularly amitriptyline and cyclobenzaprine) than for selective serotonin reuptake inhibitors (SSRIs). The only SSRI that has been extensively studied is fluoxetine [57]. The analgesic tramadol also seems to have some benefit in reducing pain, but NSAIDs do not.

Key Points

- Fibromyalgia is common in the general population, effecting up to 2% of adults.
- Fibromyalgia can cause significant morbidity, including higher rates of hospitalization and surgery; however, there is no known relation to mortality.
- Fibromyalgia is diagnosed based on the patient's report of widespread pain of $\geq$3 months duration and identification of 11 of 18 tender points.
- Before diagnosing fibromyalgia, other causes of diffuse myalgias should be considered, including medications (especially statins), hypothyroidism, osteomalacia, and connective tissue diseases.
- Aerobic exercise improves function and reduces pain in persons with fibromyalgia.
- Antidepressant medications have been shown to moderately improve symptoms in fibromyalgia, although the best evidence is for amitriptyline and other tricyclics.
- Other medications found to be beneficial include cyclobenzaprine and tramadol (with or without acetaminophen).

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