

## A Review of Advances in Treating Fibromyalgia Syndrome (FMS) Using a Multidisciplinary Approach

***Fibromyalgia syndrome (FMS) is a chronic, nonmalignant condition that affects three to six million people in the US. The etiology of FMS is unknown, although many theories have attempted to explain this syndrome. Because of the complexity of fibromyalgia, a trend is developing toward use of a multidisciplinary treatment approach, especially in patients for whom FMS has substantially diminished the quality of life. To maximize its effectiveness, the treatment plan would assign for each patient the degree of multidisciplinary involvement appropriate for that patient's symptoms. Categorizing patients and using a stepwise approach to treating FMS provides high-quality treatment that is efficient as well as cost-effective. The most effective treatment for FMS includes a combination of patient education, medication, regular exercise, physical modalities, stress reduction, and acquisition of coping skills; patients respond less well to use of a single treatment modality alone. Patient education should help patients understand that the goal of therapy for FMS is not necessarily to completely eliminate pain but to decrease intensity of the pain and to improve physical function. The choice of therapeutic agents used in treatment of FMS is guided by the symptoms the patient is experiencing, past medication history, and the profile of action of the individual medication. A review of these different treatment modalities and their importance in the treatment of FMS are discussed.***

### Introduction

Fibromyalgia syndrome (FMS; also known as fibrositis) is a nonarticular rheumatic disease that affects three to six million people in the US.<sup>1</sup> The etiology of FMS is unknown, although many associations and theories have been suggested to explain this syndrome.<sup>1,2</sup> Such theories have included disturbance of rapid eye movement (REM) sleep, change in immune system function, interplay of mechanical stresses in the cervical and lumbar spine, viral infection, psychological disorders, abnormality in neurotransmitter function, and metabolic muscle defects. However, none of these theories explain the diverse symptoms seen in FMS.<sup>2-4</sup>

FMS is seen most commonly in women between the ages of 25 years to 50 years, and incidence of FMS is highest among family members of affected people; however, no genetic patterns have been identified.<sup>5</sup> FMS is usually primary and occurs in the absence of other medical conditions, but secondary FMS occurs in some patients. These patients have other medical disorders (usually hypothyroidism and rheumatoid arthritis) in conjunction with fibromyalgia.<sup>6</sup> Primary fibromyalgia causes chronic pain and fatigue that can persist for years if left untreated but which by itself is not degenerative or deforming and is seldom associated with mortality. Fibromyalgia must be recognized because it accounts for 20% to 30% of all referrals to rheumatologists, consumes a large amount of resources, and can cause painful symptoms that lead to substantial disability.<sup>6,7</sup> When extensive diagnostic tests fail to identify a visible source for the reported pain, practitioners may think patients have a psychological problem and may refer them to a clinical specialist or to a behavioral medicine specialist.<sup>1</sup> Because they have constant pain and little relief for extended periods of time, patients with FMS tend to "shop" from practitioner to practitioner—a practice that extensively consumes expensive health care resources while often achieving poor outcomes and inadequate solutions for pain.<sup>6</sup> By the time patients are diagnosed correctly, they may have already seen several specialists and may be taking medications inappropriate for their condition. Other patients are led to believe that they are drug addicts looking for a way to legitimize their habits. These circumstances and conditions are demoralizing to patients and can cause them to feel angry, frustrated, and depressed.

FMS continues to be undertreated and unrecognized by many health care professionals because of its complex and diffuse nature. This situation produces substantial disability for patients and increases costs to the health care system.

### Pathophysiology and Etiology of FMS

FMS is characterized by widespread musculoskeletal pain and tenderness at 11 or more of 18 specific tender points at characteristic locations (Fig. 1) according to criteria published by the American College of Rheumatology.<sup>2</sup> According to these criteria, at least 11 of these 18 tender points (located prima-

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rily at the junctions) become extremely painful when a force of approximately 4 kg/cm<sup>2</sup> (ie, moderate pressure) is applied to them.<sup>1,2</sup>

The tenderness is focal (ie, not diffuse) and is present on both sides of the body (paired), above and below the waist, and at the midline.<sup>1</sup>

Although pain is the predominant symptom, most patients have additional symptoms: irritable bowel syndrome, general weakness and fatigue, chronic headache, sleep disturbance, nocturnal myoclonus, numbness and tingling, morning stiffness, generalized musculoskeletal pain not accompanied by tissue inflammation, female urethral syndrome, abnormal function of neurotransmitters (serotonin and norepinephrine), depression, and Raynaud's phenomenon. FMS is further aggravated by fatigue, tension, excessive work, immobilization, and change in weather.<sup>2,6,8</sup>

### Diagnosis of FMS

Like low back pain, FMS is a clinical syndrome that cannot be explained using current theories of pathophysiology.<sup>1</sup> FMS is not definitively diagnosed by any laboratory test or characterized by any typical x-ray abnormality, and laboratory tests (erythrocyte sedimentation rate, complete blood count, and thyroid function tests) administered to patients with primary FMS usually give normal results; physical examination and laboratory tests should therefore be used to rule out conditions that may mimic FMS—conditions such as lupus erythematosus, rheumatoid arthritis, hypothyroidism, and infection.<sup>6</sup> Any abnormal results of the above-mentioned tests warrant further search for an underlying disorder other than FMS.<sup>6</sup> Physical examination is done also to confirm the presumptive diagnosis of FMS by locating the tender points.

FMS should be considered in any patient with some or all of the signs or symptoms listed in Table 1.<sup>1,2,9</sup> Clinicians who suspect FMS on the basis of symptoms listed in Table 1 should begin treatment as soon as possible and should not take too much time to diagnose FMS in a patient that exhibits classic symptoms: doing so may lead to unnecessary use of health care resources.<sup>1,6</sup>

### Principles of Treatment

FMS has no known cure. However, the condition can be managed successfully if relevant biological, psychological, and social factors are addressed.<sup>1,6</sup> FMS is a chronic condition whose mean duration of symptoms before diagnosis is approximately five years.<sup>7</sup>

On average, patients with FMS visit outpatient health

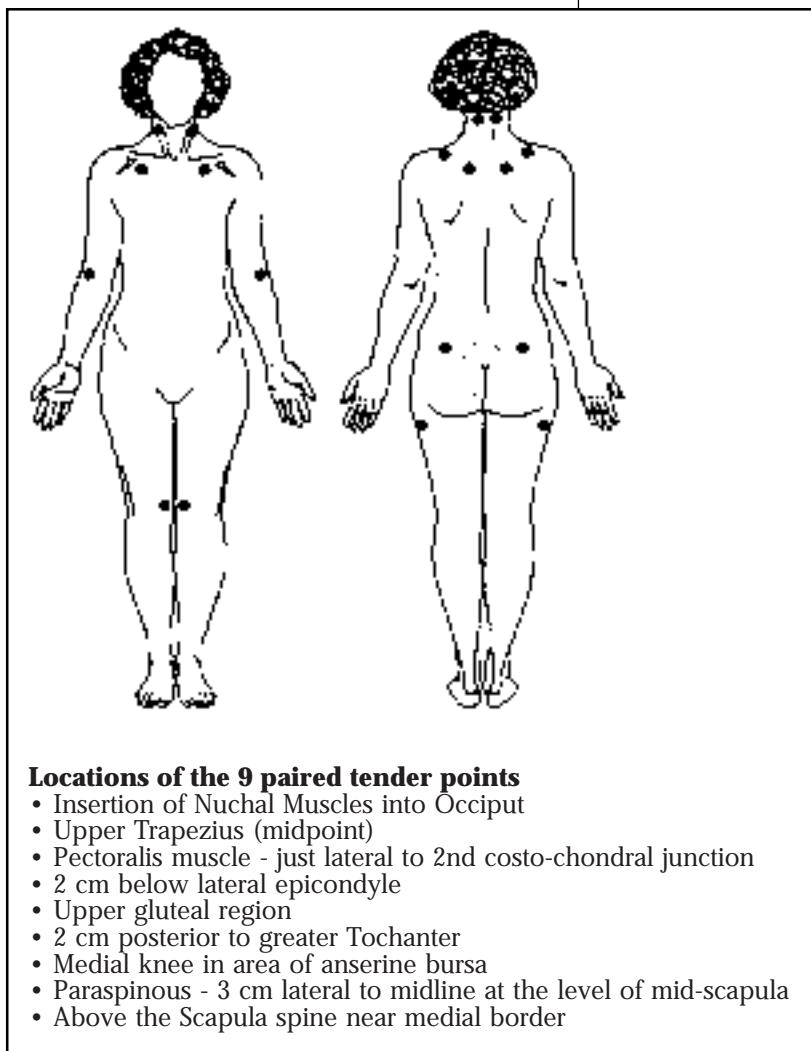


Figure 1. Specific tender areas characteristic of fibromyalgia syndrome. [Reproduced by permission of the author and publisher from: Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990;33:160-72(2)]

care facilities 13 times annually.<sup>10</sup> At these visits, patients have countless laboratory tests done, see several health care practitioners, and receive numerous prescription medications that provide minimal benefit.

The multiple components and complexity of fibromyalgia have led to a growing trend toward use of a multidisciplinary approach.<sup>4</sup> Such an approach may be a cost-effective way to treat fibromyalgia, especially in highly dysfunctional patients, because almost all issues affecting patients with FMS can be addressed decisively by experts in various disciplines, leading to better outcomes. The

**Table 1. Associated signs and symptoms of FMS<sup>2,9</sup>**

Sign or symptom	% of patients
Widespread pain	97.6
Tenderness at >11 of 18 specific tender points	90.1
Fatigue	81.4
Morning stiffness	77.0
Sleep disturbance	74.6
Headache	52.8
Anxiety	47.8
Dysmenorrhea history	40.6
Sicca symptoms	35.8
Previous depression	31.5
Irritable bowel syndrome	29.6
Urinary urgency	26.3
Raynaud's phenomenon	16.7

multidisciplinary team caring for patients with FMS usually consists of practitioners from internal medicine, anesthesiology, behavioral medicine, nursing, physical medicine, and pharmacy.

Goals of therapy should include patient education and involvement in the treatment plans, decreased pain intensity, increased physical activity, decreased reliance on narcotic pain medications, use of the most appropriate and least amount of medication to treat the pain, improved psychosocial functioning, return to work if possible, and reduced utilization of health care services. To achieve these goals, treatment plans must include all the following components to varying degrees: patient education, medication therapy, regular exercise, and physical, behavioral, and psychological modalities (stress reduction and coping skills). This multifaceted approach is necessary because studies have shown that patients respond little to any treatment modality given by itself.<sup>4,6,11</sup>

The degree of multidisciplinary involvement required by an effective treatment plan depends on each patient's symptoms. Categorizing patients with

FMS and using a stepwise approach to its treatment may provide high-quality treatment that is efficient as well as cost-effective (Fig. 2). Patients can be categorized into three groups on the basis of type of symptoms and degree of functional impairment.<sup>12</sup>

#### Group 1 Patients

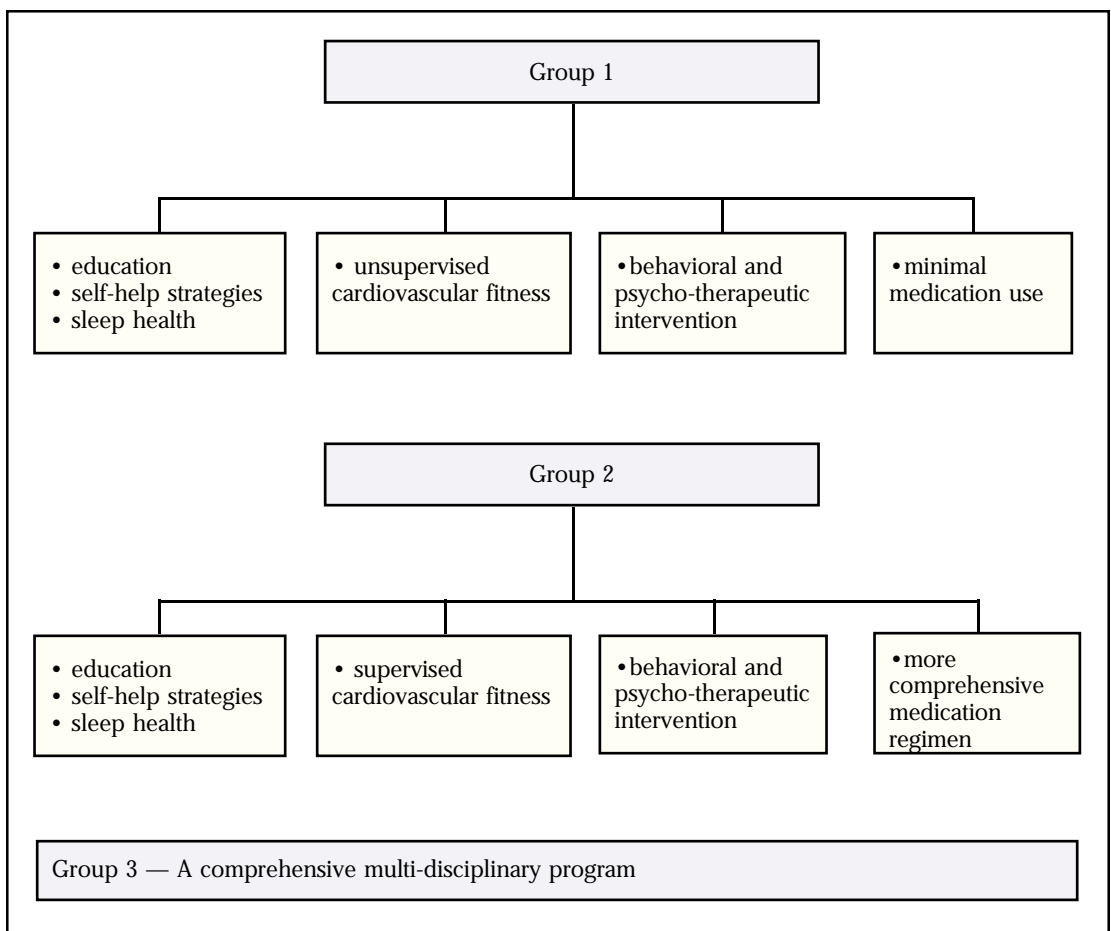
Patients in this group have had FMS for less than two years and function almost normally: they experience only low levels of fatigue or sleep disturbance and little interference with activities of daily living, work performance, or interpersonal relationships.<sup>12</sup> If these patients cannot be adequately treated by their primary care physician, referral to the multidisciplinary program may be necessary for thorough evaluation and for development of a treatment plan that incorporates education, self-help strategies, unsupervised cardiovascular fitness, sleep health, psychotherapeutic intervention, and minimal medication use. After recommendations are made, the patient returns to the primary care physician for further follow-up. The multidisciplinary team continues to act as an effective bridge between the primary care physician and the patient to maximize the effectiveness of subsequent clinician-patient interactions.<sup>4</sup>

#### Group 2 Patients

Patients in this group experience moderate interference with normal everyday functions: they have more pain and fatigue and more disruption of functioning than patients in Group 1.<sup>12</sup> Patients in group 2 have decreased work performance (absenteeism) and increased stress with interpersonal relationships.<sup>12</sup> For these patients, a multidisciplinary program provides a comprehensive treatment plan that incorporates education, a supervised cardiovascular fitness regimen, promotion of sleep health, psychotherapeutic intervention, and a more comprehensive medication regimen.<sup>12</sup> Patients who show signs of depression should be treated with full doses of the newer, selective serotonin reuptake inhibitors (eg, fluoxetine).<sup>12</sup> Analgesic agents and trigger-point injections may also be beneficial for these patients and should be used to treat pain not controlled by tricyclic antidepressant agents used alone.<sup>12</sup>

#### Group 3 Patients

Patients in this group have the highest level of dysfunction, manifested as disintegration of family life, drastically reduced job performance, and substantial overall disruption to daily life.<sup>12</sup> These patients must



*“The purpose of the CPMP is to serve as a consultative source for treating patients who have unresolved or difficult pain and to provide comprehensive care and service to patients with chronically painful medical conditions such as fibromyalgia.”*

Figure 2. Treatment strategies for FMS patients.

be enrolled for an extended period of time in a multidisciplinary pain management program that incorporates intensive patient education, medication therapy, a regular exercise program, physical modalities, stress reduction skills, and coping skills.<sup>12</sup> To improve continuity and long-term outcome treatment, primary care physicians must remain involved during the multidisciplinary process.<sup>11</sup>

**Structure of the Pain Management Program for Patients with FMS at Kaiser Permanente Medical Center, Los Angeles**

The Chronic Pain Management Program (CPMP) at Kaiser Permanente Medical Center, Los Angeles is a multidisciplinary service whose core members are the pain management coordinator, interventional anesthesiologist, physical therapist, physiatrist, psychologist, pharmacy specialist, clinical pain specialist, and administrative liaison (Fig. 3). The purpose of the CPMP is to serve as a consultative source for treating patients who

have unresolved or difficult pain and to provide comprehensive care and service to patients with chronically painful medical conditions such as fibromyalgia.

**The Triage Process**

Patients are referred to the CPMP by their primary care physician, other health care practitioner, or both. Referred patients are triaged by the pain management coordinator. Patients’ charts are then ordered and reviewed by several members of the CPMP team to obtain and confirm medical diagnoses, past and current pharmacological and nonpharmacological therapies received, and other important pertinent information. The team then determines whether the patient should be further evaluated by the team or referred back to their health care practitioner. Patients who are to be evaluated by the CPMP team are so notified by the administrative assistant, an appointment is made, and a comprehensive questionnaire is mailed to the patient.

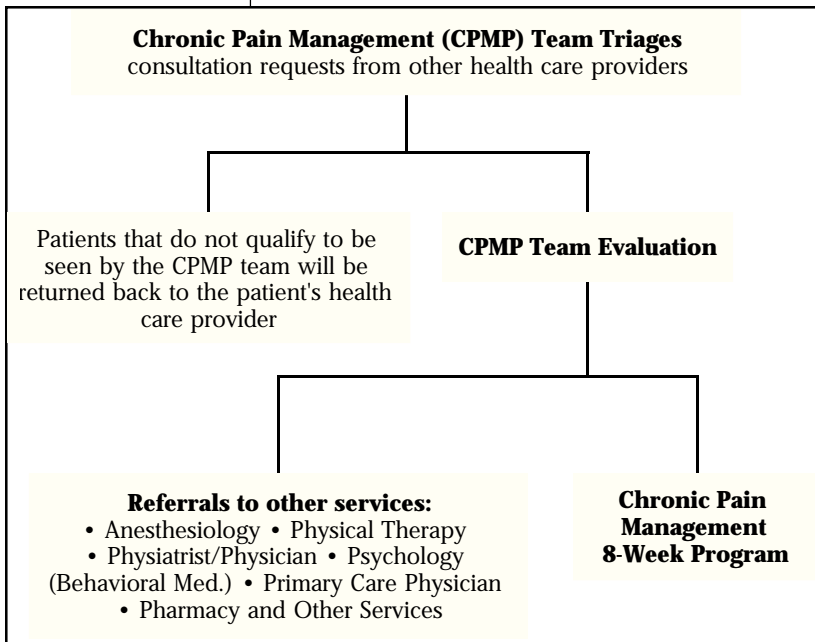


Figure 3. Structure of the Chronic Pain Management Program for patients with chronic pain and fibromyalgia at the Kaiser Permanente Los Angeles Medical Center.

**Evaluation of Patients and Referral to Other Departments**

The CPMP team’s evaluation is extensive and comprehensive: the physician examines the patient and asks pertinent medical questions, the psychologist asks questions designed to evaluate the psychological status of the patient, the physical therapist obtains information on past physical therapy treatment, and the pharmacist reviews all past drug therapy (especially as administered for pain), duration of past therapy, reasons for discontinuing past therapy, allergy profile, and current therapy. Laboratory test results and other pertinent information are also reviewed. After this comprehensive evaluation, patients are either admitted to the eight-week CPMP or are triaged to other services or disciplines as recommended by the team. Patients not admitted to the eight-week CPMP are given a detailed treatment plan and are referred to one or more of the following:

- Their health care practitioner, who is given specific treatment recommendations from the CPMP team;
- The anesthesiology department for procedures, shots, epidural injections, and highly technical interventional techniques;
- The psychiatrist for individualized treatment which may include trigger-point injections and other modalities;
- The physical therapist for individualized

treatment which is monitored by the CPMP physician, the patient’s health care practitioner, or both;

- The psychologist for complete psychological examination as well as instruction on coping skills and biofeedback techniques—all monitored by the CPMP physician, the patient’s health care provider, or both;
- The pharmacist for monitoring and adjusting each patient’s drug therapy as needed (in consultation with the CPMP physician) and for reinforcing the importance of compliance with the medication regimen.

**Comprehensive Eight-Week Program for Patients with Chronic Pain and FMS**

At the first session, a physician, physical therapist, psychologist, and pharmacist each discuss the goals of the CPMP and the responsibilities of each specialty during the eight weeks of the program. The physician evaluates each patient, educates patients about their disease, and provides the following modalities as needed: trigger-point injections, “spray and stretch” (the skin is sprayed with a local anesthetic and the muscles in that area stretched), joint mobilization and manipulation, peripheral nerve blocks, epidural nerve blocks, and medication for sympathetic blocks. The physical therapist uses gentle muscle rehabilitation, education, muscle stretching, progressive training, and endurance training to help patients resume normal or nearly normal activity. The psychologist uses cognitive behavioral therapy (CBT) as well as relaxation training to help patients cope with pain and to assist patients in developing an active, resourceful, self-management approach to coping with FMS. The pharmacist assesses each patient’s drug therapy weekly and makes any needed dosage adjustment and titration (in consultation with the CPMP physician). For patients whose therapy proves ineffective after an adequate trial, alternative treatment plans are developed. The pharmacist also educates and reinforces the importance of adherence to medication regimens, works with patients to prevent adverse drug effects and potential drug interactions, and expedites all refill prescriptions for CPMP patients during and after the eight-week CPMP. The pain management coordinator coordinates patients’ overall care with practitioners in designated departments (referring, primary care, or both) across the





continuum, conducts follow-up telephone calls on care efficacy, ensures appropriate patient management, and manages quality assurance activities. The administrative assistant provides support to the coordinator and to other members of the multidisciplinary team.

After patients have successfully completed the eight-week program, the CPMP team gives each patient an individual discharge plan that contains a set of instructions to help the patient follow recommendations of the team. Patients are requested to bring this plan with them to their next physician visit. A copy of the discharge plan is also sent to the patient's health care practitioner for inclusion in the patient's medical record.

## Nonpharmacologic Therapy

### Patient Education

Patient education about FMS is vital because patients need to know that their symptoms are not "all in their head" but that distinct recognizable symptoms distinguish FMS from other medical conditions.<sup>6</sup> Patients also need reassurance that although a painful and sometimes debilitating syndrome, FMS does not permanently damage tissues or muscle and can be managed successfully. Emphasizing this point is particularly important because some patients have been led to believe that they might have more serious conditions, eg lupus erythematosus or multiple sclerosis.<sup>7</sup>

Patients also must be helped to understand that the goal of therapy in treating FMS is not to completely eliminate pain but to decrease the intensity of the pain and to improve coping skills. Patients should understand that current therapy used to treat FMS is palliative and not curative.

### Sleep Health

Nonrestorative sleep—deep sleep that is interrupted, leaving a patient tired and feeling worse the next day—is prevalent in FMS patients. Abstaining from caffeine-containing products such as caffeinated coffee, tea, sodas, and sports drinks, is therefore important. Daytime naps and short naps at the end of the workday should also be avoided because they may interfere with nighttime sleep.<sup>12</sup> Patients should be encouraged to create a soothing atmosphere in the bedroom by not watching television, paying bills, settling family disputes, or trying to overcome stressful situations there. These practical considerations may effectively restore a modicum of normal sleep and

should be considered before resorting to enrollment in expensive sleep studies.<sup>12</sup>

### Physical Therapy and Cardiovascular Training

Some patients with FMS suffer from motor dysfunction caused by chronic muscle misuse (as occurs in inactivity, abnormal postural stress, or overuse) that must be corrected if patients are to resume normal activity.<sup>13</sup> Gentle muscle rehabilitation should be used to treat this dysfunction.<sup>4,7</sup> The long-term goal of physical therapy must incorporate muscle stretching, progressive training, and endurance training. Symptoms of FMS can be further relieved by incorporating exercise into the lifestyles of patients with FMS. Aerobic exercise is particularly beneficial because it decreases pain perception, increases duration of deep sleep, and affects symptoms of FMS by activating beta-endorphins.<sup>7,14,15</sup> Studies have also shown that cardiovascular training and flexibility exercises can substantially raise a patient's pain threshold as measured at FMS tender points; increase level of physical activity; and improve psychological well-being.<sup>7,14,15</sup>

FMS patients need a home-based program of muscle stretching, gentle strengthening, active range-of-motion exercises, and aerobic conditioning.<sup>4,13</sup> Regular exercise should become a part of lifestyle and not merely a temporary solution. Patients are advised to begin any exercise program slowly so that an over-ambitious start does not cause injury and frustration and lead patients to abandon the exercise program entirely.<sup>4</sup> Moreover, incremental improvement in exercise capacity and stretching provides positive physiological feedback. Application of hot packs combined with high-frequency, high-intensity transcutaneous electric nerve stimulation (TENS) and deep massage are sometimes helpful when used in combination with an exercise program.

### Behavioral and Psychological Therapy

Cognitive behavioral therapy and relaxation training are forms of behavioral and psychological therapy that can help patients cope with some of their FMS symptoms.

### Cognitive Behavioral Therapy (CBT)

Most patients with FMS experience psychological distress as a consequence of chronic pain.<sup>4</sup> Most commonly, these patients experience dysthymia, depression, anxiety disorders, and maladaptive pain behavior. Cognitive behavioral therapy for chronic

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<b>Table 2. Support groups and services provided for FMS patients<sup>8</sup></b>	
Group	Services offered
Fibromyalgia Alliance of America P.O. Box 21990 Columbus, OH 43221-0990 1(614)457-4222	Information, support group resources and a quarterly newsletter, all for a \$25 annual membership fee.
Arthritis Foundation (800)283-7800	FMS self-help classes, training, and support group information. (Check phone directory for local chapters.)
National Institute of Arthritis Musculoskeletal and Skin Diseases (NIAMS) P.O. Box AMS 9000 Rockville Pike Bethesda, MD 20892 (301) 495-4484 (voice) (301) 565-2966 (voice) (301) 587-4352 (fax)	Free information packets containing lists of fibromyalgia organizations, a glossary, fact sheet from the American College of Rheumatology, and articles written by experts.
Fibromyalgia Network P.O. Box 31750 Tucson, AZ 85751-1750 (602) 290-5508	Newsletter containing current information on FMS research, treatment, and coping strategies.
Fibromyalgia and You (210) 567-4661	Video programs

pain has proved beneficial in managing patients' pain, stress, anxiety, depression, and anger.<sup>12</sup> The goal of CBT is to help patients to develop an active, resourceful, self-management approach to coping with their FMS.<sup>12</sup> Cognitive therapy in FMS patients has led to improved functional ability such as spending time out of bed and increasing activity level.<sup>16</sup> A sense of control and mastery over life circumstances are also enhanced.<sup>17,18</sup> Cognitive behavioral therapy is most beneficial when used in conjunction with aerobic exercise, physiotherapy, biofeedback training, and relaxation therapy.<sup>10</sup>

**Relaxation Training**

A relaxation training program uses biofeedback-assisted relaxation training, autogenesis, progressive muscle relaxation, imagery, breathing exercises, distraction, and self-hypnosis techniques to help patients to reduce the overall level of stress in their lives. Relaxation techniques have also been effective in decreasing pain levels.<sup>12</sup>

**Support Groups**

Support groups are an important resource for patients with FMS. During the past five years, support groups and seminars on FMS around the country have been formed to offer information to educate patients about FMS.<sup>8</sup> A list of support groups is given in Table 2.

**Pharmacologic Therapy**

Drug regimens should be individually tailored to each patient's needs after an extensive drug history has been obtained. This history includes all over-the-counter and prescription medications the patient has used for pain, dosages, directions for use, and duration of therapy. This information is important, because most patients who complain about treatment failure have received the wrong therapy, subtherapeutic doses of medication, or have not received therapy long enough for the medication to be effective.<sup>15</sup> Medications used to treat FMS are listed in Table 3.

**Table 3. Medications used to treat FMS and related symptoms**

Drug	Starting dose	Maximum daily dose	Half-life (hours)
Tricyclic antidepressants:			
Amitriptyline	10 mg at bedtime	100 mg	31-46
Desipramine	10 mg at bedtime	150 mg	12-24
Doxepin	25 mg at bedtime	150 mg	8-24
Nortriptyline	10 mg at bedtime	100 mg	18-44
Other antidepressants:			
Trazodone	50 mg at bedtime	200 mg	4-9
Skeletal muscle relaxants:			
Carisoprodol	350 mg 3 times daily	1400 mg	1-3
Cyclobenzaprine	10 mg 3 times daily	60 mg	24-72
Chlorzoxazone	250 mg 3 or 4 times daily	3000 mg	1
Methocarbamol	750 mg 4 times daily		1-2
Selective serotonin re-uptake inhibitors:			
Fluoxetine	10 mg daily	80 mg	48-216
Paroxetine	20 mg daily	50 mg	21
Sertraline	50 mg daily	200 mg	26-65
Benzodiazepines:			
Alprazolam	0.5 mg at bedtime	4 mg	12-15
Clonazepam	0.5 mg at bedtime	20 mg	18-50
Nonnarcotic analgesics:			
Acetaminophen	650 mg by mouth 4 times daily	4 g	1-3
Tramadol	50 mg every 4-6 hours	400 mg	5
Miscellaneous:			
Zolpidem	5-10 mg by mouth every hour	10 mg	1.4-4.5
Gabapentin	300 mg every 4 hours (day 1) 300 mg twice daily (day 2) 300 mg 3 times daily (day 3)	1800-2400 mg	5-7



### Antidepressants and Sleep Therapy

Studies have shown that tricyclic antidepressant drugs and trazodone are beneficial in the treatment of FMS.<sup>3,6,9,15,19,20</sup> These drugs promote deep sleep by blocking reuptake of serotonin, a neurotransmitter which has been shown to be important in stage 4 deep sleep<sup>15</sup> and which has been implicated in the pathogenesis of FMS.<sup>3</sup> Patients with fibromyalgia have shown increased serotonin receptor density on their circulating platelets as well as lower serum levels of serotonin than found in the general population.<sup>21</sup> In addition to improving a patient's overall mood, TCAs and trazodone also have analgesic effects<sup>22</sup> and may reduce the symptoms of irritable bowel syndrome<sup>12</sup> because of anticholinergic side effects that lead to decreased intestinal motility. These effects address symptoms reported by FMS patients.

Improved sleep is particularly important for patients with FMS because when these patients increase the amount of deep sleep they get, other symptoms improve substantially. Tricyclic antidepressant drugs and trazodone seem to relieve muscle pain and spasms by altering pain perception in the brain. These drugs increase both the intensity of effect as well as the duration of activity of other analgesic medications when taken concurrently with these medications and may be used to reduce the need for narcotic pain medications.

Tricyclic antidepressant drugs and trazodone are usually first-line therapy for treatment of FMS. A trial of tricyclic antidepressant therapy should be considered for all patients with FMS unless this approach is contraindicated (eg, by major cardiac arrhythmia, prostatic hypertrophy, or narrow-angle glaucoma).<sup>23</sup> Initially, patients should be given the lowest possible dose (Table 3) at bedtime; this dose should be increased incrementally every few days until the patient obtains maximum relief without experiencing unacceptable side effects.

### Choice of Medication

Appropriate choice of antidepressant drugs depends on the patient's medical history and clinical symptoms as well as the side effect profile of the medication. Amitriptyline has been most widely studied and used for treatment of FMS; however, because of its long half-life and its tendency to cause sedation, orthostatic hypotension, and anticholinergic side effects (eg, dry mouth, urinary retention), amitriptyline should be avoided by elderly patients and by patients who do not have major sleep disorders. Amitriptyline also causes the most

weight gain of all the tricyclic antidepressant drugs, and this effect can be a source of noncompliance—especially in patients who are concerned about weight gain.<sup>6</sup> A trial of secondary-amine tricyclic antidepressant drugs (desipramine and nortriptyline) should be given to patients who are unable to tolerate the anticholinergic or hypotensive effects of tertiary-amine tricyclic antidepressant drugs (amitriptyline, doxepin, imipramine) or who are predisposed to toxicity from these agents. Secondary-amine tricyclic antidepressant drugs have fewer anticholinergic side effects, less potential for causing weight gain, and shorter half-lives than other tricyclic antidepressant drugs.

Doxepin has been effective in patients with coexistent psychogenic headache. Trazodone, an antidepressant drug that is structurally different from tricyclic antidepressant drugs, effectively treats FMS when anxiety is a major component of this syndrome. Trazodone also has few anticholinergic side effects, a feature which can be beneficial.<sup>22</sup>

### Dosing Recommendations

Except for trazodone and doxepin (which may be given in initial doses of 25 mg), use of tricyclic antidepressant drugs for treatment of FMS should begin with 10-mg doses. Doses of tricyclic antidepressant drugs and trazodone should be increased gradually after a few days in increments of 10 mg to 25 mg as tolerated, to the maximum doses shown in Table 3. Improvement in symptoms may be observed after about two weeks.<sup>3,22</sup> Patients who cannot tolerate the side effects of one tricyclic antidepressant drug or who obtain no relief from a maximum dose should be considered for a trial of a different tricyclic antidepressant drug with or without additional medications such as skeletal muscle relaxants, analgesic drugs, and sedatives. Alternatively, these medications may be appropriately given without tricyclic antidepressant drugs. Clinical experience suggests that lack of response to one tricyclic antidepressant drug does not necessarily indicate likelihood of a poor result with another.<sup>1</sup>

Patients with FMS may require trials of several medications in combination before finding what will work well,<sup>4,15,20,24</sup> and drug dosages used to treat FMS must be tapered or titrated carefully over time to achieve optimal outcome with minimal side effects.

In general, tricyclic antidepressant drugs and trazodone cause varying degrees of drowsiness,

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lightheadedness, impairment of memory or concentration, headache, dry mouth, blurred vision, constipation, urinary retention, and seizure.

**Other Considerations**

Even when taken correctly, tricyclic antidepressants and trazodone are effective only in about 25% to 45% of patients<sup>3</sup> and therefore are generally not used alone in treating FMS; other medications (eg, muscle relaxants, analgesic drugs, and sedatives) are used concomitantly. Moreover, physical, cognitive, and behavioral therapy must accompany medication therapy to increase physical activity and to address the negative thoughts and depression that may increase suffering and anxiety.<sup>12</sup>

**Selective Serotonin Reuptake Inhibitors**

Selective serotonin reuptake inhibitors (SSRIs) have been used to treat the depression associated with FMS when tricyclic antidepressant therapy has not been effective. However, SSRIs have been no more effective than placebo in reducing the pain associated with FMS.<sup>6</sup> Concomitant use of fluoxetine in the morning and tricyclic antidepressant drugs at bedtime has been beneficial because fluoxetine counteracts some of the side effects of tricyclic antidepressant drugs, particularly weight gain and daytime drowsiness.<sup>10,22,25</sup> This counteractive effect may help improve compliance for patients who would discontinue use of tricyclic antidepressant drugs because of weight gain and other side effects. Possible side effects of fluoxetine include insomnia, drowsiness, headache, and nausea.

**Skeletal Muscle Relaxants**

When FMS is not well controlled by using tricyclic antidepressant or trazodone therapy, causing patients to have substantial morning stiffness, addition of a skeletal muscle relaxant to the regimen may be beneficial. Skeletal muscle relaxants effectively treat the discomfort which accompanies localized skeletal muscle spasm.<sup>1,3,6</sup> Because these drugs can help improve range of movement, they can be especially beneficial for patients who are just starting physical therapy and an exercise program.<sup>3</sup> Cyclobenzaprine and carisoprodol are the muscle relaxants most often used for this purpose. Cyclobenzaprine is also the skeletal muscle relaxant preferred for pregnant women.<sup>23</sup> Possible side effects include drowsiness, dizziness, and dry mouth.

**Benzodiazepines**

Alprazolam and clonazepam have been used to obtain short-term relief of anxiety symptoms, nocturnal myoclonus, and sleep disorders associated with FMS.<sup>3,26</sup> Concomitant use with tricyclic antidepressant drugs produces an additive sedation effect that is beneficial for patients with insomnia. Alprazolam and clonazepam are used also to relieve skeletal muscle spasticity and to treat the anxiety associated with FMS. Clonazepam is especially useful because it also has anticonvulsant properties that may counteract the seizure-producing potential of tricyclic antidepressant drugs when used with these drugs. However, benzodiazepines should only be used occasionally due to the high potential for addiction. Possible side effects include drowsiness, fatigue, lightheadedness, and impairment memory or concentration.

**Nonnarcotic Analgesic Drugs**

Because an important symptom of FMS is widespread pain, analgesic drugs may be needed in addition to tricyclic antidepressant drugs.<sup>27</sup>

**Acetaminophen**

Acetaminophen is most helpful when taken regularly throughout the day and night instead of being taken on an as-needed basis. By pairing two stimuli (administration of medication with resultant momentary reduction in pain) the nervous system may become conditioned to ongoing pain.<sup>12</sup>

**Tramadol**

Tramadol has been effective for treating musculoskeletal pain in patients with FMS. In one series, tramadol produced a 60% to 70% decline from the original pain level after about three to four weeks of use.<sup>27</sup> Patients also obtained relief from morning stiffness, cold extremities, and trembling hands.<sup>27</sup> Use of tramadol concomitantly with tricyclic antidepressant drugs requires caution because an additive seizure effect may occur. Side effects of tramadol include dizziness, nausea, constipation, and headache.

**Narcotic Analgesics**

In general, narcotic analgesics should be avoided if possible because they interfere with deep sleep, leaving patients tired and feeling worse the next day.<sup>1,6</sup> Research has not shown that these medications are effective on a long-term basis. However, most patients with FMS who take these medications do so after receiving progressively stronger medications whose inadequate analgesic effects eventually led to prescription of narcotic agents. If pa-

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*“Acetaminophen is most helpful when taken regularly throughout the day and night instead of being taken on an as-needed basis.”*

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*“In general, narcotic analgesics should be avoided if possible because they interfere with deep sleep, leaving patients tired and feeling worse the next day.”<sup>1,6</sup>”*

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tients who are correctly diagnosed with FMS are helped by these medications to manage the pain, then the goal should be to adjust the medication so that patients receive the lowest effective dose. If patients do not obtain pain relief while using narcotic medications, then these should be gradually tapered off and substituted with a combination of tricyclic antidepressant drugs and skeletal muscle relaxants. Because they induce a high incidence of dependency, narcotics should be used only as a last resort. Possible side effects of narcotic drugs include drowsiness, lightheadedness, nausea, vomiting, and constipation.

#### **Steroidal And Nonsteroidal Anti-Inflammatory Medications**

The analgesic effect of anti-inflammatory drugs has been well established for pain associated with inflammation; however, inflammation is not evident in FMS.<sup>2</sup> Some studies show that combining nonsteroidal anti-inflammatory drugs (NSAIDs) with tricyclic antidepressant drugs may provide some relief.<sup>28,29</sup> However, use of these anti-inflammatory medications alone has yielded disappointing results in clinical trials.<sup>14,28</sup> In particular, prednisone, ibuprofen, and naproxen have been found no more effective than placebo.<sup>1,10,28,30,31</sup>

#### **Miscellaneous Adjunctive Medications**

##### **Zolpidem**

This nonbenzodiazepine hypnotic agent has been reported to improve subjective sleep and can be used instead of benzodiazepines because it has minimal addictive potential.<sup>32</sup> Patients treated with zolpidem required substantially less time to fall asleep, slept longer, awakened less frequently, had overall improved quality of sleep, and had more daytime energy, although use of zolpidem did not affect pain associated with FMS.<sup>33,34</sup>

##### **Gabapentin**

Gabapentin is an antiepileptic agent that has recently been used in pain management. Although studies of gabapentin use are small and often not well reported, gabapentin is being used at the Kaiser Permanente CPMP to treat patients with FMS only after other proven therapies have failed to produce the desired outcomes. Depending on the patient's tolerance to its side effects, the medication is titrated to an effective dose of about 1800 mg/day over a few days. The standard titrating dose used is 300 mg on day 1, 300 mg twice per

day on day 2, 300 mg three times per day on day 3, and then is increased as appropriate to 1800 mg per day unless adverse effects preclude doing so. The side effects of gabapentin include fatigue, weight gain, indigestion, drowsiness, dizziness, ataxia, and tremor; therefore, to limit side effects, the first dose should be administered at bedtime. Patients should be informed that fatigue and sedation may last as long as two weeks before these side effects resolve.

#### **Trigger-Point Injections**

Occasional trigger-point injections are helpful when a few trigger points are present and the muscle cannot stretch because of excessive pain.<sup>34</sup> Local anesthetic agents such as bupivacaine, lidocaine, etidocaine, or a combination of these can be injected into a trigger-point site, providing better and longer-lasting pain relief for as long as seven days after injection.<sup>34</sup> Sometimes corticosteroids such as dexamethasone and betamethasone may be combined with a local anesthetic agent to help relieve pain. Patients should be informed that corticosteroids may cause a temporary burning sensation at the injection site within 24 to 48 hours after injection but that the subsequent pain relief lasts as long as 10 days.<sup>35</sup> Trigger-point injections are most effectively used in conjunction with a comprehensive treatment program that includes stretching exercises, aerobic exercise, behavioral therapy or cognitive retraining, and medication.

#### **Other Considerations of Pharmacologic Care**

In addition to management of the biological, psychological, and social factors associated with FMS, patient education and adherence to prescribed therapy are essential to the overall healing process, whose length depends on the severity of the condition. Patients' adherence to their medication regimen must be monitored because nearly 50% of all patients who receive medications for chronic conditions do not comply with their prescribed drug regimen.<sup>36</sup> To increase compliance with medication regimens and to prevent discontinuation of treatment at the first occurrence of a side effect, patients should be informed that some tolerance develops to these side effects.<sup>23</sup> Patients on antidepressant therapies must also be informed that beneficial effects of therapy may require as long as two weeks to appear.<sup>7</sup> The most common reasons for nonadherence to therapy used to treat

*"In particular, prednisone, ibuprofen, and naproxen have been found no more effective than placebo."*



FMS include inadequate patient education, side effects, drug interactions, social stigma associated with the therapy, presumed ineffectiveness of therapy, and high cost.

#### Outcome Measurement

The optimal outcome of therapy for FMS can be measured by decreased pain relief, use of the most appropriate and least amount of medication needed

**Table 4. Optimal, cost-effective treatment plans for FMS patients by group**

Group	Sign or symptom	Treatment modality
Group 1	Recent onset of FMS (less than two years' duration) Slight fatigue Sleep disturbance Slight interference with activities of daily living, work performance, or interpersonal relationships FMS-related anxiety, nocturnal myoclonus, or sleep disorders	Education Self-help strategies Unsupervised cardiovascular fitness Sleep health Psychotherapeutic intervention Medications (see Table 3): • Tricyclic antidepressant drugs or trazodone • Acetaminophen (if pain is not controlled by tricyclic antidepressant drugs) • Benzodiazepines or zolpidem (for short-term relief)
Group 2	More pain, fatigue, and disrupted functioning than Group 1 in patients Experience a decrease in work performance Increase in absenteeism Stress with interpersonal relationships	Education Supervised cardiovascular exercise Promotion of sleep health Psychotherapeutic intervention Medication (see Table 3): • Tricyclic antidepressant drugs (or trazodone) with skeletal muscle relaxant • Analgesic drugs (acetaminophen or tramadol) • Selective serotonin uptake inhibitor (fluoxetine) if patient seems depressed • Benzodiazepine or zolpidem for short-term relief of anxiety, nocturnal myoclonus, and FMS-associated sleep disorders • Trigger-point injections • Gabapentin (if other therapies fail)
Group 3	Substantial disintegration of family life Deterioration of job performance Substantial disruption of daily life	Multidisciplinary pain management program of patient education, medication, regular exercise, physical modalities, stress reduction, and coping skills

to treat the pain, improved function, and reduced need for further health care services. Decrease in pain can be evaluated using the Fibromyalgia Impact Questionnaire, a visual analog pain scale, and a physician-conducted examination of tender points.<sup>12</sup> Improvement in function can be documented by measuring any increase in physical activity, improvement in patient's overall quality of sleep, improvement in psychosocial functioning, and ability to return to work.<sup>12</sup> Adherence to a therapeutic regimen can be most effectively monitored by reviewing the patient's complete medication profile and prescription refill history. This monitoring is most accurate for patients who fill their prescriptions at a single location or at a pharmacy linked by computer to a network of pharmacies.

### Conclusion

FMS is a complex, chronic, painful condition that can be characterized by a variety of nonspecific symptoms including palpable tender points; chronic, poorly defined, diffuse musculoskeletal pain; morning stiffness; fatigue, weakness; and sleep disturbance.<sup>4</sup> Although no laboratory test results or radiographically visible abnormalities are definitively diagnostic of FMS, distinctly recognizable symptoms do distinguish FMS from other medical conditions. Because the cause of FMS is as yet largely unknown, patients and practitioners must understand that current treatment is more palliative than curative and focuses on improving function, not abolishing the pain.<sup>4</sup> A multidisciplinary team approach to treatment of FMS is the most effective way to address its complex nature and different components. The most effective treatments include a combination of patient education, medication therapy, regular exercise, physical modalities, stress reduction, and coping skills (Table 4), because studies<sup>4,6,12</sup> have shown that patients do not respond as well to any one treatment modality administered alone. Choice of therapeutic agents used for treating FMS should be guided by each patient's FMS symptoms and by each drug's profile of action (ie, sedative drugs should be used for patients with insomnia).<sup>10</sup>

To improve continuity and long-term outcome of treatment, primary health care providers should remain involved in the patient's treatment,<sup>4,12</sup> and the multidisciplinary team should act as a bridge between primary care practitioners and patients to maximize the effectiveness of clinician-patient interactions.<sup>4</sup> ❖

*"... distinctly recognizable symptoms do distinguish FMS from other medical conditions."*

*"... current treatment is more palliative than curative and focuses on improving function, not abolishing the pain."*

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## Health, Contentment, and Goodness

"Some patients, though conscious that their condition is perilous, recover their health simply through their contentment with the goodness of the physician."

*Hippocrates,*  
Precepts

Oxalates and Their Role in Fibromyalgia Syndrome (FMS). Oxalates are non-toxic organic compounds naturally occurring in certain foods, mainly vegetables and fruits. An accumulation of oxalic acid crystals in the muscle and connective tissue cells may be the cause of the muscle aches and pain associated with FMS. FMS can be a debilitating condition, involving many systems within the body. Dr. St. Amand, author of *What Your Doctor May Not Tell You About Fibromyalgia*, promotes the use of a medication called guaifenesin to treat FMS. Guaifenesin was found to increase excretion of 60% phosphates, 30% oxalates and 30% calcium. The medication guaifenesin itself is fairly benign. Fibromyalgia syndrome (FMS) is a chronic, complex, and heterogeneous disorder of still poorly understood etiopathophysiology associated with important musculoskeletal widespread pain, fatigue, non-restorative sleep, and mood disturbances. It is estimated to afflict 2-3% of the worldwide population, with clean prevalence among women. The objective of this paper is to propose a novel treatment for symptomatic remission of FMS, grounded in biochemistry and consisting in the withdrawal from the diet of molecules that can indirectly trigger the symptoms. The editor and reviewers' affiliations are the latest provided on their Loop research profiles and may not reflect their situation at the time of review.

Table of contents. Abstract. Introduction  
Fibromyalgia syndrome (FMS) is theorized to function as an abnormal central processing pain disorder, which involves afferent augmentation of peripheral stimuli, especially of the nociceptive types, and a variety of Reprinted from Smith HS, Barkin RL. *Fibromyalgia Syndrome: A Discussion of the Syndrome and Pharmacotherapy*. *Amer Jnl Therapeutics* 2010;17(4):418-39. Available at <http://www.com>. *Dis Mon* 2011;57:248-285 0011-5029/2011 \$36.00 doi:10.1016/j.disamonth.2011.02.001 248 DM, May 2011

neuropathic qualities with symptoms, which include pain, fatigue, disturbances, and alt Introduction: Fibromyalgia syndrome (FMS) is a multi-factorial disease involving physiological as well as psychological factors. The aim of the study was to investigate a multidisciplinary inpatient treatment with emphasis on hyperthermia therapy by patients with widespread pain. Materials and methods: The study involved 104 patients suffering from severely progressive FMS. The patients were treated in an acute hospital focusing on rheumatologic pain therapy and multidisciplinary complementary medicine. One patient group was treated with inclusion of hyperthermia therapy and the other group without. Decisions to use a multidisciplinary approach to therapy should be determined based on a structured health care assessment of the individual.

22. According to American College of Rheumatology fibromyalgia syndrome (FMS) is a common health problem characterized by widespread pain and tenderness. The pain and tenderness, although chronic, present a tendency to fluctuate both in intensity and location around the body. Patients with FMS experience fatigue and often have sleep disorders. It is estimated that FMS affects two to four percent of the general population. It is most common in women, though it can also occur in men. FMS most often first occur in the middle adulthood, but it can start as early as in the teen years or in the old age.