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Treatment Strategy in Fibromyalgia Syndrome: Where Are We Now?

Piercarlo Sarzi-Puttini, MD,* Dan Buskila, MD,† Mario Carrabba, MD,‡ Andrea Doria, MD,§ and Fabiola Atzeni, MD, PhD¶

Introduction: The treatment of the fibromyalgia syndrome (FMS) is not standardized and often ineffective, and the course of disease progression is unpredictable.

Objectives: To highlight the efficacy of the pharmacologic and nonpharmacologic treatments administered to FMS patients.

Methods: Medline search for articles published between 1983 and 2007, using the keywords fibromyalgia, pharmacologic and nonpharmacologic treatment, and multidisciplinary modalities.

Results: Randomized controlled trials (RCTs) indicate that FMS has been treated by a wide range of drugs including antidepressants, opioids, nonsteroidal anti-inflammatory drugs, sedatives, muscle relaxants, and antiepileptic agents. Although the syndrome is now more widely recognized and understood, its treatment remains challenging and some physicians believe that no effective treatment exists. Only a few drugs have been shown to have clear-cut benefits in RCTs. FMS sufferers benefit from exercise and a number of the tested programs have involved more than 1 type of exercise. Two other major approaches are psychophysiologically based therapy, such as electromyography biofeedback, and interventions based on cognitive–behavioral therapy. Twelve controlled clinical studies have provided evidence supporting the efficacy of treatments administered to people with FMS by multidisciplinary teams using multicomponent strategies.

Conclusions: It is difficult to draw definite conclusions concerning the most appropriate approach to managing FMS because of the methodological limitations of the available studies and the fact that the heterogeneity and nonstandardized nature of their therapeutic programs make them difficult to compare. An individually tailored multidisciplinary pharmacologic, rehabilitative, and cognitive–behavioral approach currently seems to be the most effective.

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Keywords: *fibromyalgia, multidisciplinary approach, pharmacologic treatment, exercise, cognitive-behavioral therapy*

Fibromyalgia syndrome (FMS) is a condition of chronic and diffuse muscular pain that has a prevalence of 2 to 4% and is more common among woman than men (1). The American College of Rheumatology (ACR) classification criteria include diffuse soft-tissue pain of at least 3 months' duration, and pain on palpation in at least 11/18 tender points (2,3). Although its defining feature is chronic widespread pain, patients may also have a number of other symptoms such as sleep disturbance, fatigue, irritable bowel syndrome, headache, and mood disorders (4). FMS patients must learn to cope with a variety of symptoms, and the illness often requires significant and permanent lifestyle changes. It is a stressful experience for many patients because its etiology is unknown, treatment is not standardized and often ineffective, and the disease course is unpredictable (5). It is a complex syndrome associated with significant functional and quality-of-life impairments, and substantial financial costs (6), but appropriate management can somewhat reduce the rate of symptoms and disability (7-10).

The aim of this review was to summarize the published

*Clinical Research Scientist, Rheumatology Unit, L. Sacco University Hospital, Milan, Italy.

†Professor of Rheumatology, Department of Medicine H, Soroka Medical Center, Beer Sheva, Israel.

‡Head of Rheumatology Department, L. Sacco University Hospital, Milan, Italy.

§Associate Professor of Rheumatology, Chair of Rheumatology, University of Padua, Padua,, Italy.

¶Clinical Research Scientist, L. Sacco University Hospital, Milan, Italy.

Address reprint requests to: Piercarlo Sarzi-Puttini, MD, Rheumatology Unit-University Hospital L Sacco, Via GB Grassi 74, 20157 Milano, Italy. E-mail: sarzi@tiscali.it.

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Abbreviations	
ACR	American College of Rheumatology
CAM	complementary and alternative medicine
CBT	cognitive-behavioral therapy
EMG	electromyography
FMS	fibromyalgia syndrome
5-HT	5-hydroxytryptophan
NMDA	*N*-methyl-D-aspartate
RCTs	randomized controlled trials

data concerning the efficacy of pharmacologic and nonpharmacologic treatments in FMS patients and to provide some help in making decisions concerning their care.

METHODS

We searched Medline for English-language articles published between 1983 and 2007, using the keywords fibromyalgia, pharmacologic and nonpharmacologic treatment, and multidisciplinary modalities. The abstracts were screened for relevance, and the publications relating to FMS were obtained; additional references were identified from the bibliographies of the retrieved reports and from review articles and meta-analyses. The following information about the studies was collected: study design, type of treatment, the number of patients randomized and the number of dropouts, duration, the occurrence of adverse events, and posttreatment follow-up.

RESULTS

Pathophysiology of FMS

FMS is currently considered a disorder of pain regulation, but its etiology is not fully understood. Increasing evidence supports the existence of a genetic predisposition (11), including the possible role of polymorphisms of genes in the serotoninergic, dopaminergic, and catecholaminergic systems (12), and external factors such as emotional stress, physical trauma, medical illness (eg, infections and autoimmune disorders), and a variety of regional pain conditions may be temporally associated with its development (13). A variety of neurotransmitter and neuroendocrine disturbances, including reduced levels of biogenic amines, increased concentrations of excitatory neurotransmitters (including substance P), and dysregulation of the hypothalamic-pituitary-adrenal axis may link predisposition, the stress system, and the onset and chronicity of the disease (14-17).

The *sine qua non* of FMS is chronic, widespread pain, a fact reflected in the requirements of the ACR 1990 diagnostic criteria (2). Affected patients show abnormal pain perceptions in the form of allodynia (pain on innocuous stimulation) and hyperalgesia (increased sensitivity to painful stimuli) (3,18-20), which are also found in other forms of chronic pain and suggest a "gain" in nociceptive processing. The abnormal sensitivity to pain of FMS patients may be due to "central sensitization" (3,16,21), which has been operationally defined as heightened generalized pain sensitivity due to pathological nociceptive processing within the central nervous system (22).

Are All FMS Patients the Same?

Classification and Diagnostic Criteria

In clinical trials and observational research studies, FMS is usually diagnosed on the basis of the ACR criteria (2), which are widely accepted by investigators who accept the concept of FMS, but raise a number of problems (23,24):

- patients may have the requisite tender points, but not FMS;
- tender points and widespread pain alone do not capture the essence of FMS, multiple symptoms of which prominently include fatigue, sleep disturbance, and cognitive dysfunction (25,26).

Factorial analyses of population-based studies aimed at identifying the seminal features of these conditions have revealed that the key coaggregating symptoms are multifocal pain, fatigue, memory difficulties, and mood disturbances (27). Some studies have identified subgroups of FMS patients on the basis of their psychosocial and behavioral responses to pain (28), fear of pain (29), and readiness to adopt a self-management approach to chronic pain (30).

Turk and coworkers (31,32) were the first investigators to show that the subgroups identified by cluster analyses of the Multidimensional Pain Inventory in various chronic pain populations may also apply to a population of FMS patients, and that each of the FMS subgroups responds differently to treatment. They analyzed data from 3 empirically based subgroups of dysfunctional, interpersonally distressed, or adaptive copers, all of whom underwent a standardized treatment program, and concluded that customizing treatment on the basis of patients' psychosocial needs is likely to enhance treatment efficacy. They also pointed out that the outcome criteria would need to be different in the 3 subgroups.

Giesecke and coworkers (33) used cluster analysis to distinguish subgroups of FMS patients on the basis of (1) mood (as evaluated by the Center for Epidemiologic Studies Depression Scale [for depression] and the State-Trait Personality Inventory [for symptoms of trait-related anxiety]); (2) cognition (the Catastrophizing and Control of Pain subscales of the Coping Strategies Questionnaire); and (3) hyperalgesia/tenderness (assessed by means of dolorimetry and random pressure-pain applied at suprathreshold values). The first subgroup of patients was characterized by moderate mood ratings, moderate levels of catastrophizing and perceived control over pain, and low levels of tenderness; the second had significantly high mood scores, the highest values on the catastrophizing subscale and the lowest for perceived control over pain, and high levels of tenderness; and the third had normal

mood ratings, very low levels of catastrophizing, and the highest level of perceived control over pain but showed extreme tenderness on evoked-pain testing.

Thieme and coworkers (34) classified FMS patients as dysfunctional, interpersonally distressed, or adaptive copers, based on their responses to the Multidimensional Pain Inventory, and used hierarchical regression analyses to identify the predictors of pain behaviors for the population as a whole, and the subgroups. The dysfunctional patients had more pain behaviors than either the interpersonally distressed or the adaptive copers patients.

Further studies are needed to replicate these findings and determine whether these subgroups can really be used to identify optimal treatment strategies.

Treatment Approaches to FMS Patients

The aim of treating FMS is to decrease pain and increase function by means of a multimodal therapeutic strategy which, in most cases, includes pharmacologic and nonpharmacologic interventions (35). The main strategy is symptom management (36). As FMS patients typically present complex symptoms and comorbid conditions, they cannot realistically be managed by primary care providers alone but require the assistance of multidisciplinary teams with expertise in a variety of physical, cognitive, behavioral, and educational strategies (37).

Most of the directors of existing multidisciplinary treatment programs are rheumatologists or rehabilitation specialists, but there is no reason for excluding other informed and dedicated health professionals. Some of the programs mainly based on promoting cognitive behavioral changes only involve rheumatologists and psychologists or psychiatrists, who can often be considered essential because most FMS patients have difficulties in dealing with stress and interpersonal problems, and are at increased risk of developing depression or anxiety (38-42). As exercise is a critical aspect of FMS treatment and a key element in successful cognitive behavioral therapy, most programs would benefit from the addition of an exercise physiologist or physical therapist with expertise in prescribing stretching, aerobic conditioning, and strength training (42-45). Other possible team members or program consultants could be social workers, occupational therapists, sleep specialists, headache specialists, or massage therapists (37).

Pharmacologic Treatments

FMS has been treated by a wide range of drugs including antidepressants, opioids, nonsteroidal anti-inflammatory drugs, sedatives, muscle relaxants, and antiepileptic agents (46), but only a few have been shown to have clear-cut benefits in randomized controlled trials (RCTs) (46-50).

Analgesic and Narcotic Drugs

The results of clinical trials of anti-inflammatory medications have been generally disappointing (46-50), but 3 RCTs have found that tramadol (with or without acetaminophen) is effective in FMS (51-53). The results of 1 small, double-blind, placebo-controlled trial provided the first indication that tramadol is efficacious and well-tolerated (53), and the most recent trial, which compared the combination of tramadol 37.5 mg and acetaminophen 325 mg tablets with placebo in 315 FMS patients (52), found that discontinuation rates, pain scores, and fibromyalgia impact questionnaire scores were better in the active group. Tramadol has multiple analgesic effects: it inhibits norepinephrine and serotonin reuptake, and its major metabolite binds weakly to opioid receptors (54).

Opioids may be helpful in treating FMS pain but may induce tolerance and become habit forming and are also associated with adverse effects such as constipation, sedation, and nausea. Their use should be considered only after all other medicinal and nonmedicinal therapies have been tried (55,56).

Antidepressants

Tricyclic antidepressants have an analgesic effect that is independent of their antidepressant action (57) and is thought to be primarily due to the inhibition of norepinephrine (rather than serotonin) reuptake at spinal dorsal horn synapses, with secondary activity at the sodium channels (58,59). The most widely studied drugs are amitryptiline and cyclobenzaprine, which may help by improving sleep and reducing morning stiffness, although they are ineffective or intolerable in 60 to 70% of patients (60-64). One meta-analysis has found that they offer some benefit in terms of reducing pain and improving sleep and overall well-being, are mildly effective in reducing fatigue, and may have a beneficial effect on tender point scores (59).

Monoamine oxidase inhibitors block the catabolism of 5-HT and thus increase its levels in the brain. Preliminary studies of moclobemide, a second-generation monoamine oxidase inhibitor, failed to demonstrate any significant analgesic activity in comparison with amitriptyline (65). However, the results of a recent study of pirlindole indicated significant beneficial effects on sleep, fatigue, and mood (66).

Selective serotonin reuptake inhibitors such as fluoxetine have been tried because tricyclic antidepressants have many potential side effects, but they have not proven to be effective pain medications (67).

One RCT of serotonin/norepinephrine reuptake inhibitors found that venlafaxine 75 mg/d was not significantly different from placebo (68), but 2 small open-label studies of higher doses found it useful (68-70). Duloxetine 60 mg twice per day improves pain and the global measures of FMS in comparison with placebo (71), and the same was found when it was given for 3 months to 207

FMS patients regardless of their baseline depression status (72). Similar to duloxetine, milnacipran is a well-characterized small molecule that acts as a selective reuptake inhibitor of both serotonin and noradrenaline (73), but it is unique in its preference for norepinephrine reuptake inhibition and also binds *N*-methyl-D-aspartate (NMDA) receptors. In a phase II trial involving 125 FMS patients, Gendreau and coworkers (74) showed that its administration significantly improved global well-being, fatigue, pain, and a variety of related symptom domains, although sleep did not improve. Milnacipran was generally well tolerated, and its twice-daily administration had significantly better analgesic properties than once-daily administration.

Muscle Relaxants

Cyclobenzaprine, a structurally tricyclic muscle relaxant, has proven to be moderately effective in FMS patients at doses of 10 to 40 mg/d (75). This has recently been confirmed by a meta-analysis of 5 randomized, placebo-controlled trials, which showed that patients treated with cyclobenzaprine were approximately 3 times as likely to report symptom improvement, but there was a high dropout rate and the studies had a short duration (76). The results of another recent meta-analysis of 5 published, randomized, and controlled trials suggest that cyclobenzaprine improves the global functioning of patients with FMS and slightly improves their quality of sleep (49); there may also be a small improvement in pain, but the drug does not seem to benefit fatigue or tender points.

5-HT3 Receptor Antagonists

Clinical trials have shown that tropisetron, a selective, competitive 5-HT3 receptor antagonist, has significant clinical efficacy. When it was tested in a short-term study of 418 FMS patients (77) randomly assigned to receive placebo or daily tropisetron doses of 5, 10, or 15 mg, it was found that the 5 mg dose led to a significantly higher response rate than placebo (39% versus 26%), with a mean reduction in the pain score of 55%. The higher tropisetron doses were not effective, which is consistent with the observation that 5-HT3 receptor antagonists may have nociceptive and antinociceptive effects under different circumstances. The mechanism by which 5-HT3 receptor antagonism reduces FMS-associated pain and other symptoms is not understood, although these benefits may be secondary to reduced substance P release (78).

Anticonvulsants/Antiepileptic Drugs

Antiepileptic drugs act at a number of sites that may be relevant to pain. The precise mechanism of their analgesic effect remains unclear, but it is thought that they limit neuronal excitation and enhance inhibition (79). The relevant sites of action include voltage-gated ion channels (ie, sodium and calcium channels), ligand-gated ion channels, the excitatory receptors for glutamate and NMDA, and the inhibitory receptors for gamma-aminobutyric acid and glycine (80). Gabapentin has substantial analgesic effects in randomized, controlled clinical trials in diabetic neuropathy, post herpetic neuralgia, migraine prophylaxis, and other neuropathic pain conditions (81). In a 12-week, randomized, double-blind study designed to compare gabapentin (1200-2400 mg/d) (n = 75 patients) with placebo (n = 75 patients) in terms of their efficacy and safety in treating FMS-associated pain (82), the gabapentin-treated patients showed significantly greater improvement in the Brief Pain Inventory average pain severity score ($P = 0.015$), and a significantly larger proportion of them were responders at the endpoint (51% versus 31%; $P = 0.014$). Gabapentin was generally well tolerated.

Pregabalin is another antiepileptic drug that is effective in treating FMS. In an 8-week, multicenter, double-blind, randomized, placebo-controlled clinical trial, Crofford and coworkers (83) compared the effects of pregabalin 150, 300, and 450 mg/d on pain, sleep, fatigue, and health-related quality of life in 529 FMS patients. They found that pregabalin was superior to placebo in reducing pain, Short form of the McGill Pain Questionnaire, and sleep index scores and fatigue, had a positive effect on 4 of the 8 SF-36 domains, and was well received in terms of the patient and clinician global impression of change. The most frequent adverse events were dizziness and somnolence.

N-Methyl-D-Aspartate Receptor Antagonists

NMDA receptors may play a key role in the nervous system reorganization thought to be involved in maintaining chronic pain, and its blockade can relieve pain in patients with FMS. Two randomized, controlled trials involving 46 patients fulfilling the 1990 ACR classification criteria for FMS showed that ketamine increased endurance and reduced pain intensity, tenderness at trigger points, referred pain, temporal summation, muscular hyperalgesia, and muscle pain at rest (84,85). Both studies suggested the presence of central sensitization in FMS, that tender points are areas of secondary hyperalgesia, and deduced that the relief of these symptoms by ketamine indicated a reduction in central sensitization. However, the cognitive side effects of NMDA receptor blockade may limit the use of NMDA in FMS therapy.

Dopamine Agonists

Ropinirole is a D3/2 receptor agonist used to treat Parkinson's disease. Holman performed a 14-week, pilot, double-blind, randomized, controlled trial with a 14-week blinded extension (86) and showed a significant change from baseline in visual analog scale measured pain, as well as nonsignificant improvements in parameters such as stiffness and tender point scores; however, by the

28th week, all 30 patients had experienced adverse events, mainly vomiting and nausea.

Holman and Myers (87) tested pramipexole (a dopamine 3 receptor agonist) in a 14-week, single-center, double-blind, placebo-controlled, parallel-group, escalating-dose trial involving 60 FMS patients. They found that a dose of 4 mg improved pain, fatigue, function, and global status scores and was safe and well tolerated. The most common adverse events were transient anxiety and weight loss.

Sedative Hypnotic Agents

Sedative hypnotic agents, including zopiclone and zolpidem, improve sleep and relieve fatigue in FMS patients (49), and low doses of a number of antidepressants, such as amitriptyline and trazodone, are used for their sedative properties.

Sodium oxybate is the sodium salt of gamma-hydroxybutyrate, an endogenous short-chain fatty acid, and is used for the oral administration of exogenous gamma-hydroxybutyrate (88-90). It is likely that the supraphysiological concentrations induced by exogenous administration lead to qualitatively different neuronal actions from those produced by endogenous gamma-hydroxybutyrate. There is evidence suggesting that gamma-hydroxybutyrate plays a role as a neuromodulator/neurotransmitter. One double-blind, randomized, placebo-controlled crossover trial found that sodium oxybate reduced 6 of 7 pain/fatigue scores (overall pain, pain at rest, pain during movement, end-of-day fatigue, overall fatigue, and morning fatigue) by 29 to 33% against the 6 to 10% induced by placebo (88). In comparison with placebo, alpha intrusion, sleep latency, and rapid-eye-movement sleep significantly decreased, while slow-wave (stage 3-4) sleep significantly increased. The most frequently reported adverse events included dose-related headache, nausea, dizziness, and somnolence.

Hormone Supplements

FMS patients do not generally meet clinical definitions of hormone deficiency but, as some FMS symptoms resemble those of endocrine disorders (eg, hypothyroidism), it would seem to be prudent to treat patients individually (91). Steroid treatment is not indicated in FMS for many reasons (49), but the use of growth hormone was based on studies showing that levels of insulin-like growth factor are lower in FMS patients than in age-matched controls. A 9-month study of injectable recombinant human growth hormone in patients with low insulin-like growth factor levels at entry showed an improvement in FMS symptoms as assessed by the Fibromyalgia Impact Questionnaire total and tender point score (92). However, enthusiasm for this approach has been dampened by the appearance of adverse effects, the need for frequent injections, and high costs.

Nonpharmacologic Treatments

Exercise

Exercise has been suggested as a treatment for FMS since 1976 when Moldofsky first demonstrated that fit people were less likely to develop FMS symptoms when their stage 3 and 4 sleep was intentionally disrupted (93).

Anecdotal reports suggest that FMS patients limit physical activity because of pain and fatigue, although very little empirical work has been published that sheds light on their use of exercise. There may well be differences in the predictors of such behavior between FMS patients and healthy subjects as the former often have comorbidities and perceive themselves as disabled and may be affected by psychological conditions that can further impede exercise (94). It has been reported that depression is particularly prevalent in FMS, and this has led some researchers to suggest that it is a depressive spectrum disorder (95,96). Different studies have found that the prevalence of current depressive disorders ranges widely (29-70%), although this probably is due to differences in the methods used to assess depression (97,98). A number of studies have investigated the use of exercise in the management of depression and reported benefits in both younger adults and older people (99-102).

There is a growing body of evidence that patients with pain-functional syndromes perform a range of cognitive tasks more poorly than age-matched controls. In particular, patients with FMS have shown consistent impairments in working and episodic memory, as well as verbal fluency (103). Exercise may improve mood and cognition (104) and data suggest that regular exercise can also promote maintenance of cognitive function during aging (105).

Many health care providers know that FMS sufferers benefit from exercise and do not hesitate to advise them to engage in regular physical activity, but advice or education is insufficient motivation in the absence of self-efficacy or self-confidence. Self-efficacy (ie, a belief in one's capacity to organize and carry out actions capable of managing future situations) is essential when undertaking and continuing to engage in any activity. A number of the exercise programs tested in FMS patients have involved more than 1 type of exercise. Martin and coworkers (106) have reported that an exercise program incorporating aerobic, strengthening, and flexibility elements led to greater benefits than a relaxation program. Verstappen and coworkers (107) found an improvement in physical fitness in patients following a 6-month group activity program consisting of flexibility, strengthening, and aerobic endurance exercises in comparison with a no-treatment group of patients who continued "normal activity." A recent study by Jones and coworkers (108) randomized women to a 12-week program of strengthening or flexibility exercises: both groups showed significant improvements, with no differences between them in any of the outcome variables; furthermore, the muscle strengthen-

Table 1 Controlled Trials of Multidisciplinary Approaches (modified from Ref. 33)

Author	Sample Size (pre-/posttest): % of Dropouts	Treatment Content	Treatment Controls
Isomeri 1993	51/45; 9%	Exercise plus amitriptyline	Exercise
Burckhardt 1994	99/86; 13%	Education, exercise	No treatment until 3 months
Buckelew 1998	119/109; 8%	Education, exercise, biofeedback/relaxation	Educational/attention control program
Keel 1998	32/27; 16%	Education plus exercise plus CBT	Exercise
Mason 1998	23/21; 9%	Exercise CBT	Usual treatment
Gowans 1999	45/41; 9%	Education, exercise CBT	Usual treatment
Mannerkorpi 2000	69/58; 16%	Education plus exercise	Exercise
King 2002	170/152; 11%	Education plus exercise	Education or exercise
Fors 2002	55/52; 5%	Guided imagery Amitriptyline	Usual treatment
Gustafsson 2002	43/43; 0%	Education, exercise	Usual treatment
Lemstra 2005	79/71; 11%	Exercise, pain and stress management Education, massage	Medical care with patient's family physician
Zijlstra 2005	134//134; 0%	Thalasso-therapy, exercise, group education	Usual treatment (control treatment)

Note: ACR, American College of Rheumatology 1990 criteria; RCT, randomized controlled trial; CT, controlled trial; CBT, cognitive-behavioral therapy; FIQ, Fibromyalgia Impact Questionnaire; BDI, Beck's Depression Inventory; VAS, visual analogue scale; ASES, Arthritis Self-efficacy Scale, SE, self-efficacy.

ing regimen did not cause any pain flare-ups. There is also evidence that women with FMS are as capable of gaining physiological benefits (in terms of maximal and explosive strength and electromyography(EMG)) as healthy women (42).

In relation to aerobic exercise, McCain and coworkers (109) tested a 20-week program of cardiovascular fitness training or flexibility exercises and found improvements in cardiovascular fitness and pain threshold scores in the cardiovascular training group, but no differences in pain intensity or sleep disturbance. In 1999, a meta-analysis of 49 FMS treatment outcome studies showed that exercise was associated with significant improvements in several types of outcome measures: physical status, self-reported FMS symptoms, psychological status, and daily functioning (110). A recent systematic review has concluded that supervised aerobic exercise training has beneficial effects on physical capacity and FMS symptoms (42).

In conclusion, appropriately prescribed exercise can be performed by patients without aggravating their symptoms, especially if it is self-paced; however, high-intensity exercise should be used with caution (111). Mannerkorpi and Iversen (111) suggest that, if exercise-induced pain does occur, the frequency of exercise should be maintained to avoid any further decrease in exercise tolerance, but its intensity and/or duration should be reduced.

Education and Psychological Domains

Various techniques used in the management of FMS are based on patient education and have the aim of reducing anxiety, increasing treatment compliance, improving coping behaviors and self-efficacy, and drawing attention away from symptoms and toward improved function and quality of life (112,113). It has long been recognized that patients have an essential right to education, and the findings of this review suggest that they should be offered both exercise and education (including information and cognitive-behavioral strategies) by a multidisciplinary team in a group format (37).

One of the goals of a multidisciplinary approach should be to shift patients' perceptions from helplessness, frustration, and sometimes anger to a positive sense of behavioral self-efficacy and outcome expectancies (35). Patients with greater self-efficacy are more likely to respond favorably to treatment programs and experience better outcomes (39). Many patients believe that they cannot control the pain, disability, and negative effects of

Study Duration (Weeks)	Treatment Efficacy	Follow-up
15	Multitreatment group had less pain at end of study than the 2 groups treated with cardiovascular fitness training or amitriptyline alone	None
6	Multitreatment group better than waiting list but not education only in terms of SE	3 and 6 months multitreatment group had higher ASES and lower FIQ scores
6	Multitreatment group better than attention control in terms of SE-function and tender points	3 months and 1 and 2 years multitreatment group maintained SE improvements
15	No posttest differences	3 months multitreatment group had less pain
24	Multitreatment group less pain and lower FIQ scores	6 months maintenance of gains in multitreatment group
6	Multitreatment group improved 6-minute walk vs controls	3 months maintenance of gains in SE for pain and 6-minute walking distance in multitreatment group
24	Multitreatment group better FIQ and 6-minute walk than controls.	6 months and 2 years maintenance of FIQ and 6-minute walk improvements in multitreatment group
12	Multitreatment group improved in terms of SE control over other symptoms and 6-minute walk	3 months maintenance of SE improvement in multitreatment group
4	Group receiving pleasant distracting imagery showed decreased pain. Drug did not enhance the effect	None
12	No difference between the groups	3 months and 1 year
6	Multitreatment group improved in terms of health status, pain, and mood, but in terms of drug use or work status	Multitreatment group maintained improvements at 15 months
2	Multitreatment group improved on Rand-36 physical and mental component, tender point, and 6-minute walk	3 to 6 and 12 months only 6-minute walk was still significant

their condition, and this leads to increased distress, pain, and sleep problems; furthermore, they tend to reduce their engagement in daily-iving activities and in developing effective coping behaviors and cognitions.

Psychological interventions involve the interrelationships between the physical and psychological aspects of the illness (39,113). Two major approaches are psychophysiologically based therapy, such as EMG biofeedback, and cognitive-behavioral therapy (CBT). The basic aim of psychophysiologically based therapy is to change cognitions by manipulating physiological responses (eg, by means of EMG), whereas CBT attempts to change physiological responses by manipulating cognitions and is intended to help patients feel that they are in control of their condition (38,39,114). Education and CBT are different by definition but can be difficult to differentiate in a clinical setting.

Behavioral and cognitive–behavioral interventions lead to improvements in pain, other clinical symptoms, functional disability, pain behavior, and tender point measures. In a comparative study involving 1 group undergoing 10 weeks' behavioral therapy consisting of education, relaxation, goal setting, pacing, and the use of a support person, and another undergoing a 10-week education program based on group discussions and support (115), Nicassio and coworkers found statistically significant within-group changes in pain behavior, depression, disability, helplessness, pain coping, and myalgia scores, but no significant between-group differences. A recent study of female FMS patients by Redondo and coworkers (116) compared CBT with a physical exercise-based strategy and showed that functional ability improved significantly more with the latter; however, there were no within- or between-group differences in terms of anxiety, depression, or self-efficacy. After a follow-up of 1 year, most of the parameters had returned to baseline levels with the exception of functional ability in the physical exercise group. The improvement in self-efficacy and physical fitness was not associated with any improvement in clinical symptoms, and it seems that such interventions only temporarily improve the clinical symptoms of FMS. Similar findings have been reported in a meta-analysis of CBT-based therapies by Kendall and coworkers (117), who found that CBT alone did not lead to any consistent or sustained effects.

Complementary and Alternative Medicine

FMS is associated with considerable use of complementary and alternative medicine (CAM), which is mainly used in addition to, rather than as a substitute for, con-

Fibromyalgia multidisciplinary management in clinical practice

- Step 1 → Patient education
  - Describe the condition
  - Discuss and evaluate possible treatment modalities
- Step 2 → Pharmacologic treatment
  - monotherapy
  - combination therapy (step-up, step-down)
- Step 3 → Non pharmacologic treatment
  - exercise
  - stretching
  - aerobic conditioning
  - cognitive-behavioral treatment
  - psychotherapy
- Step 4 → Additional modalities (usually chosen by the patient)
  - acupuncture
  - complementary or alternative medicine

Figure 1 Principal steps in multidisciplinary setting in Fibromyalgia patients.

ventional treatments. However, most of the studies of alternative medical systems (homeopathy), energy therapies (magnetic therapies), and mind–body interventions (biofeedback, relaxation, and hypnotherapy) are methodologically flawed, and no definite conclusions can be drawn as to their usefulness. Another CAM therapy is chiropractic care, but there are no well-designed studies or positive results, and it is not currently recommended for the treatment of FMS (45,118-121).

There is the strongest evidence in favor of acupuncture, and nutritional supplementation (magnesium, S-adenosylmethionine) and massage therapy have both shown moderate evidence of effectiveness (122,123).

Multimodal/Multidisciplinary Approaches

Multimodal therapeutic programs use a multidimensional approach to managing FMS and are usually delivered in a multidisciplinary setting (35,37,124-126). They may include various treatments mentioned above, such as exercise, CBT, and/or education, as well as specific manual techniques and medications. A number of reviews have been recently published and include studies of physical therapy and exercise (39-41), pain management (35,37), cognitive-behavioral strategies (38), coping skills training (39), educational programs (43), mind–body therapies (44), CAM techniques (45,118-121), and drug treatments (47,49). There are also 3 evaluations of multidisciplinary rehabilitation (127-129), 1 review of nonpharmacologic treatments (35), and 2 general reviews of treatments that included drug trials (35,37). These all suggest that a number of treatments are effective for decreasing FMS symptoms, albeit with varying levels of confidence and caution.

The multidisciplinary approach to FMS is guided by the 3 following assumptions:

- patients need skills to manage their symptoms on a day-to-day basis,
- they can learn to self-manage their symptoms,
- the effective practice of healthy behavior will lead to positive changes in symptoms and health status,

and the use of appropriate medications is usually indicated.

Nineteen studies have provided evidence supporting the efficacy of treatments administered to people with FMS by multidisciplinary teams using multicomponent strategies. Table 1 summarizes the major aspects of 12 controlled clinical trials: 10 randomized (130-139) and 2

that had an appropriate comparison group but did not involve randomization (140,141). The length of the treatments ranged from 4 to 24 weeks, and all but 2 of the studies found that the members of the experimental group did significantly better than those in the control group in terms of at least 1 of the primary treatment outcomes. Follow-up data were collected 1 to 3 years after the completion of the experimental treatment in 8 of the trials and showed that the treatment gains were maintained in 6. A number of uncontrolled single-group clinical trials have also reported significant results using multidisciplinary approaches (142,143).

DISCUSSION

A number of reasons make it difficult to draw any definite conclusions concerning the most appropriate approach to managing FMS, including the methodologically limited nature of the available studies, and the fact that their heterogeneous and nonstandardized therapeutic programs complicate comparisons.

Although the situation is likely to change in the future, of all the drugs mentioned in this review, only pregagalin (Lyrica) is currently approved by the US Food and Drug Administration or by the European registry for the treatment of FMS, and many are older agents for which approval is unlikely to be sought. Some other recent drugs (duloxetine and milnacipram) are moderately efficacious in terms of some clinical parameters in randomized and placebo-controlled studies, and they are likely to be approved for the treatment of FMS in the near future (72-74,83).

An increasing number of methodologically rigorous studies have provided evidence supporting the use of exercise in the management of FMS. Psychologically based interventions such as CBT have also proven to be useful when combined with exercise as part of a multimodal program, but not when used alone (112-117). However, no single treatment is completely effective in all patients, which suggests that multiple pathogenic mechanisms may contribute to FMS and that their influence may differ from 1 patient to another. Multidisciplinary treatments may therefore be the best strategy in clinical practice (37).

The many unanswered questions that still limit our understanding of appropriate targeted therapies in FMS patients include the following.

Type of Multidisciplinary Treatment

The evidence in favor of a multidisciplinary approach to FMS treatment is moderate to strong, and all of the studies indicate the very real possibility of giving patients tools and skills that will lessen the impact of their symptoms and, particularly, decrease their pain. Multimodal therapeutic programs may include various components of the treatments mentioned above, but it is not known which combinations are the best and/or whether they should be individually tailored.

Assessing FMS Patients

There is still a lack of specific and sensitive tools capable of assessing the effects of treatment in patients with FMS. The wide variety of methods used to assess specific symptoms has led to considerable heterogeneity in the way the disease and potential treatments are evaluated in clinical trials. One of the main problems is the lack of a consensus concerning response criteria, and we therefore need standardized criteria for assessing clinical results to compare different trials.

Program Duration and Follow-Up

A relatively short but intense treatment program may give patients the necessary skills and sense of self-efficacy to alleviate some of their symptoms but may also require more follow-up by the members of the medical team to support lasting changes and document the results.

Patients are more likely to maintain any changes if they continue to practice the experimental activity over the long term and therefore especially need strategies that help them to do so. Unlike cognitive skills strategies which, once learned, are likely to become part of a person's coping repertoire, exercise and behavioral strategies, such as progressive muscle relaxation, need to be performed consistently to be effective.

Lack of Combined Trials

One distinct limitation of the studies performed so far is the lack of trials testing the combined use of medications and nonpharmacologic treatments. Only 2 studies have included a drug (amitriptyline) as a major treatment variable, although a number of others have involved drug monitoring and ensured that there were no appreciable changes during the course of the trial. However, an optimal multidisciplinary approach must include pharmacological treatment, and so more high-quality RCTs with a drug component are clearly necessary.

Defining Patient Subgroups for Different Multimodal Approaches

Identifying subsets of FMS patients may be important when selecting appropriate treatment and their subjective responses to treatment, and the acceptability of the interventions in terms of personal beliefs and lifestyles should be carefully evaluated. There is also a need for studies capable of identifying the characteristics of the patients who successfully develop long-term behavioral changes that can be expected to become permanent; this would allow the selection of appropriate and specific therapeutic strategies early in the treatment process. Thus, an explicit diagnosis of FMS on the basis of the ACR criteria may be insufficient in itself.

Recommendation for FMS Treatment in Clinical Practice

Treating FMS is especially challenging because of our limited understanding of its etiology and the patients' poor response to conventional pain treatments. Current evidence supports a multifaceted program that emphasizes patient education, medications for improving symptoms, and the aggressive use of exercise and cognitive-behavioral approaches to retain or restore function (Fig. 1) (144). Physicians and patients should be educated about the current theories concerning the pathophysiologic mechanisms underlying FMS and then set realistic goals for all treatment modalities. A number of medical treatments have been used to treat the various symptoms of FMS, in the first instance to control pain, but also for sleep problems, anxiety, and depression, with the final aim of improving the patients' quality of life. Some treatments are used on the basis of a supposed physiopathologic process, and others are used because of their specific effect on certain symptoms. Every medication should be periodically reevaluated and tapered to document its ongoing use. Controlled studies have shown that tricyclic antidepressants such as amitriptyline, selective serotonin reuptake inhibitors such as fluoxetine, and dual serotonin and norepinephrine inhibitors such as venlafaxine, milnacipram, and duloxetine may be useful in treating FMS, but only a small proportion of patients respond to each alone. Cyclobenzaprine (which is usually marketed as a muscle relaxant but has the structure of a tricyclic compound), tramadol (a weak μ-opioid receptor agonist), and anticonvulsants such as gabapentin and pregabalin seem to be effective in reducing FMS symptoms (57). Some of these drugs may be combined in resistant patients.

Pharmacologic agents should be used as part of a comprehensive management program because optimal treatment involves both pharmacologic and nonpharmacologic therapy. Psychological and physical therapy may sometimes be more effective than pharmacologic treatment. Several studies have evaluated the effect of moderately intense exercise, a level of exercise that is best suited to usually deconditioned and unfit FMS patients. Exercise should have 2 major components: stretching to increase soft-tissue length and joint mobility, and aerobic conditioning to increase fitness. As some FMS patients may also be mentally deconditioned, a combined mind–body approach (eg, exercise plus CBT) may have a synergistic effect: CBT addresses the mental barriers to improvement, whereas exercise changes the physiologic factors that contribute to FMS symptoms.

Although no conclusive evidence is available concerning the effectiveness of multidisciplinary rehabilitation, adequately powered, high-quality studies may change the widespread pessimism concerning prognosis. Drug therapy will need to be associated with nonpharmacologic therapies to relieve pain and its associated symptoms and preserve social and professional life.

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