

Complementary and Alternative Medical Therapies in Fibromyalgia

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Abstract: This article describes the studies that have been performed evaluating complementary or alternative medical (CAM) therapies for efficacy and some adverse events fibromyalgia (FM). There is no permanent cure for FM; therefore, adequate symptom control should be goal of treatment. Clinicians can choose from a variety of pharmacologic and nonpharmacologic modalities. Unfortunately, controlled studies of most current treatments have failed to demonstrate sustained, clinically significant responses. CAM has gained increasing popularity, particularly among individuals with FM for which traditional medicine has generally been ineffective. Some herbal and nutritional supplements (magnesium, S-adenosylmethionine) and massage therapy have the best evidence for effectiveness with FM. Other CAM therapies such as chlorella, biofeedback, relaxation have either been evaluated in only one randomised controlled trials (RCT) with positive results, in multiple RCTs with mixed results (magnet therapies) or have positive results from studies with methodological flaws (homeopathy, botanical oils, balneotherapy, anthocyanidins and dietary modifications). Another CAM therapy such as chiropractic care has neither well-designed studies nor positive results and is not currently recommended for FM treatment. Once CAM therapies have been better evaluated for safety and long-term efficacy in randomised, placebo-controlled trials, they may prove to be beneficial in treatments for FM. It would then be important to assess studies assessing cost-benefit analyses comparing conventional therapies and CAM.

Key Words: Fibromyalgia, Complementary or alternative medical therapies, Nutritional and Herbal supplementation, Manipulative techniques, cold and heat therapy.

INTRODUCTION

Fibromyalgia Syndrome (FM) is a common, chronically painful, frequently disabling disorder of unknown origin. There is no permanent cure for fibromyalgia; therefore, adequate symptom control should be goal of treatment. Clinicians can choose from a variety of pharmacologic and nonpharmacologic modalities. Unfortunately, controlled studies of most current treatments have failed to demonstrate sustained clinically significant responses [1]. Bennett [2] rightly observed that this realisation can overlook valid clinical successes and foster therapeutic nihilism.

Why do FM patients respond differently to different treatments? It seems to depend on the different pathogenetic mechanisms in the subgroups of FM patients. Principally at least four different phenomena play a role within this: disturbances in the inhibitory system [3]; neuro-endocrine disturbances [4, 5]; disturbances in neuropeptides [6]; and a pathologic decreased secretion of the growth hormone [7]. Furthermore, recent findings suggest that cytokines [8-11], biogenic amines [12], nitric oxide [13], microcirculatory changes [14] and prostaglandins [15] may contribute to FM pain [16].

No pharmaceutical therapies have been successful in treating FM over the long term. Most patients have numerous symptoms in addition to pain, including sleep disturbance, fatigue, irritable bowel and psychologic distress. Because all of these symptoms are unresponsive to

conventional pharmacologic treatments, patients with FM often present their treating physicians a list of vitamin, minerals, supplements and prescribed therapies [17].

Historically, complementary or alternative medical (CAM) has been defined as medical interventions that are not routinely prescribed by practitioners of conventional Western medicine, taught in medical schools or reimbursed by third party payers. The National Institutes of Health (NIH) classifies CAM in five ways: (a) alternative medical systems such as traditional Chinese medicine (including acupuncture), naturopathic medicine, ayurvedic medicine and homeopathy; (b) biological-based therapies, including herbal, special dietary and individual biological treatments not accepted by the Food and Drug Administration; (c) energy therapies such as reiki, therapeutic touch, magnet therapy, qi gong and intercessory prayer; (d) manipulative and body-based systems, for example, chiropractic, osteopathy and massage; and (e) mind-body interventions such as meditation, biofeedback, hypnotherapy and the relaxation response [18].

CAM therapies are becoming more popular for the treatment and management of pain. Eisenberg *et al.* [19] found that one in three adults had used alternative medicine at one time in their lives. This trend has continued through the past decade, with some data suggesting that patients visit alternative medical practitioners more frequently than they visit their primary care physicians [19, 20].

FM is a chronic pain related syndrome associated with high rates of CAM use. As many as 66% to 90% of patients with FM use at least one form of alternative medicine, in part because there are no curative treatments or consistently effective therapies for FM in Western medicine [21, 22].

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CAM has gained increasing popularity, particularly among individuals with FM for which traditional medicine has generally been ineffective. Holdcraft *et al.* [23] for a systematic review of randomised controlled trials (RCTs) and non-RCTs on CAM studies for FM carried out to evaluate the empirical evidence for their effectiveness. In their study, authors stated that few RCTs achieved high scores on the Consolidated Standards of Reporting Trials, a standardised evaluation of the quality of methodology reporting. Acupuncture, some herbal and nutritional supplements (magnesium, S-adenosylmethionine) and massage therapy have the best evidence for effectiveness with FM. Other CAM therapies have either been evaluated in only one RCT with positive results (Chlorella, biofeedback, relaxation), in multiple RCTs with mixed results (magnet therapies) or have positive results from studies with methodological flaws (homeopathy, botanical oils, balneotherapy, anthocyanidins and dietary modifications). Lastly, other CAM therapies have neither well-designed studies nor positive results and are not currently recommended for FM treatment (chiropractic care).

In general, the literature on CAM therapy for FM is characterised by small-poor quality studies that use many different outcome measures. A recent systematic review of FM therapy found that nonpharmacologic interventions were at least as effective as pharmacologic interventions [24].

Pöyhia's research shows a correlation between decreased pain and concurrent increased use of CAM therapies by patients with FM [24]. Current research indicates that FM patients resort to CAM when they experience higher pain and disability in the hope that CAM will provide some relief [25-28].

This article describes the studies that have been performed evaluating these CAM therapies for efficacy and some adverse events in FM.

NUTRITIONAL, HERBAL AND HORMONAL SUPPLEMENTATION

Quite a few studies have investigated the effects of herbal and nutritional supplements and dietary modifications on FM but few have been RCTs. The vast majority of herbal and nutritional supplements have not been empirically evaluated for the treatment of FM with the exception of magnesium, botanical oils, sulphur baths (balneotherapy) and a few dietary supplements.

In an excellent review article, Crofford and Appleton [17] summarised herbal and nutritional supplements in FM. Alternative medicinal and pharmacologically active treatments can be categorised into groups of herbal and nutritional supplements. Herbal supplements are derived from plants and flowers and may be found raw, prepared in teas, tinctures and ointments or combined with other herbs or mixtures. Nutritional supplements include vitamins, minerals and organics (eg. oils, white royal jelly, glycosaminoglycans). A variety of nonregulated supplements such as ginkgobiloba, echinacea, ginseng, feverfew, St. John's wort and kava kava have widespread availability and are marketed for specific symptoms. Clinical interest in and study of interest of these substances has increased over the past decade [29]. Two most important nutrients that are found to

be particularly useful for FM are: magnesium and 5-Hydroxytryptophan (5-HTP), a supplement. One can not always be certain how much, if any active agents is consumed by patients depending on the sources used; this and the lack of full-scale clinical trials are criticisms of the use of these supplements. Herbs can be used to alleviate FM by reducing inflammation, stimulating hormones, providing immune system support and eliminating pain. Fortunately, most of these herbs and additives do not cause serious adverse reactions in most clinical trials [29]. Nevertheless, some can interact with other medications such as warfarin, loop diuretics and monoaminoxidase inhibitors enhancing or diminishing the pharmacologic activities of these drugs [17].

ST. JOHN'S WORT

St. John's wort (*Hypericum perforatum*) is a yellow flowered plant that has gained popularity as an alternative treatment for mild depression. St. John's wort is a natural antidepressant and influences the adrenal gland hormones to help relieve stress. St. John's wort affects nerves and is effective for sharp, and shooting nerve patients. It also has antiviral properties.

Meta analyses of randomised, double-blind and controlled trials have shown that St. John's wort is comparable to conventional antidepressants in treating mild depression [29]. There are no trials of St. John's wort in patients with FM. However, St. John's wort has been found to have properties similar to anti-depressants, in particular, selective serotonin reuptake inhibitors (SSRIs) and to a lesser degree, monoamine oxidase inhibitors (MAOIs). However, unlike tricyclic antidepressants and SSRIs, anticholinergic effects are minimal. Because tricyclic and SSRI antidepressants are used in FM and have been shown to have a beneficial effect, St. John's wort may be considered as an alternative treatment for FM or for coexisting symptoms of depression in FM. There are some well documented side effects of St. John's wort and its interactions with other medications. One concerns the concomitant use of antidepressant medications. Patients who are prescribed antidepressants may not tell their physicians that they are or will be taking St. John's wort and may take it sporadically; patients should be forewarned of the additive effects of taking antidepressants with St. John's wort, possibly resulting in the equivalent of SSRI overdose [30]. Along with compounding antidepressant effects, other drug interactions may occur with St. John's wort. Induction of cytochrome p450 enzymes with the efficacy and concentration of the agents such as protease inhibitors, digoxin, theophylline, warfarin, cyclosporin, estrogen and oral contraceptives have been shown to be reduced if taken in combination with St. John's wort [17, 29, 31].

SIBERIAN GINSENG

Siberian Ginseng is an energising herb that can help to resolve the fatigue associated with FM. Ginseng is reported to induce caffeine-like, energising and anti-fatigue effects without nicotinic actions. Side effects with ginseng include insomnia, suggesting that its use in FM may be counterproductive in some cases [32]. Further studies that examine effects on sleep cycle, specifically evaluating ginseng use in patients with FM are necessary [33]. In addition,

because of hormone mimicry of estrogens and insulin, there are potential side-effect, including hypoglycemia. Central nervous system stimulatory effects such as tremors may occur with use of this supplement [17].

VALERIA

Valerian root had sedative properties that may improve sleep in patients with FM [34]. Studies have shown that it is well tolerated and effective in terms of perception of sleep quality. Valerian has not been evaluated formally in trials with patients with FM. However, in a double-blind, cross-over, placebo-controlled, trial of 450 and 900 mg of aqueous extract, there were dose dependent reductions in sleep latency and wake time after sleep onset based on subject self-ratings and EEG readings [35]. In a study of 16 patients diagnosed with insomnia, the patients had measures of sleep efficacy, arousal index score and sleep stage analysis [36]. No outcome measure changed with single dose valerian compared to placebo. However, significant increases in sleep efficacy were noted after multiple doses were taken. Rapid eye movement sleep percentage was increased, non-REM sleep percentage was decreased and slow-wave sleep latency was reduced in valerian users compared to the placebo group. Few adverse events with *radix valerianae* were noted [17].

BOTANICAL OIL

Primrose oil and borage seed oil are well known to contain gammalinolenic acid and have been proposed to have anti-inflammatory properties. While studies have shown that these substances may have NSAID-like anti-inflammatory properties in osteoarthritis and rheumatoid arthritis, the efficacy of these agents as analgesics and in diminishing stiffness in joints is relatively weak [17, 29].

Ginger oil may be beneficial in patients who have rheumatic complaints [37]. Powdered ginger was beneficial in an open-label study with 18 patients with osteoarthritis and 10 patients with muscular discomfort. All of the patients with muscular discomfort and 14 of the patients with osteoarthritis had some pain relief. In these patients, no side-effects were reported at up to 2.5 years [17].

A German study found that pain, disturbed sleep and tender point count differed when using pine oil or valerian baths compared with plain water whirl baths in 30 patients with FM (38). Pine oil and valerian baths improved sense of well-being, but shinbone and deltoid tenderness increased in pine oil baths, whereas sleep improved, tender points decreased and well-being improved after valerian baths. Plain whirl baths significantly reduced pain intensity. Study limitations included a small sample size, no patient blinding and the lack of an intention-to-treat analysis (9 subjects were dropped from the data analysis).

MELATONIN

Melatonin has been considered as a therapy for jet lag and circadian sleep disturbances [39]. Although there have been some findings of depressed melatonin levels in patients with FM and hypotheses that disturbances in serotonin activity and hypothalamic-pituitary-adrenal axis function

could be linked to hyposcretion of melatonin in FM, more recent findings suggest that melatonin levels and circadian cyclic production in patients with FM are not significantly different from healthy controls [40, 41].

Wikner *et al.* [42] describe a lower nocturnal peak and a decreased secretion of melatonin in women with FM when compared with healthy matched controls. Low serum levels of both serotonin and its precursor tryptophan appear to prevail in patients with FM. The reduced absorption of tryptophan in FM and consequent decrease of available serotonin could be responsible for reduced melatonin synthesis, abnormal sleep pattern and pain typical of FM. [41]. Since serotonin affects not only restorative sleep but also pain perception, low serum levels of these compounds might have a bearing on some of the fibromyalgia-like symptoms. Tryptophan and serotonin are melatonin precursors. Melatonin has sleep-promoting properties. Hence, it may well be that the sleep problems most patients with FM complain, at least in part might be caused by low nocturnal melatonin secretion [42].

No controlled studies of melatonin have been performed in patients with FM; however, an open labeled 4-week pilot trial of melatonin has been reported [43]. Nineteen patients with FM and 20 age and sex matched controls took 3 mg of melatonin at bedtime and completed assessments before and after treatment. There was significant improvement in median visual analogue scale scores for sleep, patient and physician global assessments and tender point counts. Controlled trials evaluating sleep enhancing properties of melatonin have been reported showing decrease in sleep latency to stage-2 sleep and increased sleep deficiency using doses ranging from 0.1 mg to 10 mg in healthy persons (44). A single-blind, cross-over, placebo-controlled trial of 10 mg melatonin found a significant increase in total sleep time in diurnal sleep. In a double-blind, randomised placebo-controlled cross-over study in insomnia, a subjective improvement in total sleep time during active treatment with 5 mg of melatonin was <found in 7 of 15 subjects [45]. In a placebo-controlled, double-blind cross-over trial with 15 middle aged healthy subjects, sleep time, sleep efficiency, non-REM sleep and REM sleep latency improved significantly with 1 mg of melatonin compared with placebo [46].

Fibromyalgia is problematic to treat. Although most studies are open studies, results are encouraging to utilise melatonin in the treatment, since lower levels of melatonin were found in fibromyalgia patients compared to normal controls, although circadian disturbances cannot be the cause of FM [47]. Thirty-day replacement with 3 mg melatonin did reduce complaints [43]. Whether melatonin might receive the status of adjuvant therapy in various pain-therapies is still in its infancy, but will have a follow-up, pain reduction in FM could have been the beginning.

MAGNESIUM

Low magnesium levels are a common finding in patients with FM. Magnesium is critical to many cellular functions, including energy production, protein formation and cellular replication. Magnesium participates in more than three hundred enzymatic reactions in the body, particularly those processes that produce energy. When magnesium levels are

low, energy levels are low. Magnesium supplementation has produced very good results in treating both FM and chronic fatigue syndrome (CFS). This improvement may be due to magnesium's importance to serotonin function and the production of cellular energy. Magnesium is relaxing and improve muscle and nerve function. The combination of magnesium and malic acid helps to increase energy. These nutrients are precursors to the Krebs cycle, a series of enzyme reactions that are a key part of the production of energy on the cellular level. The combination magnesium and malic acid may also be helping the bodies handle physiologic stress better.

Magnesium has been proposed as a therapy for FM based in part on its properties in muscle metabolism, which include enhancing mitochondrial ATP production. In addition, Abraham and Flechas [48] have suggested magnesium deficiency as a possible mechanism in FM related pain. However, there is little support for clinical magnesium deficiency in FM [49]. Relief of symptoms and fewer tender points were reported in a preliminary, open-label study in patients with FM taking 300 to 600 mg of magnesium malate daily [48]. A randomised double-blind, placebo-controlled trial of the same therapy was subsequently performed with 24 patients with primary FM [50]. Results showed that the therapy was safe, but the trial did not find a significant improvement in visual analogue scale pain scores and tender point scores with the preparation during the randomised controlled phase of the study. However, pain and tender point scores improved significantly after 2 months in the open-label dose escalation phase. Improvement in tender point scores was sustained at 6 months [17]. The findings of these two trials on magnesium supplementation for FM should be interpreted with caution because the sample sizes were very small and neither had long-term follow-up. Furthermore, the first study was not double-blind and lacked objective outcomes.

SERUM DEHYDROEPIANDOSTERONE SULPHATE (DHEAS)

DHEAS regulates the immune system and maintains the metabolic and structural integrity of the nervous system. DHEAS has been shown to be antiviral and has benefited conditions as serious as HIV infection and AIDS. DHEAS levels have been found to be inversely related to stress and therefore, may have a role in mechanisms of FM. HPA axis disturbances have been demonstrated in FM [51] and abnormalities of androgen and anabolic metabolism have been hypothesised. Serum DHEAS has not been evaluated as a treatment for FM in a randomised controlled trial. DHEAS has been evaluated as a treatment for systemic lupus erythematosus in which low levels have been documented [52, 53].

NICOTINAMIDE ADENINE DEHYDROGENASE (NADH)

NADH is an antioxidant enzyme that occurs in all living cells. It facilitates the production of neurotransmitters such as dopamine and noradrenaline. Low levels of neurotransmitters are often associated with fibromyalgia. Adenosine triphosphate (ATP) deficiency has been a proposed theory in

FM and CFS; NADH is believed to enhance the production of ATP. A 4-week crossover randomised, placebo-controlled trial evaluated 10 mg of oral NADH in 26 patients with CFS [54]. Based on a symptom rating scale, eight patients attained a 10% improvement with NADH compared with two on placebo. Compliance was monitored at weeks 4 and 12 and no serious adverse events were reported [17].

S- ADENOSYLMETHIONINE (SAM OR SAM-E)

S- adenosylmethionine (SAM or SAM-e) is an amino acid derivative that has been shown in clinical trials to reduce the number of trigger points and areas of pain, lessen pain and fatigue and improve mood. SAM-e, which is a dietary supplement considered to have antidepressant and anti-inflammatory properties, has beneficial effect in the treatment of FM [1, 55, 56].

In a recent review of its efficacy in FM as shown in seven clinical trials (four of which were RCTs) [55-59], SAM-e decreased the number of tender points or intensity of tender point scores in five of the seven trials [59]. Similarly, depression ratings improved on at least one measure in six of the seven trials. However, in one of the larger, well-designed RCTs, the treatment and control groups did not differ on pain ratings on a VAS, number of tender points, self-reported depression and physician-rated global assessment [59]. Four patients withdrew from this study owing to adverse events.

SAM has been evaluated in several double-blind randomised controlled trials [55-57]. Although fairly well designed, all were small and had mixed results. Only one used the oral form of the drug. While the drug appears to be relatively safe, it is expensive and interactions with antidepressants and other drugs have been reported [60].

GROWTH HORMONE

Growth hormone deficiency in adults has been associated with symptoms that are similar to those described by patients with FM: low energy [61], poor general health [62], reduced exercise capacity [63], muscle weakness [64], cold intolerance [61], impaired cognition [65] and dysthymia [61]. Furthermore, growth hormone is important in maintaining muscle homeostasis [66] and it was theorised that suboptimal levels may be a factor in the impaired resolution of muscle micro trauma in FM [67].

In a study by Bennet *et al.* [68] (randomised, placebo-controlled, double blind study in 50 women with FM) it was demonstrated that women with FM and low insulin-like growth factor 1 levels experienced an improvement in their overall symptomatology and number of tender points after 9 months of daily recombinant human growth hormone therapy. In addition, authors suggest that a secondary growth hormone deficiency may be responsible for some of the symptoms of FM. After discontinuation of treatment, patients experienced a worsening of symptoms. Due to the high cost of treatment, it was not recommended by the authors for use in patients with FM [68].

CHLORELLA PYRENOIDOSA

Chlorella pyrenoidosa is a unicellular green alga that grows in fresh water. It has the highest content of chloro-

phyll of any known plant and also contains high concentrations of certain vitamins, minerals, dietary fiber, nucleic acids, amino acids, enzymes and other substances [69]. Nutritional approaches, however, have received little attention. The results of the study with FM indicate that, for some subjects, taking chlorella daily can improve sleep and reduce anxiety levels. These 2 factors might in turn lead to a reduction in perceived pain and the number of tender points in the same way that medications improve sleep or reduce anxiety produce relief of FM symptoms. Another interesting avenue of speculation for chlorella's action comes from the observation that some of the clinical features of FM resemble those seen in adults with growth hormone deficiency syndrome. It remains to be seen whether consumption of chlorella works in some way to increase production of growth hormone and whether, by doing so, it reduces symptoms of FM [69].

Merchant *et al.* [69] have conducted two clinical trials of chlorella in patients with FM. The first study was an open-label pilot study that involved 18 subjects with FM who supplemented their diet with 10 g of chlorella tablets and 100 mL of chlorella extract each day for 2 months [70]. Dietary supplementation with these 2 chlorella products led to a mean net decrease of 2 tender points from 17 at baseline to 15 by the end of the study. The average TPI, which was 32 at baseline, decreased to 25, representing a statistically significant decrease in the intensity of pain of 22%. The results from patients' questionnaires also suggested that they had experienced modest improvements in most of their symptoms of FM. Second was randomised, placebo-controlled and double-blind crossover study in 37 FM patients. The results of this well designed study lead the authors to conclude that for most subjects with FM, dietary chlorella supplementation helped to relieve symptoms [69]. These findings await replication by other investigators and should be considered preliminary because sample sizes were small and there was no long-term improvement [23].

5-HYDROXYTRYPTOPHAN COMBINATION THERAPY

5-HTP is a supplement that is manufactured from the seeds of an African plant (*Griffonia simplicifolia*). 5-HTP is converted to the important neurotransmitter serotonin. 5-HTP is believed to raise the levels of serotonin. Serotonin plays a key role in insomnia and depression. In addition to increasing the levels of serotonin, 5-HTP also causes an increase in the levels of endorphin and other neurotransmitters.

The use of 5-HTP in the treatment of FM began with studies on a drug known as fenclonene. This drug blocks the enzyme that enables the conversion of tryptophan to 5-HTP and as a result, it effectively blocks serotonin production. When subjects took this drug, they experienced severe symptoms of FM. This association led to the discovery of the link between low serotonin levels and fibromyalgia as well as to the use of 5-HTP in the treatment of FM.

Several clinical studies confirm the usefulness of 5-HTP in treating FM. In one double-blind study, fifty patients with FM were given either 5-HTP (100 mg) or a placebo three times per day. The group that received the 5-HTP experi-

enced significant improvements in their symptoms. In contrast, the group that received the placebo did not improve much at all. 5-HTP was rated significantly better than the placebo by subjects and evaluating physicians. Patients receiving 5-HTP have shown improvements in all symptoms such as number of painful areas, morning stiffness, sleep patterns, anxiety and fatigue. People who take 5-HTP begin to show improvements in their FM symptoms within thirty days. Better results are obtained at ninety days of use. The beneficial effects of 5-HTP are thought to be due to elevation of serotonin levels, which increases pain tolerance and improves sleep quality. No significant adverse effects have been reported in clinical trials of 5-HTP. Side effects appear to be limited to occasional mild digestive distress and possible allergic reactions.

DIETARY SUPPLEMENT

Many FM patients wonder whether certain foods affect their symptoms [71]. One questionnaire-based survey found that 23% of patients with FM had changed their diets in an attempt to control symptoms [71]. Vegetarian diets have been theorised to relieve FM symptoms because brain tryptophan has been reported to be low in FM and intake of protein rich in large amino acids such as animal products, has been hypothesised to cause this low level of brain tryptophan [72].

There are few controlled trials for nonpharmacologic management and the existing studies are often criticised for methodologic flaws, small sample sizes, insufficient duration of follow-up and lack of appropriate control interventions [73]. Nevertheless, a majority of patients with FM use complementary therapies such as herbs and lotions, multi-vitamins, spiritual healing and dietary manipulation [1].

One complementary therapy that may have some therapeutic effect is a regimen that eliminates a group of alleged "dietary excitoxins". In a series of case studies, Florida researchers reported dramatic improvement in patients who eliminated monosodium glutamate aspartame, food additives and/or a variety of allergens. While such anecdotal evidence is certainly not definitive proof, at least two of the suspected toxins- monosodium glutamate and aspartame- have been previously linked to fibromyalgia-like symptoms [74].

FM symptoms are worsened by a poor diet; an investigator suggests that this deterioration may be due to impaired glycolysis and carbohydrate metabolism. Dietary changes are both essential to improvement of symptoms and challenging to achieve. Although there are many diet possibilities, many are as unhealthy as the patient's current diet. No dietary approach has been accepted universally, so the physician must choose an approach that is balanced and safe.

Investigators have found that between 26% and 40% of FM patients attempt dietary changes – the addition and/or elimination of foods [21, 75]. Although not particularly robust, there is evidence to suggest that dietary modifications may be beneficial in some FM patients as measured both subjectively and objectively [28, 76-79].

An excellent review by Panush and Henderson [37] of studies in a variety of rheumatic conditions in which dietary supplements were evaluated has been published recently.

They cited a study by Dykman *et al.* [80, 81], which included patients with FM as having methodologic shortcomings. Patients were interviewed about symptoms at least 1 month after use of nutritional supplement products (containing aloe vera gel extract and other plant-derived saccharides, freeze-dried fruits and vegetables, endocrine support supplements or vitamins and minerals). Follow-up interviews took place 9 months later, after the introduction of a second generation nutritional supplement, which contained additional saccharides [80, 81]. With medical treatments approximately 25 percent of FM patients improve, but these beneficial effects rarely persist for more than a few months. The authors reported improvement in a list of 21 symptoms in most of the subjects, based on a 5-point severity scale. Further research is needed to verify these results, specifically crossover designs in well-defined populations. The taking of these nutritional supplements has been shown to help with the initial symptoms and throughout treatment for FM. No significant conclusions about efficacy and safety of the supplements can be derived from this nonrandomised study because of the numerous sources of potential bias, including placebo effect, selection and investigator bias [17].

A 3-week vegetarian diet improved subjective well being in FM patients, along with significant reductions in serum peroxides, plasma fibrinogen, apolipoproteins A and B and serum total cholesterol [82]. A "living-foods" vegan diet was used in a 3-month non-randomised controlled study of FM subjects [77]. In the intervention group there were significant improvements in pain scores, quality of sleep, morning stiffness, health assessment questionnaire scores and general health questionnaire. These studies, along with anecdotal evidence that we have gathered, indicate that a mostly raw food vegetarian diet is helpful in breaking the cycle of suffering of FM patients [83].

One recent placebo-controlled study examined 12 patients with moderate to severe FM treated with 40, 80 and 120 mg of anthocyanidins, a compound found in cranberries and blueberries [84]. At 3 months, patients treated with the active agent at a dose of 80 mg showed a significant improvement in sleep, fatigue and general health questionnaire scores. However, only 10 patients completed this study and the duration was limited to 3 months [17].

A double-blind, placebo-controlled crossover study performed by Fisher [85] evaluated *Rhus toxicodendron* 6C (poison ivy) in patients with FM involved 1 month on active treatment and 1 month on placebo. There was a 25% reduction in tender point count and improvement in other outcome variables such as VAS, with active treatment compared to control. Almost twice as many subjects reported improvement in sleep or pain on active treatment than placebo. The study has significant weakness [17].

A nonrandomised study using *Rhus toxicodendron* 6X (a less dilute preparation and therefore considered lower potency based on homeopathic principles) found no improvement in symptoms in subjects with FM [86].

Phosphatidylserine, a type of lipid, can be helpful if memory problems accompany fibromyalgia. It often yields rapid and impressive improvement in memory and mental alertness. Unfortunately, it is relatively expensive (Ginkgo

Biloba is a cheaper alternative). Ginkgo *biloba* improves circulation and brain function. *Calendula* taken orally in high doses has a positive effect in reversing symptoms of FM. A combination of burdock, slippery elm, sheep sorrel and Turkish rhubarb was shown good results in improving FM. Topical applications of cayenne (capsicum) powder mixed with wintergreen oil (1 part cayenne powder to 3 parts wintergreen oil) can help relieve muscle pain. Cayenne contains capsaicin, a substance that appears to inhibit the release of neurotransmitters responsible for communicating pain sensations. Cayenne can also be taken orally, in capsule form. Unfortunately, it is unclear if these herbal medications are effective because there is an absence of randomised double-blind and controlled studies.

Overall, the evidence for dietary modifications is limited and they can not be recommended as effective treatments for FM based on current evidence. Furthermore, because benefits are supposed to last only as long as the diet is followed, a major caveat is the difficulty of adhering to restricted diets indefinitely [71].

MANUAL AND MANIPULATIVE TECHNIQUE

These techniques involve soft tissue massage therapy, stretching and chiropractic and osteopathic manipulation. They are intended to reduce pain, enhance muscle and joint mobility, strength, proprioceptive training and to limit further joint and muscle damage. Fiechtner and Brodeur have reviewed studies evaluating these techniques. The safety of these techniques has been questioned, particularly for spinal manipulations with regard to spinal cord damage. A major criticism of these techniques is that, although, they may be effective and safe in diminishing pain and increasing mobility, the effects may be short-lived [17].

MASSAGE

Massage is one of the oldest healing therapies having been used for thousands of years in Egypt and China [87]. Although considered a complementary therapy in the United States, it is more popular in Europe. Patients typically rate the experience as satisfying or pleasant, which may be the reason why it is so popular, particularly among those with FM. One article rated massage as the second best alternative therapy for patients with FM [20, 21].

It is used to treat a wide range of conditions from specific physical problems and injuries to generalised, management of stress and tension. It is thought to influence various bodily systems, including blood supply to the tissues, energy levels, elimination of toxic waste stored in muscles, functioning of the immune system, posture and flexibility and blood pressure.

Massage is the application of systematic manipulation to the soft tissue of the body for therapeutic purposes. Massage is thought to have both physiological and psychological components, the effects of which are highly interactive. Physiological effect can be either mechanical or reflexive in nature. There are no studies evaluating the effectiveness in FM. Pioro-Boisset and Esdaile [21] report that patients with FM who pursued alternative medical interventions expressed the most satisfaction with massage therapy when a more

toned down and less rigorous massage was used. However, massage use alone does not promote self efficacy or increase activity and should rarely be prescribed independently of other therapeutic interventions. In the current socioeconomic climate surrounding health care systems the continued use of massage will be threatened unless both therapeutic efficacy and cost effectiveness can be demonstrated [88].

Although massage featured in three studies [89-91] in only two [90, 92] were its effects able to be isolated. The type of massage, however, differed across these two studies. In the study by Brattberg [90] connective tissue massage was provided with demonstrable effect on three outcomes. This type of massage seeks to promote arterial circulation. In contrast, Haanen *et al.* [91] used a form massage aimed at promoting relaxation with no demonstrable effect, relative to hypnotherapy [93].

Lymph drainage can be very beneficial as it helps to detoxify muscle and body tissue. Asplund [94] studied 17 women with long standing FM in a 4-week period, an open-labeled trial with manual lymph drainage therapy. Author suggests that manual lymph drainage therapy can be an alternative and safe treatment for symptom relief in patients with FM.

HOMEOPATHY

Homeopathy is a system of medicine that enjoys worldwide use. It is based on the principals of similars. Thus, homeopathy postulates that a substance that can induce and cause symptoms in a healthy person could also reserve those symptoms if they occurred during illness when such a substance is used to promote self-healing [95, 96]. The substances used are diluted past Avorado's number and critics have therefore dismissed any residual biologic activity. In their review, Merrell and Shalts [97] confirmed the difficulties assessing homeopathic studies. Recent analyses with double-blind, placebo-controlled design reveal statistical improvement using homeopathy. Obviously, more rigorous studies with strong methodologic design are required. The debate regarding homeopathy continues in conventional medical circles, but the general public has been enthusiastic in its support [82].

Homeopathy had its origins in the late 1800s. Its principles are based on two beliefs, one being that a condition is treated effectively by an agent that produces similar symptoms and the other is that these agents can retain their biologic activity when repeatedly diluted to their lowest possible concentrations [99]. The sources of these agents are often plants or roots; the compounds created from these agents are diluted to the point that there is no perceivable risk of significant pharmacologic activity or side effects [17].

There is nothing in the medical literature addressing the efficacy of safety of these substances in treating chronic pain and clinical literature is lacking in regard to homeopathic preparations. Jonas *et al.* [100] performed a meta-analysis of homeopathic trials for rheumatic diseases. Included in the analysis were one trial of patients with FM and one trial of patients with myalgia [17].

In a study by Gamber *et al.* [101] found osteopathic manipulative treatment combined with standard medical care

was more efficacious for treating FM than standard care alone. This finding needs to be replicated to determine if cost savings are incurred when treatments for FM incorporate nonpharmacologic approaches such as osteopathic manipulative treatment [102].

AYURVEDIC

Ayurvedic is an ancient Indian Medical system using herbal and mineral compounds to promote health. Dietary regimens, physical therapy and surgery in association with yoga attempt to be establish an harmony within the body. The basic philosophy is similar to Chinese traditional medicine, linking the universe with human and plant energy. Ayurvedic also uses Marma pressure on specific sensitive regions and therapy can be either palliative or purifying with eradication of disease. Some of the drugs used are similar to homeopathy [98].

CHIROPRACTIC CARE

Surveys of FM patients indicate that 19-49% seek chiropractic treatment [21, 103, 104], with 46% reporting symptom relief [104]. Chiropractic interventions are thought to correct misalignments and manipulate soft tissues to relieve pain in the body part manipulated as well as are unrelated areas.

One RCT has investigated the effects of chiropractic care in FM patients. In a crossover design, 19 FM patients were assigned to either a wait-list control or a 4-week chiropractic treatment group [71].

A study of manipulation in FM found significant improvement in pain relief, sleep and reduction in tender points over a 4-week treatment period. Chiropractic seems to be one of the most popular alternative medicine treatments. There is a strong emphasis on homeostasis of the neuromuscular system through manipulation and other techniques. The chiropractic management, consisting of soft-tissue massage, stretching, spinal manipulation and education, administered three or four times per week, did not influence pain, strength, range of motion or disability [23].

Thus, the evidence for a therapeutic benefit of chiropractic treatment is insufficient. Nonetheless, a large, well-designed, randomised placebo-controlled trial is warranted due to the very small sample size and lack of adequate power to detect clinically significant differences in the RCT that has been conducted. Any RCT should follow-up participants in the long-term as a criticism of chiropractic intervention is that the positive effects are short-acting [23].

SUPERFICIAL COLD AND HEAT THERAPY

A high percentage of FM patients indicate that their symptoms were influenced by a number of factors such as cold, repetitive motion, posture and heat [105]. Superficial cold reduces blood flow, decreases metabolic activities and lessens muscle tone. Superficial cold also increases gastrointestinal motility, slows nerve conduction and leads to analgesia. Cryotherapy can be used in association with exercise and other therapy approaches [88].

Whole body cryotherapy with temperatures as low as -175°C influences cortisol concentration [106]. Proposed

mechanisms of the effects include: an increase of serum dopamine concentration and a decrease of beta-endorphin, serotonin and inhibition of the C-fiber system and muscle relaxation [107]. Samborski and Startz [108] compared in a crossover study the short term effect of whole body cryotherapy and hot mud pack in patients with fibromyalgia. The authors found an increase of the pressure pain threshold, a decrease of the number of tender points as well as a positive -150°C in a cryo-chamber in 17 patients with FM. In contrast, only the pain scores showed a slight improvement after application of hot mud packs. The authors conclude that whole body cryotherapy has a similar value in the therapy of FM as heat modalities. Similar results were obtained by Gutenbrunner and Englert [107] who compared a natural sulfur bath and cryo-chamber exposition (-67°C) in 17 FM patients. However, there are number of questions in these studies which need to be addressed in further trials: what is the optimal duration and the number of repeated expositions at which temperature? Is there any long term effect? Until then there is not sufficient evidence to support the routine use of whole body cryotherapy in the therapy for FM. However, this modality may serve as an useful adjunct in a comprehensive treatment program [88].

The basic therapeutic use of heat is based on analgesia, hyperemia, local and systemic hyperthermia and reduction of muscle tone. There a number different forms of applying heat (i.e. hot packs, heat lamps; hydrotherapy in different forms; hot baths, contrast baths, sauna, warm springs and peloid baths). Piso and Gutenbrunner [109] reported significant increase of the pressure pain threshold at the ACR tender points after 12 sauna sessions over a period of 6 weeks. Yurtkuran and Celiktas [110] investigated the effect of a series of 10 balneotherapy session of 20 minutes duration in a 37°C warm therapeutic pool over a period of 2 weeks. The authors found a significant reduction in pain ratings and an increase in the pressure pain threshold. This effect was sustained even 6 weeks after the end of the treatment. One RCT examined the effects of sulphur bath balneotherapy on 48 patients with FM. Subjects at a Dead Sea spa were randomly assigned to receive daily 20-min sulphur baths with water from the Dead Sea or no treatment over a 10-day period. Blinded assessments revealed that although both groups improved on almost all areas measured, the improvements were particularly remarkable in the treatment group and lasted for at least 3 months. Of note, the effects of hot water baths alone were not considered, so future RCTs should include such a placebo condition [111]. Samborski and Startz [108], however, reported an increase in pain reported by FM patients after therapy with hot mud packs [88].

The physical therapist can instruct patients in the use of heat at home to increase local blood flow and to decrease muscle tension. The physical therapist can also instruct patients in proper use of cold modalities (ice packs, cool baths, contrast baths) to reduce pain in local areas where needed [112]. Hot baths or showers or other heat modalities may also be useful in facilitating stretching or reducing the muscle tone which tend to be increased in a cold environment especially in FM patients. But the clinician should be aware that some patients might develop more pain after the

use of a hot bath depending on the temperature and the duration of administration [109].

OTHER INTERVENTIONS

In their study Huuhka *et al.* [113] investigated the effect of electroconvulsive therapy on depression and other symptoms of FM in a prospective, 3-month trial in 13 patients with FM and concomitant depression. Authors concluded that electroconvulsive therapy is a safe and effective treatment for depression in FM patients, but has no effect on the pain or other physical symptoms of these patients.

Hypnotherapy may be worth considering in selected patients. One controlled study found it superior to physical therapy in patients with FM with refractory symptoms and greater subjective suffering [1]. Haanen *et al.* [91] showed significant improvements on five outcome measures in a group treated with hypnotherapy compared with a physical therapy program. In the Haanen *et al.* [91] study physical therapy refers to massage and relaxation, whereas in the study by Burckhardt *et al.* [114] it is referred to as comprising aerobic exercise. A similar situation occurs in the study by Blunt *et al.* [89], where chiropractic treatment comprised massage, manipulation, exercise and education and may thus be better classed as a combination therapy [93].

In addition, a number of studies examined what might be termed "unorthodox" interventions for the treatment of FM: meditation [115], treatment with staphylococcus toxoid [116], music vibration therapy [117], magnetic therapy [118] and laser therapy [119, 120]. These are generally safe and relatively inexpensive interventions and the limited studies to date suggest a benefit. It is important that conventional therapies for fibromyalgia be given an opportunity to help the patient. Where evidence is lacking, the cost and potential harm of alternative therapy must be balanced against uncertain efficacy.

CONCLUSIONS

Alternative medicine is meeting with a great deal of enthusiasm with the public and the slowly gaining acceptance in the scientific community. The FDA, a major skeptic concerning CAM therapies, is now slowly recognising the merits of some CAM therapy agents. Chiropractic and massage are now well accepted worldwide. Future strictly designed studies using different modalities will allow data generation and should provide patients with greater opportunities for relief and reduction in chronic pain [98]. In the review by Sim and Adams, authors suggested that the number of studies evaluating specific interventions seems insufficient for meaningful conclusions to be derived. Nonetheless, studies that used a combination approach showed greater improvements than those comparing a single intervention. Given the multidimensional nature of FM, it is suggested that management of this patient group should be undertaken by a multidisciplinary team or at least by practitioners whose training and experience allows them to engage effectively with the range of features encountered in FM, thereby facilitating a coordinated and comprehensive approach to management [93].

A discussion of the integration of CAM into clinical practice is beyond the scope of this chapter. Nevertheless, although each clinical situation is unique, a few generalisations are in order. First, when integrating CAM into clinical practice, it is important to maintain an open mind towards interventions with no known biomedical mechanism, particularly because many traditional interventions are ineffective for FM. Second, because it can be difficult to evaluate the quality of CAM providers, having a trusted referral source of obtaining knowledge and training on CAM techniques is essential. Third, monitoring of the FM patient's symptoms and status is important. Uncritical acceptance of CAM modalities in the absence of benefit can lead to long-term use and expense. Finally, clinicians should be aware of the adverse effects of CAM interventions used by their FM patients and those with unwanted effects should be avoided [23]. Once CAM therapies have been better evaluated for safety and long-term efficacy in randomised, placebo-controlled trials, they may prove to be beneficial in treatments for FM. It would then be important to assess studies assessing cost-benefit analyses comparing conventional therapies and CAM.

ABBREVIATIONS

FM	=	Fibromyalgia Syndrome
CAM	=	Complementary or alternative medical
NIH	=	The National Institutes of Health
RCTs	=	Randomised controlled trials
5-HTP	=	5-Hydroxytryptophan
SSRIs	=	Selective serotonin reuptake inhibitors
MAOIs	=	Monoamine oxidase inhibitors
CFS	=	Chronic fatigue syndrome
DHEAS	=	Dehydroepiandrosterone sulphate
NADH	=	Nicotinamide adenine dehydrogenase
SAM or SAM-e	=	S-adenosylmethionine

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