



ALTERNATIVE AND INTEGRATIVE TREATMENT OF FIBROMYALGIA AND CHRONIC FATIGUE SYNDROME

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FIBROMYALGIA

Overview

The fibromyalgia syndrome (FMS) is the most common rheumatic cause of chronic diffuse pain and affects up to 5% of patients from a general medical practice with a female predominance of >75%. It is characterized by widespread chronic pain for at least 3 months and multiple tender points (11 of 18 tender points of the American College of Rheumatology Criteria for Fibromyalgia) but is not simply a muscle pain syndrome. Over 90% of patients diagnosed with FMS report fatigue, generalized pain, morning fatigue, and stiffness. Other common symptoms include paresthesias, psychologic disturbances, restless legs, irritable bowel syndrome, joint pain, headaches, and other nonspecific symptoms. Eliciting tenderness by applying pressure of approximately 4 kg/cm (enough to blanch the thumbnail bed) over a trigger point is the main physical diagnostic finding. A positive test is one in which the patient reports "pain" and not just "tenderness" during the exam. Some pertinent negative findings on physical exam are that there is usually no muscle weakness associated with the pain, and no obvious signs of inflammation such as redness or swelling.

It can be difficult to distinguish fibromyalgia from other diseases associated with chronic widespread pain, and important to realize that frequently patients with fibromyalgia do not have pain limited to "tender points" but are more sensitive to pain throughout their entire body. Recent studies indicate that FMS may be a disease of pain perception and

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that these patients experience discomfort at lower levels of stimulation. This is also known as allodynia, the perception of pain from stimuli that are not usually considered painful.

FMS is a clinical diagnosis and the main value of laboratory tests for evaluation of FMS is to rule out other diseases including hypothyroidism, hepatitis, and other rheumatologic conditions. A thyroid profile, complete blood count, chemistry profile, erythrocyte sedimentation rate, antinuclear antibody, and rheumatoid factor ought be done [1]. There is no specific lab test that establishes a diagnosis of FMS, and pathologic examination of biopsies of trigger points reveal no specific findings.

Etiology

It is theorized that FMS occurs in genetically predisposed individuals after exposure to certain biologic triggers or stressors. Examples of these environmental triggers include infection (Epstein-Barr virus, hepatitis C, parvovirus), physical trauma, catastrophic events (war), and psychological or emotional distress. The resultant pathophysiologic changes that lead to alteration of pain perception are being extensively studied. Pain perception, also known as nociception, occurs at three different levels: peripherally where the stimulus is felt, the spinal cord where the stimulus is processed, and the brain where it is interpreted. Theories suggest that the heightened perception of stimuli as pain, in fibromyalgia, is caused by abnormal processing in the spinal cord and brain. Neuroendocrine axis imbalance, which affects the sensory processing, and sleep disruption are probably central to the cause of fibromyalgia, though the primary cause remains undetermined. Many studies have shown a disturbed non-REM sleep in FMS, whereas others have suggested impaired functioning of the hypothalamic-pituitary-adrenal axis, low insulin-like growth factor-1 levels, decreased serotonin and tryptophan levels, altered levels of substance P and norepinephrine, and decreased regional cerebral blood flow. Autonomic nervous system function abnormalities such as stress intolerance, baseline low sympathetic tone, orthostatic intolerance, vasomotor instability, and visceral dysfunction have been found to be present in some FMS patients. The sleep disorders may be a result of (rather than a cause of) FMS, though disturbed sleep may exacerbate the symptoms of FMS. It is also possible that impaired muscle metabolism or impaired blood flow plays a role [2–4].

Treatment

Treatment is usually a multimodal approach. Like all chronic pain conditions, discussing patient expectations about therapeutic outcomes is important early in the physician-patient relationship. There is no cure for FMS, and the main goal of treatment is to control symptoms. Therapy is frequently divided into pharmacologic and nonpharmacologic treatments. The main focus of this article is to review the available treatments,

in particular complementary and alternative medicine (CAM) therapies, and provide the reader with a current level of evidence-based recommendations regarding best treatments based on a review of the literature.

Most physicians are familiar with conventional pharmacologic therapies that have been reported to be effective. The two medications most widely studied and shown consistently to be effective are the tricyclic antidepressants, specifically amitriptyline, typically in low dose, and muscle relaxants, specifically cyclobenzaprine. Treatment with non-steroidal anti-inflammatories (NSAIDs) alone has not been shown to improve FMS symptoms in multiple studies [5]. Other commonly used conventional therapies include selective serotonin reuptake inhibitors, tramadol and other analgesics, trigger point injections with lidocaine or dry needles, and behavioral therapy [3]. Sleep disruption is commonly treated not only with amitriptyline but also zolpidem [5,6].

Physical therapy can also be useful and may include myofascial release therapy, deep tissue massage, heat, stretching, transcutaneous electrical nerve stimulation (TENS) ultrasonography, iontophoresis, and hydrotherapy [1]. These are the usual approaches taken by well-trained family physicians.

MIND-BODY THERAPIES

When these approaches are not useful, alternative therapies should be considered as integral to the care of this chronic disease. Mind-body therapies such as cognitive behavioral therapy (CBT), biofeedback, hypnotherapy, meditation, relaxation, imagery, and improving self-efficacy all have an important role in the treatment of FMS [7,8]. A review of mind-body therapies in musculoskeletal disorders in the elderly [9] suggests that many of these techniques are efficacious but that controlled research, caused by the complexity of the mind-body process, remains limited. This review stated that the following therapies had demonstrated “at least anecdotal evidence of value”: social support, activation of the placebo effect, CBT, music therapy, tai chi, and qi gong. The authors concluded that, at least in elderly populations, the use of hypnosis, imagery, meditation, and spirituality in musculoskeletal conditions remained speculative mainly because of the paucity of clinical trials of these approaches.

It is important, however, when initiating mind-body therapies, to acknowledge the reality of the patient’s pain experience. Recommending psychologic therapies needs to be done carefully, as such a suggestion amplifies the fears many FMS patients already have of this condition being psychosomatic. The best evidence for mind-body therapies in FMS includes biofeedback, hypnotherapy, and cognitive behavioral therapy [10].

Biofeedback

Electromyographic (EMG) biofeedback has been found useful in fibromyalgia, though it is not widely used. Improvements in pain indices,

morning stiffness, and self-efficacy have been identified in several prospective studies [11–14]. Exercise combined with biofeedback was found to be more effective than biofeedback alone [11]. An interesting finding in a negative study was that EMG biofeedback training reduced plasma adrenocorticotrophic hormone (ACTH) and beta-endorphin during treatment indicating an opioid or neuroendocrine basis for some of the observed effects in FMS [14,15].

Hypnotherapy

Hypnotherapy has not been widely tested in FMS, but one small study ($n = 40$) comparing it with physical therapy showed a positive result [16]. This suggests a need for further clarification of its role and additional studies with an improved control group. In this study, visual analogue pain ratings, fatigue on waking, sleep disturbance, patient global assessments, and somatic and psychologic discomfort scores showed significant sustained improvements over a 24-week follow-up in the hypnotherapy group. Treatments were given over only the first 12 weeks, so sustained benefit was found after active intervention ceased. Hypnosis is being studied more extensively for its usefulness in chronic pain in general [17].

Cognitive Behavioral Therapy

CBT is a process that helps patients reframe their thinking and help them to shape new thought and behavior patterns related to chronic conditions [17]. Several studies have reported benefit of CBT in FMS, generally combined with other multidisciplinary approaches such as aerobic exercise, physical therapy, relaxation training, breath control, and meditation. Such benefits were sustained as long as 30 months after treatment, using outcome measures such as sense of control and mastery over life's circumstances, improved affect, decreased perceived pain severity, and decreased interference of pain with daily activities [10,18].

Another study on the use of cognitive behavioral therapy in FMS utilized an educational component focusing on the mind-body connection, a portion focusing on relaxation response mechanisms (primarily mindfulness meditation techniques), and a qi gong movement therapy session. Twenty patients followed over an 8-week period showed statistically significant reduction in pain, fatigue, and sleeplessness; and improved function; mood state, and general health [19]. Though uncontrolled and based on patient self-report, this was a well-conducted pilot study, and the benefits observed certainly indicate a need for further study with a larger sample size.

Other Mind-Body Therapies

Meditation was studied in an uncontrolled trial, with moderate to marked improvement in multiple outcome measures reported by the 50%

of patients responding to this approach [8]. Music therapy was reported to reduce pain and disability in one trial that included FMS patients [20].

Treatment of FMS with nonpharmacologic therapies has been hindered by the fact that, in many studies, patients continue with their medications. Studies using a wait-list design to address the combination of pharmacological and nonpharmacologic therapy specifically conclude that the combination of education, physical exercise, and some type of psychological intervention appears to be efficacious in the treatment of FMS [5].

Attention to psychosocial aspects of their disease is more important to the sufferers of FMS than to their rheumatologists according to one study [21]. Many of the disability-related problems with this chronic disease are associated with feelings of helplessness and maladaptive coping strategies that need to be addressed in a holistic treatment plan [5].

EXERCISE

Graded aerobic exercise at least three times a week is essential to the treatment of FMS not only to prevent and treat deconditioning, but to decrease pain [22,23]. Many patients tolerate exercise poorly, however, and incremental increases in exercise must be done very slowly, adding perhaps as little as 5 minutes of exercise or less per week to a minimal regime of aerobic exercise. Sleep and fatigue may not be affected by exercise, and long-lasting effects of exercise were not found in one prospective study [3,24]. A positive approach to regular exercise, however, seems most prudent in terms of emphasizing capability rather than disability, maintaining condition, improving attitude, and preserving overall function as well as reducing all-cause morbidity. Tai chi, yoga, and qi gong are low-impact exercises that could be tried in FMS patients intolerant of regular aerobic exercise. The Feldenkrais method of movement education is another low-impact program to consider [25].

Overall, exercise is an approach that has been widely studied for fibromyalgia and has significant support in the literature. The benefits include improved fitness, strength, and flexibility, resistance to microtrauma, and overall improved level of activity. Psychologic benefits include improved self-efficacy, relaxation, decreased depression, and better stress management [14,26].

MULTIMODAL AND MULTIDISCIPLINARY PROGRAMS

Multimodal and multidisciplinary programs have been studied for FMS and include a wide variety of approaches. A sample of the types of interventions used in these programs include patient education, reassurance, emotional support and empathy, stress management, home stretching exercises, massage and use of a heating pad, aerobic exercises to improve conditioning, improvement of sleep quality, and use of simple

analgesics and NSAIDs [27]. Other multimodal and interdisciplinary studies included education, exercise therapy, functional re-education, and cognitive behavioral therapy. Some programs also included diaphragmatic breathing, progressive muscle relaxation, hand-warming, guided imagery, and distraction system arousal. Others utilize sleep therapy, fatigue management, and coping skills strategy. Disciplinary teams included in these kinds of approaches included psychologists, occupational therapists, physical therapists, and biofeedback therapists.

Though many of these approaches show significant evidence of benefit, lack of standardization across programs confounds our ability to make definitive conclusions or recommendations [14]. Improvements in fibromyalgia may depend on factors such as increased endurance and more effective coping skills rather than on changes in tender point and generalized pain sensitivity [14,28].

MANUAL THERAPIES

Chiropractic

Chiropractic was found to be the most commonly used complementary therapy by FMS patients [29]. Little research demonstrates, however, that chiropractic manipulation is useful for FMS. One study showed that chiropractic was not effective in FMS [30], though patients did show some increased range of motion. Because of the high usage of this therapeutic approach, more studies are required to define its role.

Massage

Patients with FMS expressed positive satisfaction with gentle massage therapy but not deep-tissue massage [29]. One study of massage therapy compared with no treatment or an attention control found greater relief of pain and depression, and improvement in quality of life, but no improvement in activities or sleep. After 3 months, however, no difference remained between the treatment and control group [31,32].

Acupuncture

Acupuncture has been reported in a meta-analysis of seven studies to be effective in FMS; however, because only one of the studies provided high-quality data, further randomized trials are needed to provide more robust data on effectiveness [33]. Acupuncture was suggested as possibly useful in FMS by the National Institutes of Health (NIH) Consensus Panel on Acupuncture [34] but concluded that the evidence for the benefits of acupuncture is more impressive for acute rather than chronic pain. Many of the studies on which this consensus statement was based were of poor methodologic quality. Acupuncturists routinely treat patients for chronic

pain conditions including FMS with positive results, though the clinically observed results have not yet been fully validated by well-conducted clinical trials.

One high-quality, randomized, controlled study that did report a benefit from acupuncture in FMS compared electro-acupuncture versus sham acupuncture given in a series of six sessions over a 3-week period [35]. Significant improvements were reported in the treatment group compared with the sham treatment group on pain threshold, pain medication used, visual analogue pain scores, sleep quality, and both physician and patient global assessment scores. Twenty-five percent of subjects improved markedly, 50% had satisfactory relief of symptoms, and 25% had no benefit. [32] In fact, pain threshold improved by 70% in the electro-acupuncture group compared with 4% in the control group [33].

One problem with either treating FMS or studying clinical results from acupuncture is that some patients experience exacerbation of pain as a result of treatment that results in their stopping treatment prematurely [33]. In acupuncture practice, this type of temporary exacerbation is not an unusual initial response, yet it leaves the question as to what would have happened to the FMS patients in a number of studies had they continued therapy.

BIOLOGICALLY-BASED THERAPIES

Supplements

A variety of supplements have been reported to be useful in treating FMS though high quality clinical studies supporting them are sparse. Two alternative supplements deserve special mention as they have shown beneficial effects in blinded placebo-controlled trials. First is S-adenosyl-L-methionine (SAME) (800 mg/d) [5,77–80]. It is an anti-inflammatory drug with analgesic and antidepressant effects. Second is 5-hydroxytryptophan (5-HTP) (100 mg tid) which is a precursor to L-tryptophan and serotonin and is used to alleviate concurrent depression and insomnia [5]. Naturopathic physicians prescribe 5-hydroxy tryptophan (5-HTP) to improve serotonin levels either alone or in combination with St. John's wort [36–38] and emphasize the role of magnesium replacement in FMS [37,39].

Numerous other supplements are recommended to patients by alternative medicine practitioners, in books [6], literature, and on the Internet. Most of these have not had adequate clinical studies to recommend them on an evidence-based level; however, some seem to have potential beneficial effect. We mention them here so that practitioners may become more familiar with what their patients may be using outside of traditionally prescribed therapies, and to expose them to what supplements may need to be further studied and reviewed in the future.

Among these are guaifenesin (600 mg bid) which is thought to reduce phosphate excretion; magnesium (200 mg bid-tid) combined with malic acid (1200 mg qd–bid) to relieve pain, tenderness, and fatigue [40]; vitamin

C (1000 mg tid–qid) to reduce inflammation and support immune function; coenzyme Q10 (50–100 mg qd–bid) to improve tissue oxygenation, and as an antioxidant; chromium picolinate (200 mcg with meals) to reduce reactive hypoglycemia that may aggravate symptoms; B complex vitamin to reduce negative effects of stress; melatonin (0.5–3 mg qhs) as a sleep aid [41]; zinc (30 mg/d) for healthy immune function; and phosphatidyl choline and phosphatidylserine (300 mg/d) to improve cerebral function.

Herbal Therapies

Herbal therapies such as Siberian ginseng (*Eleutherococcus senticosus*), schisandra berry (*Schisandra chinensis*), ashwagandha root (*Withania somniferum*), gotu kola (*Centella asiatica*), and astragalus root (*Astragalus membranaceus*) have been found to act as adaptogens strengthening resistance to stress and improving immunity and are recommended by some practitioners. Specific studies, however, have not reported the clinical effects of these in FMS. A randomized, double-blind, placebo-controlled, cross-over study found statistically significant benefits in FMS patients taking the algae, *Chlorella pyrenoidosa*, in terms of the Fibromyalgia Impact Questionnaire (FIQ) and tender point index (TPI)—leading the authors to suggest the use of *Chlorella* for symptom relief in FMS [42,83]. *Chlorella* is imputed to enhance the immune system nonspecifically and to promote healing. Topical *Capsaicin* was found useful in reducing tenderness and improving grip strength but not in improving pain scores compared with placebo in a small pilot study [43]. St John's wort has been recommended to improve serotonin levels in FMS but has not been substantiated in a randomized controlled trial (RCT). It may also be useful in treating the sleep disturbance associated with this condition.

Diet Therapies

One study of a vegan diet with no animal products but high in raw foods such as nuts, grains, legumes, fruits, and vegetables was found to relieve the symptoms of FMS in a cohort trial, compared with standard diet over a 3-month period [44]. An open, uncontrolled, longitudinal trial of glyconutritionals (saccharide-enriched nutritional supplement) for patients with FMS, CFS, or both found statistically significant benefits in improving 21 symptoms of FMS and CFS [45]. No conclusions can be drawn, however, from this trial because of its methodological weaknesses.

Nutritionally-oriented physicians recommend eliminating all food allergens from the diet, and using an elimination/challenge trial if needed in FMS. The most common allergenic foods are dairy, soy, peanuts, wheat, fish, eggs, citrus, corn, tomatoes, and chocolate. Prevention or treatment of underlying food allergy may be a useful strategy when other methods have failed or in a patient with a strong personal or family history of atopy. We could find no clinical trials to support this recommendation, but in terms of safety and cost, it may be worth a therapeutic trial.

OTHER ALTERNATIVE THERAPIES

Electrotherapy treatments such as TENS, hydrogalvanic bath, and interferential currents have not been demonstrated to be successful in FMS [14]. Homeopathy was found to reduce tender points, pain, and sleep disturbance but not global assessment in an RCT involving 30 patients and using the remedy *Rhus Toxicodendron* [46].

CLINICAL RECOMMENDATIONS AND THE TREATMENT OF FIBROMYALGIA

Many patients are using complementary medicine for the treatment of FMS (Table 1). One study has shown that up to 91% of FMS patients had used a form of alternative therapy in the preceding year compared with 63% usage among other rheumatology patients [29]. It is important that further research be done in this area, and that physicians be familiar with current alternative treatments many patients are already using. Emphasis in treatment should focus on functional restoration at least as much as pain reduction and should always address the psychological aspects of this condition. Patient education and self-management programs show encouraging results [14,47,48] and, given their safety and efficacy, ought also to be recommended as part of an overall treatment plan or as part of multimodal and interdisciplinary approaches.

Based on the research that has been done up to this date, the treatment recommendations for fibromyalgia optimally would include non-pharmacologic therapies, the most effective being cognitive behavioral therapy and graded exercise therapy. These can be used in conjunction with the most effective biologically-based therapies which are amitriptyline, cyclobenzaprine, SAME, and 5-HTP.

Though evidence for other alternative therapies is not yet robust, this does not mean that such treatments may not be useful in individual patients. It is hoped that future research will define their roles more clearly, particularly for promising results in mind-body therapies and acupuncture and for widely used manipulative techniques such as chiropractic and massage. Also, the inclusion of low-impact exercise such as tai chi, qi gong, and yoga are worthwhile to consider for those patients whose exercise tolerance does not allow more strenuous activity or for those who prefer the relaxation induced by these meditative movement therapies.

CHRONIC FATIGUE SYNDROME

Overview

Sharing many similarities with fibromyalgia, except musculoskeletal pain, CFS poses another difficult diagnostic and therapeutic dilemma

TABLE 1.
Fibromyalgia Syndrome

	Best Evidence^a	Possibly Effective^b	Limited Evidence for Effectiveness^c
Alternative systems		Acupuncture [33,35]	Tai Chi Yoga
Mind-body therapies		CBT Biofeedback therapy	Qi gong Meditation Relaxation therapy Support groups Growth hormone NSAID
Biologically based therapies	5-HTP (100 mg tid) [36] SAMe (800 mg [5,77–80] qd) Tricyclic antidepressants (TCA) (amitriptyline 25–50 mg qhs) Cyclobenzaprine (5–20 mg tid–prn or hs) GET	SSRI (fluoxetine 20 mg qd) [81] St. John's wort (300 mg tid) Tramadol and analgesics (50 mg qid–prn) Mg+ (200 mg bid–tid) malic acid (1200 mg qd–bid) [82] Capsaicin (0.023% cream qid) [43] Chlorella (10 gram tablet & 100 mL of liquid extract qd) [83] Zolpidem for sleep (5–10 mg qts)	Diet (vegan, food allergy ie, wheat/dairy, ↓ caffeine/alcohol high fiber) CoQ10
Manual therapies		Trigger point injections Physical therapy	Chromium Picolinate Guaifenesin Omega 3 fatty acids Phosphatidyl choline/serine vitamins B+C Zinc Ashwaganda root Astragalus root Ginseng Gotu kola Schizandra berry Osteopathy Gentle massage therapy Chiropractics Feldenkrais Magnets
Bioenergetic therapies			

^aBest evidence, based on well done RCTs, meta-analysis, or systematic reviews.

^bPossibly effective, therapies that are often helpful but have only modest scientific evidence for efficacy and safety.

^cLimited evidence for effectiveness; therapies that may be useful but have limited or no scientific evidence for efficacy and safety.

CBT, cognitive behavioral therapy; GET, graded exercise therapy; NSAID, non-steroidal anti-inflammatory; SSRI, selective serotonin reuptake inhibitor.

for the physician or other healthcare practitioner. Many patients suffer from both CFS and FMS, and they overlap as “disorders of perception” of symptoms and disability. Estimates of prevalence of CFS among individuals suffering from chronic fatigue in the United States and Great Britain are between 11.5% and 15% by Centers for Disease Control (CDC) criteria, and as high as 38% using the less-strict Australian criteria. About 80% of the sufferers are women between the ages of 25 and 45 [49]. The CFS criteria developed by the CDC are divided into major criteria, both of which are required for the diagnosis: (1) new onset of fatigue causing 50% reduction in activity for at least 6 months, and (2) exclusion of other illnesses that can cause fatigue; and minor criteria, of which 6–8 of 11 symptoms and 2 of 3 signs are required for diagnosis. The symptoms include: mild fever, recurrent sore throat, painful lymph nodes, muscle weakness, muscle pain, prolonged fatigue after exercise, recurrent headache, neurologic or psychological complaints (sensitivity to bright light, forgetfulness, confusion, inability to concentrate, excessive irritability, depression), sleep disturbance (hypersomnia or insomnia), and sudden onset of symptom complex. The signs include: low-grade fever, nonexudative pharyngitis, and palpable or tender lymph nodes [50]. Other symptoms often reported include achiness (often in association with fibromyalgia), “brain fog,” increased thirst, frequent infections, increased urination, and decreased immunity [6].

Etiology

The most important first step in establishing the diagnosis of CFS is to exclude other treatable causes. Although depression leads the list [51], many other conditions can cause fatigue and thus mimic this condition. These include hypothyroidism, anemia, chronic hepatitis or other liver disease, Lyme disease or other chronic infections, metabolic diseases such as diabetes and hypoglycemia, connective tissue disease, malignancy, drugs, food allergy, chronic sinus infection, sleep disorder, cardiopulmonary disease, multiple sclerosis, chronic pain, chronic inflammation, and others.

Research into CFS has identified several interesting etiologies, and like FMS, CFS may be the final common end point for several types of conditions that are made manifest according to individual genetic, metabolic, immunologic, endocrinologic, or psychologic factors. Perhaps the most compelling assessment of etiology is that CFS represents an immune system disorder [52]. Thus, this condition is sometimes referred to as chronic fatigue immuno-deficiency syndrome (CFIDS). Another term, coined by British researchers, to describe this enigmatic condition is myalgic encephalomyelitis (ME), emphasizing association with an infectious etiology.

Initially, CFS was hypothesized to be a form of chronic Epstein-Barr virus (EBV) or other viral entity because of the combination of severe fatigue and influenza-like symptoms that characterized the history of the

case definitions of the disease [53]. Other chronic infections such as cytomegalovirus (CMV) and candidiasis, among others, have long been blamed for this condition. The belief that CFS is a result of chronic EBV infection has been dispelled, as has any association with the human herpes virus [54–56].

Though no specific infectious agent was determined to be responsible for the etiology of CFS, most patients with this disease do report a history of a viral-like illness. This has raised the possibility that CFS is linked to the antiviral response pathway. Recent studies have found a specific dysfunction in the 2,5A synthetase ribonuclease-L antiviral defense pathway of mononuclear cells, which is integral to the action of interferon [57]. This is an area of heightened research and could result in a biochemical marker, which would be useful for correct diagnosis of CFS.

There are multiple other areas of research into the etiology of this complex disease.

Neurally-mediated hypotension was reported to cause this condition in one study and, when this abnormal cardiovascular reflex was treated, it led to a resolution of chronic fatigue [58]. Other clinicians suspect adrenal depletion and impaired function of the hypothalamic-pituitary-adrenal axis [59] from chronic stress, overwork, and other factors with resultant low dehydroepi-androsterone (DHEA) levels. Exposure to chemicals in those with sensitivity to paints, refinishing oils, or other chemicals [60], food allergies and sensitivities, diets with excessive sugar, caffeine, alcohol, and/or chronic nutrient deficiency, toxicity from dental mercury amalgam fillings, low red blood cell magnesium levels [61], intestinal parasites, and dysbiosis (leaky gut syndrome) are alternative etiologies [49]. Low levels of serine, a precursor to serotonin has also been suggested as a causative factor in some subgroups. An association has been reported with CFS, FMS, and temporomandibular joint disorder (TMJ syndrome), suggesting that the etiology of these conditions are all potentially related [62].

Aside from the immune-mediated hypothesis for the etiology of CFS, the other most prevalent current thought is that CFS may be a psychiatric illness or a form of somatization disorder. Physicians who do not believe there is an underlying organic cause of CFS are more likely to diagnose it as one of these. CFS patients tend to have more somatic complaints than depressed patients, but as few as 5% meet DSM-IV criteria for somatization disorder [53]. Many of these patients do have psychiatric comorbid conditions and will do better if these symptoms are treated, although it may not improve their somatic complaints. It is important to recognize that even if CFS is not necessarily a psychological disorder, patient prognosis for recovery is improved with CBT in many instances, as it changes their belief about illness and recovery. It is equally important to recognize that just because patients benefit from CBT does not confirm that it is a psychiatric illness.

In a pragmatic approach to clinical management, Demitrack [51] introduces an interesting topology to the discussion of both CFS and FMS. He describes vulnerabilities for the development and persistence

of CFS and FMS as follows: (1) predisposing factors: stressful life events (acute or chronic), psychiatric illness, personality factors (somatization); (2) constitutional factors: chronic medical illness, history of atopy or allergies; (3) precipitating factors: severe infectious illness, physical trauma (surgery, accidental trauma), severe emotional stressors; (4) perpetuating factors: untreated psychiatric illness, ongoing unaddressed psychosocial stressors, unrecognized medical illness, disruptions in rest-activity cycle, particularly with avoidance of physical activity, abnormal illness attributions (eg, the fixed belief in an ongoing infectious cause unsupported by empirical evidence), and prolonged time away from work or usual activities.

Treatment

As you may suspect, if the etiology is unclear or if CFS is an expression of different etiologies in subgroups of patients, the treatment plan must remain flexible and individualized. Most practitioners who treat this condition suggest several basic treatment approaches including graded exercise and CBT, which are the treatments best supported by evidence [63].

Additional treatments include gamma globulin injections, though these have a high side-effect profile and have not been found to be useful. Hydrocortisone has also been used for those with suspected adrenal exhaustion and hypothalamic-pituitary-adrenal (HPA) axis defects, but it is not as yet confirmed as effective according to a recent systematic review [63].

Other conventional therapies for which there is inconclusive evidence include fludrocortisone (for neurally-mediated hypotension), acyclovir (chronic viral infection), oral nicotinamide adenine dinucleotide (NADH) (low energy), fluoxetine (depression), growth hormone, selegiline, ampicillin (immunodeficiency), terfenadine (chronic *Candida*), alpha-interferon (immuno-deficiency), moclobemide, and staphylococcus toxoid. This review of conventional therapies emphasized the need for standardized outcome measures and more methodologically sound studies [63].

The clinical approach Demitrack [51] recommends includes a thorough initial evaluation by eliciting a full psychosocial history, a sleep history, activity log, the patient's perspective on the problem, and avoiding excessive testing. Treatment planning is recommended to avoid polypharmacy but include antidepressants, NSAIDs, or other symptom-specific drugs, nonpharmacologic treatment to improve sleep, encouragement of physical activity, and the use of cognitive behavioral or other psychotherapies as indicated. It is important to review use of alternative therapies with the patient, with an assessment of outcome from them. Overall outcome assessment includes a broad-based functional outcome assessment that deals with fatigue, pain management, psychosocial adjustment, sleep pattern, and activity pattern. It is essential to evaluate closely any new or unusual symptoms, avoiding premature diagnostic closure, but at the same time avoiding overinvestigation.

BIOLOGICALLY-BASED ALTERNATIVE THERAPIES

Supplements

Supplements such as magnesium [61], antioxidants, and co-enzyme Q10 have been used in CFS. Magnesium was found to have had mixed reviews [64,65] following an initial report of its benefit. Nutritional strategies for CFS were supported by a recent review [66] that suggested a number of marginal nutritional deficiencies including various B vitamins, vitamin C, magnesium, sodium, zinc, L-tryptophan, L-carnitine, coenzyme Q10, and essential fatty acids. The authors suggested that these deficiencies were primarily caused by the illness rather than from inadequate diets but were detrimental to the healing process. The use of NADH (10 mg/d) was supported in a single study [67] that found no serious adverse effects and 31% of patients responding favorably compared with 8% in the placebo arm. L-carnitine was found to yield clinical improvements in CFS in a RCT ($n = 30$) cross-over study over a 2-month period [68]. A small, uncontrolled study of amino acid supplementation ($n = 20$) yielded positive results in 15/20 patients [69].

Herbal Therapies

Licorice (1–2 g/d of powdered root or 250–500 mg/d of solid extract) is also recommended by some to address low blood pressure in those suffering from neurally-mediated hypotension [37,70]. Siberian ginseng (*Eleutherococcus senticosus*) may be useful to support low blood pressure, low energy, and deficient immune status [71]. Although two placebo-controlled trials have been conducted on the use of evening primrose oil, no conclusions can be drawn on its effectiveness [32,72]. In general, few herbs have been clinically investigated in CFS despite widespread use and rational application of the principles of phytotherapy [32].

Dietary Approach

Naturopathic authors recommend a diet high in fiber and low in protein, fat, sugar, caffeine, alcohol, and allergenic foods such as wheat and dairy [37].

OTHER ALTERNATIVE THERAPIES

Other recommendations for treatment of CFS include support groups, traditional Chinese medicine including qi gong exercise, homeopathy [73], and oxygen therapy [49,56]. Chiropractic and osteopathy were reported to prove better than no intervention over a 12-month period in a nonrandomized trial [74]. Relaxation therapy was found significantly less effective than CBT [75,84].

Combination Protocol

A protocol developed by a physician (Teitlebaum) specializing in both CFS and FMS [6,76] involves a wide array of approaches. This protocol is popular among both patients and holistic practitioners. Each therapeutic approach is based on some clinical or laboratory studies; however, RCTs to support a combination protocol have not yet been done.

The protocol is as follows: (1) nutritional treatments include B-complex multivitamins, magnesium, malic acid, l-carnitine, co-Q10, calcium, iron, and B12; (2) sleeping aids (for FMS) include amitriptyline, cyclobenzaprine, trazodone, zolpidem, carisoprodol, clonazepam, valerian root, passion flower, lemon balm, chamomile, hops, and melatonin; (3) hormonal treatments include thyroid, Cortef, DHEA, fludrocortisone, oxytocin, choline, inositol, triestrogen (natural estrogen), natural progesterone, and testosterone; (4) antifungals include acidophilus, nystatin, fluconazole, itraconazole; (5) antiparasitics used are metronidazole, *Artemisia annua*, Tricyclin; and (6) nonspecific treatments include nitroglycerin, *Rhus toxicodendron*, homeopathic naphazoline, nimodipine, mexiletine, pyridostigmine, hydralazine, ranitidine, sentracine, diazepam, panoxitine, fluoxetine extensive, venlafaxine, nefazodone, or gabapentin [6]. As you can tell from this extensive list, patients are evaluated and managed according to the practitioner's best assessment as to which of the presumed etiologies of CFS is predominant.

CLINICAL RECOMMENDATIONS AND THE TREATMENT OF CHRONIC FATIGUE SYNDROME

Chronic fatigue is notoriously resistant to treatment. With a wide variety of possible pathophysiological etiologies, potentially significant psychosocial overlay, and its chronic disabling nature, CFS is one of the most challenging of conditions to manage in a primary care practice. Clinicians can help by maintaining an open, inquisitive attitude toward the dilemmas CFS presents in the boundary between body and mind. They can strive to untangle suggestive etiologies from the tapestry of the patient's history. Offering compassionate and sustained care to the sufferer are the first rungs of the ladder to a holistic and integrative approach to the problem.

Among the plethora of proposed therapies (Table 2), the best evidence from clinical trials has supported only CBT and graded exercise therapy. These should be offered in every case. As in FMS, psychological intervention must be approached sensitively and rationally. The use of medications such as antidepressants and sleep aids may be helpful but, like many medical treatments, are supported only tentatively by inconclusive studies with unstandardized outcome measures and methodological limitations.

Among the alternative therapies, there is likewise insufficient evidence to make conclusive recommendations for the treatment of CFS. The weight of evidence at this time supports only a few therapies, L-carnitine, NADH, and possibly magnesium.

TABLE 2.
Chronic Fatigue Syndrome

	Best Evidence^a	Possibly Effective^b	Limited Evidence for Effectiveness^c
Alternative Systems		Tai Chi exercise Yoga	Homeopathy Traditional Chinese medicine Qi gong
Mind-Body therapies	CBT [75,84]	Support groups	Relaxation therapy Biofeedback Hypnosis Alpha-interferon Ampligen Fluoxetine Gamma globulin injections Growth hormone hydro/ fludro-cortisone Moclobemide Selegiline Staphylococcus toxoid Terfenadine Thyroid
Biologically based therapies	GET	L-Carnitine (1000 mg bid-tid) Magnesium (200 mg tid) NADH (10–15 mg qd or every other day)	Diet (vegan, food allergy i.e. wheat/dairy, ↓caffeine/ alcohol high fiber) CoQ10 DHEA Essential fatty acids Vitamins B/C Zinc Evening primrose oil Ginseng Licorice Oxygen therapy
Manual therapies			Chiropractic Massage Osteopathic

^aBest evidence based on well done RCTs, meta-analysis, or systematic reviews.

^bPossibly effective, therapies that are often helpful but have only modest scientific evidence for efficacy and safety.

^cLimited evidence for effectiveness, therapies that may be useful but have limited or no scientific evidence for efficacy and safety.

SUMMARY

We look forward to future, standardized and methodologically sound studies on such frontier approaches as naturopathy and the Teitlebaum protocol, as well as hands-on therapies, nutritional supplements, and botanical medicine. While many therapies for CFS exist, an individualized approach utilizing both clinical art and clinical science will ultimately prove most beneficial for this enigmatic condition.

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Key Points

- Emphasis in treatment of fibromyalgia should focus on functional restoration at least as much as pain reduction and should always address the psychological aspects of this condition.
- Fibromyalgia treatment recommendations include cognitive behavioral therapy and graded exercise therapy, which can be used in conjunction with the amitriptyline, cyclobenzaprine, SAMe and 5-HTP.
- The best evidence from clinical trials supports cognitive behavioral therapy and graded exercise therapy for treating CFS. The use of medications such as antidepressants and sleep aids may be useful. Supplement therapies include L-carnitine, NADH, and possibly magnesium.
- Acupuncture, spinal manipulation and water injections are worth trying to treat low back pain. Use these in conjunction with analgesics and regular physical exercise. Keep up normal activity as much as possible and reassure patients that having back problems is not a disease but entirely normal.

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