Management of Fibromyalgia

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Despite extensive clinical study, there is no distinct consensus on the optimal management of fibromyalgia. The cause of fibromyalgia has not been clearly defined, but several mechanisms may be involved. Abnormalities in sleep patterns, muscle structure, and cerebral blood flow have been associated with the syndrome, but it is unclear whether a causal relation exists between these abnormalities and fibromyalgia. Recent evidence suggests that alterations in the metabolism and function of the neurotransmitters serotonin, norepinephrine, and substance P may contribute to the development of fibromyalgia. No pharmacologic agents are indicated specifically for the treatment of fibromyalgia in the United States, and most pharmacologic therapies show only limited success, although drugs that affect serotonin or norepinephrine at the receptor site (such as antidepressants or tramadol) seem to generate the most consistent results. Tricyclic antidepressants may diminish the sleep disturbance and pain caused by fibromyalgia, whereas selective serotonin reuptake inhibitors may be more useful for sleep and coexistent depression only. Among the commonly used analgesics, preliminary data suggest that tramadol may be useful for treatment of fibromyalgia pain and that trigger-point injections may be helpful. Controlled trials of anti-inflammatory agents have demonstrated little usefulness of these drugs, and oral opioids have not been studied for this condition. Miscellaneous agents, such as growth hormone, tropisetron or ondansetron, 5-hydroxytryptophan, γ-hydroxybutyrate, and *S*-adenosyl-L-methionine, have also shown promising preliminary results, but their clinical roles remain to be defined. Nonpharmacologic interventions (such as exercise, biofeedback, and electroacupuncture) have likewise shown some success. Therefore, a multidisciplinary approach that includes both pharmacologic and nonpharmacologic strategies is recommended.

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Fibromyalgia is a syndrome whose main features include chronic, widespread musculoskeletal pain and stiffness in association with fatigue, poor sleep, and the presence of discrete tender points. It affects an estimated 3.7 million people in the United States (1), and women (most often ranging in age from the mid-thirties to the late fifties) account for more than 75% of patients (2). The annual direct costs per patient associated with fibromyalgia have been estimated at approximately $1000 in 1991 dollars (3) and $2274 in 1996 dollars (4).

The purpose of this paper is to provide useful information to assist in the treatment of the patient with fibromyalgia. Primary sources were drawn from a MEDLINE database search for English-language articles on the treatment of fibromyalgia and fibrositis. Original articles from the bibliographies of these primary articles were also reviewed. Research reports, review articles, and abstracts addressing the pathogenesis and management of fibromyalgia were selected with attention to study design and quality.

Diagnosing Fibromyalgia

In the late 1980s, the Fibromyalgia Multicenter Criteria Committee was formed under the auspices of the American College of Rheumatology. Its classification criteria, adopted in 1990, provided a starting point from which to standardize the study of patients with this condition (5). These criteria include the presence of widespread pain (defined as pain in the left and right sides of the body as well as both above and below the waist) for at least 3 months. Axial skeletal pain, defined as pain in the cervical spine, anterior chest, thoracic spine, or low back, must also be present. In addition, the patient must report pain in at least 11 of 18 tender point sites (**Figure**) on digital palpation with an approximate force of 4 kg/cm.

Fatigue, a nonrestorative sleep pattern, or stiffness on waking in the morning has been reported in more than 75% of patients with fibromyalgia (2). Other common features include the irritable bowel syndrome, Raynaud syndrome–like symptoms, headache, subjective swelling, nondermatomal paresthesia, psychological distress, and significant functional disability (2, 6).

Pathophysiology

A review of the potential pathophysiologic mechanisms of fibromyalgia is necessary to understand the roles of various therapies for this condition. Although the cause and pathophysiology of fibromyalgia are unknown, various physiologic alterations have been observed in patients with this syndrome. These alterations can be categorized as sleep, muscle, neuroendocrine, neurotransmitter, and cerebral blood flow abnormalities. Evidence for and against the role of each of these abnormalities in the cause and pathophysiology of fibromyalgia is discussed below.

More than 75% of patients with fibromyalgia experience a nonrestorative sleep pattern (2), most likely due to intrusion of faster alpha waves during non–rapid eye movement (REM) sleep (stages 2, 3, and 4) (7). Although alpha-wave intrusion has been reported in normal persons (8), dysthymic persons (9), and persons with postaccident pain (10), this alpha-wave non-REM sleep may occur with increased frequency in patients with fibromyalgia (8, 10). Of note, disturbance of non-REM sleep in normal persons resulted in the development of several symptoms observed in fibromyalgia, including alpha-wave intrusion, musculoskeletal aching or stiffness, and generalized tender points (11). However, it is unknown whether disturbance of non-REM sleep leads to fibromyalgia or is the consequence of fibromyalgia or other nocturnal pain syndromes (12).

Alterations in muscle, including reports of "moth-eaten" and "ragged-red" muscle fibers (13, 14), local muscle hypoxia (15), reduced high-energy phosphate levels (15, 16), and "rubber band" (also called "taut band") structure (17, 18), have been observed in patients with fibromyalgia. However, these findings have not been replicated and have not been adequately compared with those in sedentary controls. Although "ragged-red" muscle fibers, local hypoxia, and reduced levels of high-energy phosphate are suggestive of abnormal muscle metabolism, phosphorus nuclear magnetic resonance imaging has not consistently revealed significant differences in muscle metabolic variables between patients and condition-matched controls (19–21). It may be that the above muscle abnormalities are not specific to fibromyalgia but are merely the result of the disuse or deconditioning often observed in patients with chronic pain. In fact, after reviewing the relevant literature, Simms (22) concluded that muscle abnormalities (both structural and functional) do not appear to play a role in the pathophysiology of fibromyalgia.

Impaired functioning of the hypothalamic–pituitary–adrenal axis has been observed in patients with fibromyalgia. In particular, 24-hour levels of free cortisol in urine that are low compared with those in normal persons and patients with rheumatoid arthritis have been found, despite normal morning levels and elevated evening levels (23). In addition, decreased cortisol levels after exercise (24), as well as blunted cortisol response to exogenous corticotropin-releasing hormone and insulin-induced hypoglycemia (23, 25), have been reported. Insulin-induced hypoglycemia has been reported to increase (26) or decrease (27) adrenocorticotropic hormone release. To date, no consistent pattern of hypothalamic–pituitary–adrenal dysfunction has been identified, and serum cortisol levels are usually normal. Not surprisingly, corticosteroids have been shown to be unsuccessful in treating fibromyalgia (28). Low serum levels of insulin-like growth factor-1 have also been observed in patients with fibromyalgia (29). This may be secondary to the abnormalities in stage 4 sleep often observed in these patients, because growth hormone secretion occurs during this sleep stage.

Serotonin has been found to play an important role in the modulation of pain and stage 4 sleep (30, 31). Decreased levels of serotonin result in decreased slow-wave sleep and increased somatic symptoms and perceived pain (30, 32, 33). Findings on the relation between serotonin and fibromyalgia include decreased serum levels of serotonin and tryptophan and an increased density of serotonin receptors on circulating platelets in patients with fibromyalgia (34, 35), as well as abnormal transport of serum tryptophan (36). Large doses of oral tryptophan, however, have not been found to affect

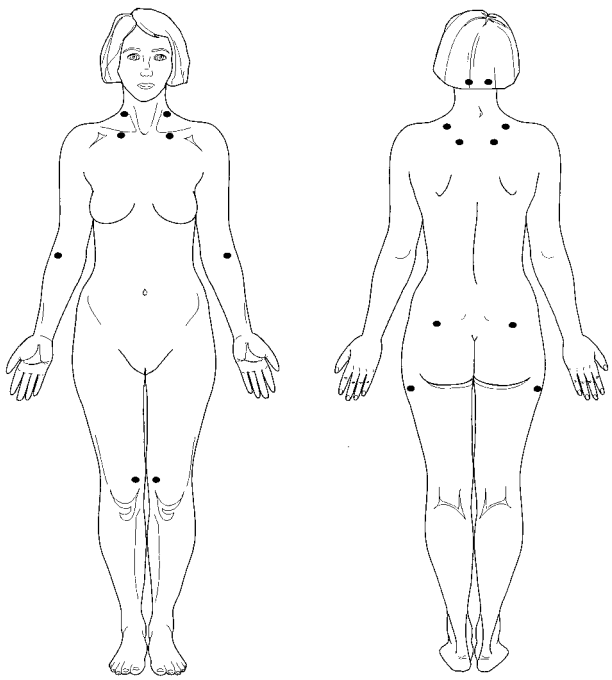

Figure. Tender points in patients with fibromyalgia.

sleep or intensity of pain in patients with fibromyalgia (37).

Substance P and norepinephrine may also be involved in fibromyalgia; increased cerebrospinal fluid levels of the former substance (38–41) and decreased cerebrospinal levels of the latter (42) have been reported. In addition, circadian rhythms of the autonomic nervous system may be blunted in patients with fibromyalgia, resulting in a constant level of sympathetic activity and diminished response to stressors (43). All of these neurotransmitter abnormalities require further study before a causal relation can be established.

There is evidence that patients with fibromyalgia experience decreased regional cerebral blood flow (44, 45). However, small sample size, sex differences in cerebral blood flow, medication effects, and lack of specificity of these changes to fibromyalgia per se suggest caution in interpreting these results.

In conclusion, adequate evidence supports a hypothesis of neurotransmitter abnormalities in the pathophysiology of fibromyalgia. It is likely that insulin-like growth factor-1, but not the hypothalamic–pituitary–adrenal axis, may also be involved. It is unclear whether sleep disorders are a cause or a result of fibromyalgia. In the absence of additional evidence, a possible role of impaired muscle metabolism or impaired blood flow seems unlikely.

Treatment

Treatment success in fibromyalgia, both pharmacologic and nonpharmacologic, is often limited; fewer than 50% of patients experience adequate symptom relief (46). In fact, at a 3-year follow-up, one study found that only 3% of patients experienced remission of all pain symptoms (47). Pharmacologic and nonpharmacologic treatments of fibromyalgia are reviewed below and are summarized in **Tables 1** and **2**.

Pharmacologic Treatment

Although no drugs are currently indicated specifically for the treatment of fibromyalgia, many agents have been studied, and active research into the therapeutic potential of several other agents is ongoing.

Antidepressants

Tricyclic antidepressants. Serotonin modulates both pain and sleep, systems that seem to function abnormally in patients with fibromyalgia. The beneficial effects of tricyclic antidepressants in the treatment of fibromyalgia are believed to be related to their ability to inhibit reuptake of serotonin and possibly norepinephrine. Amitriptyline is the most widely prescribed pharmacologic agent for treatment of fibromyalgia (104) and has consistently been found to alleviate fibromyalgia symptoms (48–51). It is estimated, however, that only 25% to 30% of patients experience clinically significant improvement with amitriptyline (52). Tachyphylaxis may occur after 2 to 3 months of continued treatment, although a 2- to 4-week drug holiday may restore the efficacy of amitriptyline. During this time, therapy with alprazolam is a possible alternative (105). Side effects of tricyclic antidepressants, such as weight gain, constipation, orthostatic hypotension, and agitation, occur in up to 20% of patients (54) and may limit use of these agents. A long-term comparison of amitriptyline, cyclobenzaprine (a tricyclic amine salt marketed as a skeletal muscle relaxant), and placebo revealed that the two active treatments were more effective than placebo after 1 month, although they did not significantly differ from placebo after 3 and 6 months, indicating tolerance to effect (53). Cyclobenzaprine was also found to be effective: In a 12-week double-blind study, cyclobenzaprine treatment (up to 40 mg/d) was associated with a significant decrease in severity of pain and a significant increase in quality of sleep (55). Venlafaxine, a nontricyclic antidepressant, significantly improved pain, fatigue, sleep quality, morning stiffness, depression, anxiety, and patient global assessment of fibromyalgia in a small, open-label clinical trial (56).

Selective serotonin reuptake inhibitors. On the basis of the effectiveness of tricyclic antidepressants, selective serotonin reuptake inhibitors were also investigated in fibromyalgia. Although initial case reports or case series of fluoxetine reported positive effects in the treatment of fibromyalgia (57, 58), results of more recent open-label and controlled studies have been equivocal (59–61). Improvements in sleep disturbances and depression were reported in all of the recent studies, but none found a positive effect on tender-point score or pain relief. It thus appears that the benefit of selective serotonin reuptake inhibitors in the treatment of fibromyalgia is related to their ability to relieve concomitant depression and sleep disorders rather than to any specific effect on pain. Because members of this class of medications can disturb as well as improve sleep, it is recommended that they be combined with a tricyclic antidepressant at bedtime. Such a combination (fluoxetine and amitriptyline) was found to alleviate fibromyalgia symptoms significantly more than either agent alone (61). Symptom improvement was not observed in a randomized, double-blind, placebo-controlled study of citalopram (62).

Benzodiazepines. Few studies have evaluated benzodiazepines in the treatment of fibromyalgia. The one published study of alprazolam found that pa-

Table 1. Pharmacologic Treatment Options for Fibromyalgia Pain

Agent (Reference)	Dose Studied	Effective*	Adverse Effects	Comments
Amitriptyline (48–53)	25–75 mg/d	Yes	Sedative and anticholinergic effects, cardiac toxicity†	Only effective in approximately 30% of patients. Tachyphylaxis can occur with continued treatment. Anticholinergic side effects may limit use (54).
Cyclobenzaprine (53, 55)	≤40 mg/d	Yes	Anticholinergic and central nervous system effects	Tachyphylaxis can occur with continued treatment. Side effects may limit use.
Venlafaxine (56)	37.5–300 mg/d	Yes	Headache, sexual dysfunction	Evaluated in only one small, open-label trial.
Fluoxetine (57–61)	20 mg/d	No	Sexual dysfunction, anxiety, weight loss, insomnia	Has been found to improve sleep and depression but not pain.
Citalopram (62)	20–40 mg/d	No	Sexual dysfunction, nausea	Evaluated in only one study.
Alprazolam (63)	0.5–3.0 mg/d	Unknown	Sedative and hypnotic effects	Significant improvement observed with alprazolam but also with placebo.
Bromazepam plus tenoxicam (64)	3 mg/d and 20 mg/d, respectively	Unknown	Sedative and hypnotic effects, gastrointestinal† and renal toxicity	Combination therapy is more effective than tenoxicam alone but does not differ from placebo. Neither drug is available in the United States.
Tramadol (65–69)	50–400 mg/d	Yes	Nausea, dizziness	Dual mechanism of action may address altered neurotransmitters and pain signals of fibromyalgia.
Nonsteroidal anti-inflammatory drugs, including ibuprofen and naproxen (28, 49, 70)	Dose range as recommended for each drug by manufacturer	No	Gastrointestinal and renal toxicity†	Benefits do not clearly outweigh the risks of use as long-term therapy for fibromyalgia.
Prednisone (28)	15 mg/d	No	Muscle and bone effects†, cataracts†, fluid and lipid accumulation†	Benefits do not clearly outweigh the risks of use as long-term therapy for fibromyalgia.
Lidocaine (71)	0.5–1.0 mL of 0.5% solution	Yes	Allergic reactions	Benefits may be due to mechanical effects of needling (72).
Opioids	–	Unknown	Sedative effects, nausea	No clinical evidence suggesting efficacy. Tolerance or dependence may develop with long-term use.
S-adenosyl-L-methionine (73, 74)	200 mg/d subcutaneously, 400 mg/d intravenously, 800 mg/d orally	Yes	None documented	Available in the United States as an over-the-counter dietary supplement.
5-Hydroxytryptophan (75)	100 mg three times daily	Yes	Gastric pain, diarrhea	Available in the United States as an over-the-counter dietary supplement.
Calcitonin (76)	100 IU/d subcutaneously	No	Diarrhea, flushing, loss of appetite, nausea	Evaluated in only one study; serotonin levels were not determined during therapy. Intranasal administration not evaluated.
Ondansetron or tropisetron (77, 78)	Ondansetron: 8 mg twice daily, tropisetron: 5–15 mg/d	Yes	Constipation	Adverse gastrointestinal effects appear to be dose related. Tropisetron is not available in the United States.
Growth hormone (79)	Treat to insulin-like growth factor-1 target	Yes	Carpal tunnel symptoms	Evaluated in only one study. Expense may be prohibitive. Insulin-like growth factor target for therapy is 250 ng/mL.
Malic acid (80)	600–2000 mg/d	Unknown	Diarrhea, nausea	Evaluated in only one study. Improvement was observed in the open-label phase but not in the double-blind phase.
γ-Hydroxybutyrate (81)	2.25-g injection at bedtime and 4 hours later	Unknown	Rebound alertness	Nighttime dosing and rebound alertness may limit clinical usefulness. Only available as an oral solution in the United States for use in narcolepsy.

* As demonstrated in clinical studies of fibromyalgia.
† This adverse effect is commonly seen only with long-term use of the agent.

tients randomly assigned to receive alprazolam plus ibuprofen, alprazolam plus placebo, placebo plus ibuprofen, or placebo plus placebo all had significant improvement in mean change in outcome variables from baseline to study end ($P \leq 0.002$ for active treatment groups; $P = 0.01$ for nonactive treatment group) (63). Outcome variables included clinical measures of tenderness, functional status, and psychological status. Further analysis using the recently developed one-sided Conover–Salsburg test revealed that patients taking alprazolam combined with ibuprofen felt significantly better and experienced a significantly greater decrease in tenderness on palpation of tender points than those taking placebo (63). Of note, this analysis was not completed in the other active treatment groups. Bromazepam and tenoxicam (agents not currently available in the United States) in combination were found to be significantly more effective than tenoxicam alone, although no statistically significant difference was seen between combination treatment and placebo (64). Potential dependence and withdrawal seizures associated with benzodiazepine therapy suggest caution in the long-term use of benzodiazepines for chronic conditions such as fibromyalgia.

Analgesics

Tramadol. Tramadol may be useful for treatment of fibromyalgia pain. In a randomized, double-blind, placebo-controlled study of 100 patients, significantly fewer tramadol recipients (27%) than placebo recipients (57%) withdrew from the study because of inadequate pain relief (65). Statistically significant improvements in patient-reported pain scores and pain relief ratings were also demonstrated (68). In addition, a double-blind, placebo-controlled, cross-over study resulted in greater pain relief for patients receiving injections of tramadol solution than those receiving placebo injections, but the number of tender points was not significantly altered by either therapy (66). Tramadol has been found to be as effective as acetaminophen with codeine in elderly patients with various chronic painful conditions, including fibromyalgia (67). Tramadol has also been found to be effective in treating the pain of osteoarthritis (69), a disorder that can coexist with fibromyalgia in elderly persons (106).

Anti-inflammatory drugs. Neither nonsteroidal anti-inflammatory drugs nor corticosteroids have been found to be significantly effective in treating fibromyalgia (28, 49, 70), although they are used by an estimated 90% and 24% of patients, respectively (4).

Lidocaine. Lidocaine is typically used for localized pain relief, but multiple injections into tender points may offer some benefit to patients with fibromyalgia. Multiple tender point injections with lidocaine in patients with fibromyalgia resulted in small but significant improvements in pain intensity and range of motion 2 weeks after treatment (71). However, patients with fibromyalgia gained less benefit from tender point injections with lidocaine than did patients with localized myofascial pain. Furthermore, patients with fibromyalgia experienced more postinjection soreness, possibly due to heightened responsiveness to painful stimuli. In a separate study comparing lidocaine tender point injections with saline or dry needling, increases in met-enkephalin levels after the procedure were similar in all three groups, suggesting that some of the benefits may be attributed to mechanistic effects of needling rather than the pharmacologic effects of lidocaine (72).

Opioids. When therapy with other analgesics fails because of ineffectiveness, intolerable side effects, or toxicity, opioid analgesics remain an option for persistent, moderate to severe non–cancer-related pain. Concerns about opioid abuse, dependency, tolerance, and toxicity are common, and opioid underutilization can result from physician, patient, and societal barriers, often because of misinformation about opioids (107, 108). However, no clinical data are available to suggest efficacy of opioids in fibromyalgia nor to indicate what their safety would be with long-term use in this subset of patients with chronic pain.

Miscellaneous Agents

S-*adenosyl-L-methionine.* *S*-adenosyl-L-methionine (SAMe), which is administered as a salt, is a naturally occurring active derivative of methionine present in all body tissue. Over the past 25 years, antidepressant, analgesic, and anti-inflammatory properties of SAMe have been identified. In the past 10 years, its possible role in the treatment of fibromyalgia has been evaluated in several small, short-duration, double-blind studies. Significant improvement of symptoms, including depression, pain, and number of tender points, has been reported with oral, intravenous, and intramuscular administration of SAMe (73, 109, 110), although one study failed to find significant beneficial effects (74). The lack of an inflammatory component in fibromyalgia suggests that the effectiveness of SAMe is related to its antidepressant or analgesic mechanism rather than to its anti-inflammatory mechanism. Whereas SAMe is available only by prescription in Europe, it is currently marketed as an over-the-counter "supplement" in the United States.

Other agents. On the basis of evidence that serotonin levels are decreased in patients with fibromyalgia (30, 31), a double-blind, placebo-controlled study of the serotonin precursor 5-hydroxytryptophan was undertaken in 50 patients with at least seven tender points (75). Administration of 100 mg of 5-hydroxytryptophan three times daily for 30 days resulted in significant improvement in the number of tender points and patient ratings of pain, stiff-

Table 2. Nonpharmacologic Treatment Options for Fibromyalgia Pain

Treatment (Reference)	Effective?*	Comments
Exercise (82–87)	Yes	No particular symptom showed consistent improvement across studies.
Biofeedback (88, 89)	Yes	
Hypnotherapy (90)	Yes	Compared to physical therapy in refractory patients.
Acupuncture (91–93)	Yes	The National Institutes of Health acknowledges the potential benefit of acupuncture in the treatment of fibromyalgia (94).
Multidisciplinary treatment (95–103)	Yes	In all studies, patients were allowed to continue their pharmacologic treatment.

* As demonstrated in clinical studies of fibromyalgia.

ness, anxiety, and fatigue. However, placebo recipients also reported significant improvement in quality of sleep and intensity of pain during the study.

Calcitonin is another serotonin precursor that is commonly prescribed for pain management. When 100 IU of calcitonin was administered to 11 patients daily for 4 weeks in a double-blind cross-over study, no significant improvement was seen, although the effect of calcitonin on plasma serotonin levels was not determined (76).

Conversely, blockade of the serotonin receptor subtype 5-HT_3 with tropisetron or ondansetron has been reported to significantly improve pain and decrease the number of tender points (77). However, the incidence of constipation with these agents, particularly at higher doses (77), may limit their usefulness, and 5-HT_3 antagonists may only be effective in certain subsets of patients with fibromyalgia (78).

The finding of low levels of insulin-like growth factor-1 in patients with fibromyalgia (29) led to the evaluation of growth hormone in the treatment of fibromyalgia symptoms (79). After receiving 9 months of daily growth hormone injections, patients demonstrated significant improvement in symptoms compared with placebo recipients. Symptoms worsened after treatment was discontinued.

Other agents that deserve mention include malic acid, an organic dicarboxylic acid, and γ-hydroxybutyrate. In patients with fibromyalgia, treatment with malic acid was evaluated secondary to reported deficiencies in high-energy phosphate, including adenosine triphosphate in muscle (16) and in erythrocytes (111). Malic acid and magnesium, both involved in generation of adenosine triphosphate, were administered in combination to patients in a study that included a 2-week, double-blind, fixed-dose phase followed by a 6-month, open-label, dose-escalation phase (80). Fibromyalgia symptoms were alleviated only in the open-label phase. The authors attributed the absence of a significant effect in the double-blind phase to the lower doses of malic acid and magnesium used and to the shorter treatment course of this phase.

In an open-label study, 11 patients with at least five tender points were given injections of γ-hydroxybutyrate at bedtime and again 4 hours later (81). Patients reported significant decreases in pain and fatigue and improvement in overall wellness from baseline, but objective sleep measurements were not significantly improved in this small group. Unfortunately, γ-hydroxybutyrate has a short half-life and has been associated with rebound alertness; multiple nighttime injections may therefore be required, limiting the clinical value of this agent in the management of fibromyalgia.

Nonpharmacologic Treatment

When 80 patients with fibromyalgia and 221 controls were surveyed, patients with fibromyalgia were significantly more likely to report current use of alternative therapies (91%), particularly dietary modifications, chiropractic, or massage therapy (112). Many patients are interested in the usefulness of nonprescription or "alternative" therapies because traditional pharmacologic therapies provide inadequate control of fibromyalgia symptoms.

Exercise

Because many fibromyalgia symptoms are also associated with deconditioning, the effect of various types of exercise, including aerobic dance, stationary cycling, and aerobic walking, has been evaluated (82–87). A review of these studies suggests that aerobic exercise three times a week can reduce tender-point tenderness. Overall pain may also decrease, although sleep and level of fatigue are likely to be unaffected. These benefits also do not appear to be long-lasting (85). In addition, among all studies, no specific symptom alleviation was consistently found with exercise.

Biofeedback

Abnormal electromyographic activity (113, 114) and reduced muscular sensitivity (89) have been reported in fibromyalgia. Electromyographic biofeedback training may therefore be a therapeutic option in treating fibromyalgia pain. Studies of biofeedback show that patients with fibromyalgia who received treatment experienced a significant decrease in the number of tender points, overall pain intensity, and morning stiffness compared with pretreatment assessment (88, 89); one study reported beneficial effects lasting 6 months after treatment cessation (88). A recent study demonstrated that the addition of exercise training to biofeedback and relaxation training intervention resulted in significantly greater benefit and longer-lasting improvements than did either treatment alone (115).

Hypnotherapy

In a controlled study comparing eight sessions of hypnotherapy with physical therapy, patients with refractory fibromyalgia experienced greater benefit from hypnotherapy (90). It is important to note that the patients in this study were already refractory to physical therapy, resulting in a selection bias in favor of hypnotherapy. However, because patients with refractory fibromyalgia have great difficulty controlling their symptoms and have often already exhausted several treatment options, hypnotherapy offers another alternative in this group.

Acupuncture

Although acupuncture has been found effective in the management of chronic pain in general (116–118), few studies have assessed its potential value in treating the chronic pain of fibromyalgia. In an early account of acupuncture treatment of fibromyalgia, 67% of patients reported a positive treatment effect (91). In a more recent randomized study, 3 weeks of electroacupuncture resulted in improvement in five of the eight outcome measures evaluated (including pain threshold at tender points, self-reported pain, morning stiffness, and patient and physician overall assessment) compared with a sham treatment group, with approximately one quarter of the patients experiencing almost complete symptom remission (92). There is some question about the methodologic soundness of the study, however, including the use of electroacupuncture rather than ordinary acupuncture as well as the stimulation of sites only 2 cm away from actual tender points in the control group (119). In a third study, the number of tender points and self-reported pain decreased in patients with fibromyalgia after six weekly acupuncture treatments (93). Serum levels of serotonin and substance P significantly increased after treatment, suggesting a physiologic mechanism for the reported pain relief.

On the basis of the available evidence, a recent National Institutes of Health consensus statement on acupuncture concluded that in some situations, including fibromyalgia, "acupuncture may be useful as an adjunct treatment or an acceptable alternative or may be included in a comprehensive management program" (94).

Cognitive-Behavioral Treatment

Several studies have evaluated inpatient and outpatient cognitive-behavioral treatment programs for patients with fibromyalgia (95–103). All studies reported at least some benefit. Such treatment programs include combinations of relaxation training, meditation, cognitive restructuring, aerobic exercise and stretching, activity pacing, and patient and family education. In all of the studies, patients were allowed to continue their pharmacologic treatment. Length of treatment ranged from 3 to 24 weeks. At the end of treatment, improvement was observed in the overall impact of fibromyalgia, pain intensity, number of tender points, emotional distress, and sense of control over pain. Some aspects of improvement remained at short-term (6-month) follow-up (99) and long-term (30-month) follow-up (102).

However, in a prospective study comparing a group that received intensive cognitive intervention with a control group that received less structured group discussions about pain and coping, efficacy did not significantly differ between the two groups (96). Similar results were obtained when group relaxation training was compared with integrated group therapy (97); the efficacy of the two treatments was generally similar for fibromyalgia symptoms, although integrated therapy provided modest but significant improvements. In both studies, the efficacy of all treatments may have been tempered by the long duration of fibromyalgia in the patients studied; these patients may be more refractory to changing their coping behaviors and personal beliefs about their health. Therefore, integrated behavioral therapy shows promise in patients with fibromyalgia of more recent onset.

Conclusions

Fibromyalgia is a chronic painful syndrome of unknown cause. Although there is no cure, symptoms can be controlled to a moderate degree with various treatments. Reliably effective pharmacologic treatment options are limited. A comprehensive, multidisciplinary approach incorporating both pharmacologic and nonpharmacologic interventions is often necessary to achieve clinically significant improvement.

Overall, clinical evidence suggests that the most effective agents in managing the pain of fibromyalgia are those that affect neurotransmitter metabolism at the receptor site. Among antidepressants, tricyclic agents seem to be an effective treatment option for one third of patients at best, and the usefulness of selective serotonin reuptake inhibitors is less clear. With respect to analgesics, no studies on oral opioids have been published to date. Although nonsteroidal anti-inflammatory drugs have had a small amount of anecdotal success, prospective, controlled clinical trials have failed to demonstrate efficacy. A lack of proven benefit and significant adverse events make corticosteroids an inappropriate treatment choice as well. On the basis of preliminary studies, tramadol or tender point injections show promise in the management of pain associated with fibromyalgia. Alternative agents, including growth hormone, 5-hydroxytryptophan, and γ-hydroxybutyrate, have also proved effective, but their clinical role in the management of patients with fibromyalgia remains to be determined.

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