



Is complementary and alternative medicine in multiple sclerosis evidence based?

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ABSTRACT – The use of complementary and alternative medicine (CAM) is common in multiple sclerosis (MS). It includes approaches to MS that are not generally considered as part of conventional medicine. There is very limited research evaluating the safety and effectiveness of CAM in MS. CAM therapies in MS exhibit a broad range of risk-benefit profiles; some of these therapies are low risk and possibly beneficial, whereas others are ineffective, dangerous, or unstudied. However, in recent years, much effort has been invested in research in this very important area. Health professionals who provide objective, evidence based and practical information about the risks and benefits of CAM therapies may improve the quality of care for those with MS.

Key words: alternative therapy, complementary therapy, multiple sclerosis

INTRODUCTION

Multiple sclerosis (MS) is a chronic, often disabling disease, which affects mainly young people. Given the fact that the etiology and pathogenesis of MS are not completely understood, conventional therapy is more or less effective in individual patients, and there are limitations in terms of high prices, side effects, and so far, no proven efficacy in primary progressive form of the disease. These are the reasons why a large number of MS patients use complementary and alternative medicine (CAM) despite an approved and registered effective conventional therapy. CAM is growing in popularity and prevalence, but the problem is that patients mostly use various types of CAM therapies with-

out consulting a neurologist. Due to the insufficient information because of a small number of randomized controlled clinical trials of CAM therapies in MS and an even smaller number of those that have proven their effectiveness, the uncontrolled use of CAM therapies in MS is not safe and may be harmful (1). Despite polarization of attitudes among neurologists about CAM therapies in MS, on counseling patients are required to follow only evidence based facts. Some forms of therapy are promising, others are ineffective and potentially harmful, and most of them require randomized controlled clinical trials.

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DEFINITION OF COMPLEMENTARY AND ALTERNATIVE MEDICINE

The National Center for Complementary and Alternative Medicine (NCCAM), which was established in 1998 by the US Congress as a new institute of the National Institutes of Health (NIH), defines CAM as "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine" (2). Complementary is defined as a pool of all therapeutic approaches that are used together with and alternative instead of evidence based medicine (EBM). The NCCAM classifies CAM into five categories (2):

- 1) Biological-based therapies: natural and biologically based products, practices and interventions, e.g., herbs, supplements, diet therapy;
- 2) Mind-body therapies: behavioral, social, psychological and spiritual approaches to health, e.g., yoga, meditation, hypnosis;
- 3) Manipulative and body-based systems: systems based on manipulation and/or movement of the body, e.g., massage, reflexology, chiropractic, osteopathic manipulative treatment;
- 4) Energy therapies: systems that use energy fields in and around the body, e.g., therapeutic touch, Reiki; and
- 5) Alternative medical systems, e.g., homeopathy, naturopathy, traditional Chinese medicine-acupuncture.

FREQUENCY AND FACTORS INFLUENCING THE UTILIZATION OF CAM

There have been a number of studies reporting the prevalence of CAM use by MS patients, and the range of prevalence is 33%-70% (3-5). The age, duration of illness and severity of MS influence CAM utilization. It seems that MS patients are turning towards CAM when the disease proceeds and conventional medication is less effective (6). Patient characteristics that are predictive of CAM use in MS are reported to be similar to those reported in the general population and include female sex, high education and patient reports of poor health status (7-9).

DIETARY SUPPLEMENTS IN MULTIPLE SCLEROSIS

VITAMIN D

Vitamin D is a group of fat-soluble prohormones, the two major forms of which are vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol). Vitamin D regulates immune function (10-13). A latitude gradient in the prevalence of MS was recognized first in the 1920s (14,15) with the MS prevalence increasing with distance from the equator in both the northern and southern hemispheres. The latitude gradient might be caused by reduction in exposure to UV radiation and thus lower vitamin D status as latitude increases. A strong correlation with ambient UV radiation levels during the first trimester of pregnancy suggests that this pattern could be linked to reduced maternal vitamin D status in winter as a result of lower ambient UV radiation during this time and people with MS are more likely to be born in late spring in both the southern (November) and northern (May) hemispheres compared to the general population (16,17). Epidemiologic studies have found that low vitamin D intake and low serum vitamin D levels may increase the risk of MS (18,19).

Despite the accumulating evidence to support a role of vitamin D in MS, only a few studies have directly measured the effect of vitamin D supplements on MS activity, but the interest is growing after publications of recent study results.

A study of the safety and efficacy of vitamin D₃ as an add-on therapy to interferon β -1b (IFN β) in MS patients showed that once weekly dose of 20,000 IU (500 μ g) of vitamin D₃ as add-on treatment to IFN β reduces magnetic resonance imaging (MRI) disease activity in MS. Patients in the vitamin D group showed fewer new T₂ lesions ($p=0.286$) and a significantly lower number of T₁ enhancing lesions ($p=0.004$), as well as a tendency to reduced disability accumulation ($p=0.071$) and improved timed tandem walk ($p=0.076$) (20).

A recent study has reported that every 50 nmol/L increment in average serum 25-hydroxyvitamin D levels observed at baseline translated into a 57% lower rate of new active MS defining lesions ($p=0.0009$). It was found that higher baseline differences in 25-hydroxyvitamin D levels were associated with a 57% lower relapse rate ($p=0.03$), 25% lower increase in T₂ lesion volume ($p=0.00004$), 0.41% lower yearly loss in brain volume ($p=0.07$) from 12 to 60 months and fewer active lesions on

MRI (hazard ratio 0.73, $p=0.002$). Lower disability demonstrated by small reduction in the Expanded Disability Status Scale (EDSS) score (mean difference 0.17 points, $p=0.004$) was also found (21).

Daily supplement of 4000 IU of vitamin D in late fall and winter and 1000-2000 IU in spring and summer seems warranted for people who do not get a lot of exposure to sunlight in summer months. It is considered that a dose of 4000 IU is safe and because of the potential adverse effect on kidney, serum calcium levels and kidney function needs to be controlled from time to time. However, a number of studies looking at the effect and optimum doses of vitamin D supplements in MS are currently underway or planned: vitamin D as an add-on to injectable disease modifying treatments (SOLAR study (22), CHOLINE trial (23)), vitamin D as a treatment to reduce relapse rate in relapsing remitting MS (EVIDIMS study (24)) or to prevent the diagnosis of MS following the person's presentation with the first episode of symptoms – people with clinically isolated syndrome (PREVANZ study (25)).

ANTIOXIDANTS

Theoretically, antioxidants should be beneficial for MS because they neutralize free radicals, which may be involved in myelin and axonal damage (26). However, antioxidants stimulate the immune system, which could offset any benefits and even be harmful (27). Nevertheless, various antioxidants, including lipoic acid and the combination of selenium and vitamins C and E, have been well tolerated in small, short-term studies in MS. Whether antioxidants have disease-modifying effects has not been verified. Association of the intake of carotenoids, vitamin C and vitamin E with the risk of MS was assessed prospectively in two cohorts of women, one including 81,683 women (Nurses' Health Study I) followed-up for 12 years, and the other one (Nurses' Health Study II) including 95,056 women followed-up for 6 years (28). The findings in this study do not support the hypotheses relating higher intakes of dietary carotenoids, vitamin C and vitamin E to a reduced risk of MS in women.

Another study examined alpha-tocopherol concentrations and their relationship to disease activity in Norwegian MS patients. The prospective cohort study included 88 relapsing-remitting MS (RRMS) patients followed-up for two years, originally included in a randomized placebo-controlled trial of omega-3 fatty acids (the OFAMS study), be-

fore and during treatment with IFNB (29). During treatment with IFNB, increasing serum concentrations of alpha-tocopherol were associated with reduced odds for MRI disease activity in RRMS patients. New T1 gadolinium enhancing lesions two months later were reduced by 65.4% ($p=0.019$), and new T2 lesions by 61.0% ($p=0.023$).

Despite promising results in animal models, there is limited and conflicting evidence for the potential therapeutic effects of antioxidants such as vitamins C and E in treating MS.

VITAMIN B

Studies have reported a significantly higher rate of vitamin B12 deficiency in people with MS than in people without MS, which is suspected to be due to the problems with binding and transport of vitamin B12 (30). People with vitamin B12 deficiency have destruction of both the myelin and the underlying axon, which can cause MS-like symptoms. There are no large studies using vitamin B12 in people with MS. A placebo-controlled study of injected vitamin B12 (combined with lofepramine and l-phenylalanine) showed small (but statistically nonsignificant) beneficial effects in the treatment group (31).

LOW FAT DIET

Fat is an essential nutrient for the body. While some fats are deemed 'bad', others, such as polyunsaturated fats, actually help lower cholesterol and the risk of heart disease. These polyunsaturated fats were the focus of MS studies with some evidence pointing to effect on inflammation and benefits for RRMS (32). The Swank diet is a low saturated fat diet proposed for the treatment of MS and introduced by Roy L. Swank (33). There is no medical evidence to support the claims made for the Swank diet because his work was methodologically insufficient (34).

The most common dietary interventions are supplementation with polyunsaturated fatty acids (PUFA), omega-3 and omega-6 fatty acids. Omega-3 PUFAs (e.g., α -linolenic acid) are primarily derived from fish oils, whereas omega-6 PUFAs (e.g., linoleic acid) are obtained from plant sources, including sunflower, safflower, corn, wheat germ, soybean oils and evening primrose oil. In 2012, the Cochrane Collaboration conducted a systematic review into dietary therapies for MS (35). Six randomized controlled trials that investigated PUFAs in a total of 794 randomized patients met the

inclusion criteria in terms of methodological quality. PUFAs did not have a significant effect on disease progression at 24 months. Neither omega-6 fatty acids nor omega-3 fatty acids showed any benefit in MS patients. Slight potential benefits in relapse outcomes were associated with omega-6 fatty acids in some studies, however, these findings were limited by the reduced validity of the endpoints, and the trial quality was rated as poor.

GINSENG

Ginseng is one of the herbal medicines possessing antifatigue properties, and its administration in MS for such a purpose has been evaluated. A randomized placebo controlled double blind study of ginseng efficacy and safety in the treatment of fatigue and quality of life of MS patients was conducted recently. This study has indicated that 3-month ginseng treatment can reduce fatigue and has a significant positive effect on the quality of life (36). Further studies are needed to confirm the efficacy of ginseng in this field.

Ginkgo biloba

Ginkgo biloba is an herb and popular supplement that some believe can help in MS symptoms, especially cognitive functions. A new randomized placebo controlled trial has provided Class I evidence that treatment with ginkgo 120 mg twice a day for 12 weeks does not improve cognitive performance in people with MS (37).

CARNITINE

Some research suggests that acetyl-L-carnitine can improve fatigue associated with MS. Acetyl-L-carnitine is a form of L-carnitine, an amino acid that is found in nearly all cells of the body and plays a critical role in the production of energy from long-chain fatty acids. In addition, it increases the activity of certain nerve cells in the central nervous system. A recent systematic review published in 2012 concludes that there is still insufficient evidence that carnitine offers therapeutic advantage over placebo or other medications (38).

CRANBERRY

Bladder dysfunction occurs at some time in most MS patients and these patients are prone to recurrent urinary tract infections. Cranberry has been traditionally used for the treatment and prophylaxis

of urinary tract infections. A recent trial has shown that taking cranberry extract *versus* placebo twice a day did not prevent the occurrence of urinary tract infections in MS patients with urinary disorders (39).

CANNABINOIDS

Multiple sclerosis is associated with chronic symptoms, including muscle stiffness, spasms, pain and insomnia. The Cannabinoids in Multiple Sclerosis (CAMS) study included 657 people with MS. Study subjects received either cannabis oil, synthetic tetrahydrocannabinol (THC, active ingredient in marijuana) or inactive placebo for 13 weeks. Following the treatment period, those on active treatment had no objective improvement in muscle spasticity as measured by a standardized scale. However, treated subjects reported improvements in walking speed, spasticity, muscle spasms, sleep and pain (40). To test the effectiveness and long term safety of cannabinoids in MS, in the CAMS study follow up (41), a total of 630 MS patients with muscle spasticity were randomized to receive oral Δ^9 -tetrahydrocannabinol (Δ^9 -THC), cannabis extract, or placebo for 12 months and showed evidence of a small treatment effect on muscle spasticity as measured by Ashworth score and on some aspects of disability. These data provide limited evidence for a longer term treatment effect of cannabinoids. A long term placebo controlled study is now needed to establish whether cannabinoids may have a role beyond symptom amelioration in MS.

Results of the Multiple Sclerosis and Extract of Cannabis (MUSEC) double blind, placebo controlled, phase III study had a screening period with a 2-week dose titration phase from 5 mg to a maximum of 25 mg of THC daily and a 10-week maintenance phase (42). The rate of relief from muscle stiffness after 12 weeks was almost twice as high with cannabis extract as with placebo. Laboratory evidence indicated that cannabinoids might have a neuroprotective action. The CUPID study examined the effect of oral dronabinol (Δ^9 -THC) on slowing the course of progressive MS. The results showed that dronabinol had no overall effect on the progression of MS in the progressive phase (43).

LOW-DOSE NALTREXONE (LDN)

Naltrexone is approved in the United States for the treatment of alcohol and opioid addictions. The postulated mechanism of naltrexone is mediating

prevention of oxidative damage to neuronal cells and oligodendrocytes (44). A sixth-month phase II multicenter-pilot trial with a low dose of the opiate antagonist naltrexone (LDN) was carried out in 40 patients with primary progressive multiple sclerosis (PPMS). A significant reduction of spasticity was measured at the end of the trial (45).

GENERAL NUTRITION IN MULTIPLE SCLEROSIS

Maintenance of general good health is very important for persons with MS or any chronic disorder. Obesity and malnutrition are frequently observed in MS. Weight gain has been related to reduced mobility and fatigue. Weight loss has been related to dysphagia, reduced cognition and poor appetite. In patients with MS, malnutrition has been associated with impairment of the immune system, which can exacerbate the MS symptoms. These findings emphasize the need of nutritional support in MS patients. A number of nutritional screening tools can be helpful for nutritional status screening, for instance, the Subjective Global Assessment (SGA), Mini Nutritional Assessment (MNA), Malnutrition Universal Screening Tool (MUST), and Nutritional Risk Screening 2002 (NRS 2002) (46). These screening tools combine a number of questions with or without anthropometric measurements and helps identify patients at risk of malnutrition early. It is important to obtain thorough history, anthropometric measures and laboratory tests such as complete blood count (hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, lymphocytes) and serum albumin or prealbumin concentration, before initiation of nutrition therapy. In patients with good nutritional status, a 'healthy diet' is recommended, which is in concordance with current healthy eating recommendations.

CAUTION WITH HERBS

Herbs should be used with caution by people with MS. There are many herbs with no well-documented benefits, which may potentially worsen MS or interact with MS medications. There are many immunostimulatory herbs including alfalfa, arnica, astragalus, boneset, calendula, cat's claw, celandine, drosera, echinacea, garlic, Asian and Siberian ginseng, licorice, mistletoe, reishi mushroom, saw palmetto, shiitake mushroom, and stinging nettle, which needs to be avoided because of the already overactive immune system in MS (47).

CYP3A4 liver enzymes play a major role in drug breakdown and detoxification by the liver. Echinacea, milk thistle and chamomile all interfere with this enzyme and thus increase or decrease the effects of some medications, leading to increased side effects or reduced benefit from taking these drugs. Echinacea can decrease the efficacy of immunosuppressant and increase toxicity of corticosteroids, ephedra can increase toxicity of sympathomimetics and decrease efficacy of corticosteroids, St John's wort decreases the efficacy of tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), benzodiazepines and cyclophosphamides, and kava and yeast red rice increase the toxicity of benzodiazepines (48). Dosing is an important factor with vitamin or mineral supplements. Vitamins or minerals taken at a certain dose may be beneficial. However, taken at a higher dose, the same vitamin or mineral may be harmful.

OTHER CAM THERAPIES

COOLING THERAPY

Cooling demyelinated nerves can reduce conduction block, potentially improving symptoms of MS. The therapeutic effects of cooling in patients with MS have not been convincingly demonstrated because prior studies were limited by uncontrolled designs, non-blinded evaluations, reliance on subjective outcome measures, and small sample sizes. Patients reported less fatigue during the month of daily cooling, concurrently on the Rochester Fatigue Diary and retrospectively on the Modified Fatigue Impact Scale. Cooling therapy was associated with objectively measurable but modest improvements in motor and visual function as well as persistent subjective benefits (49).

HYPERBARIC OXYGEN THERAPY

It has been suggested that Hyperbaric Oxygen Therapy (HBO(2)T) may slow or reverse the progress of the disease. In 2004, the Cochrane Collaboration conducted a systematic review of clinical evidence for the use of HBO(2)T in the treatment of MS (50). In 2010, a literature review appeared on HBO(2)T, focused on the interaction of hyperbaric oxygenation and MS. There were 12 randomized studies in the field, all of which were performed between 1983 and 1987. A meta-analysis of this evidence suggests that there is no clinically significant benefit from the administration of HBO(2)T. No

plausible benefit of HBO(2)T on the clinical course of MS was identified in this review (51). At this time, the routine treatment of MS with HBO(2)T is not recommended.

BEE VENOM THERAPY

Bee venom contains proteins that affect the immune system. However, the exact mechanism remains unknown. This therapy can produce rare but potentially serious adverse effects, including severe allergic reactions and death. A recent clinical trial demonstrated that bee venom was no better than placebo for treating MS (52).

MIND-BODY INTERVENTIONS

The evidence for mind-body medicine (yoga, mindfulness, relaxation and biofeedback) in MS is limited. Mind-body modalities appear safe, can be prescribed as an adjunct to conventional care (53), and can be effective for treating common MS symptoms, including fatigue, anxiety, depression, incontinence and quality of life. The placebo effect demonstrates the powerful influence that the mind may have over the body (or brain). This mind-body effect may be underutilized in conventional medicine and may be an important component of some forms of CAM.

MANIPULATIVE AND BODY BASED THERAPY

Manipulative and body-based therapy and psychological counseling seem to improve depression, anxiety and self-esteem. Massage and bodywork are among alternatives recommended by the National Multiple Sclerosis Society, but research in these areas is minimal. In a small study of MS patients, it was found that massage lowered anxiety, improved depressed mood, and increased self-esteem and body image (54). Another study in 53 MS patients showed the effectiveness of reflexology for improving spasticity, paresthesias (numbing and tingling sensations), and urinary symptoms (55). A study of Feldenkrais bodywork in 20 MS patients showed benefits of decreased perceived stress and lowered anxiety, but no improvement in physical functioning (56). Aromatherapy massage showed improvements in sleep, mobility and sense of well-being, but yet there is no comprehensive review of evidence for MS. There is no evidence that chiropractic can alter the underlying disease process or the disease course in MS. While there is anecdotal

evidence that people with MS have experienced some symptom relief, there are no controlled clinical trials demonstrating treatment safety or efficacy in MS (57). In a pilot study, osteopathic manipulative treatment combined with maximal-effort exercise showed beneficial effects in the activities of daily living in female patients with MS (58).

ENERGY THERAPY

Magnetic field therapy and neural therapy appear to have a short-term beneficial effect on the physical symptoms of MS (59).

ALTERNATIVE MEDICAL SYSTEM

Homeopathic substances are mostly natural but there is no evidence that homeopathy can prevent MS progressing or cure the MS symptoms. In a pilot study, naturopathy, stimulation of self-healing capacities of the individual by using clinical nutrition/diet counseling, herbs, nutritional supplements, homeopathy, physical medicine, and psychological counseling combined with usual care for MS showed a trend of improvement in the General Health subscale of the SF-36, Timed Walk and EDSS (60). There is little medical research to back up the claims of any specific benefits of acupuncture in MS. Acupuncture is generally well tolerated and appears to be associated with benefits for a proportion of patients with fatigue who are resistant to conventional drugs such as amantadine (61) and can provide relief of MS-related symptoms like pain, spasticity, fatigue, numbness, tingling, bowel and bladder issues, anxiety and depression.

CONCLUSION

Conservative estimate is that at least one-third of MS patients use CAM therapies. Results from large clinical trials are needed to determine whether vitamin D supplementation and what dosage is a potential treatment for MS. For now, 4000 IU is considered safe with serum calcium and kidney function control. Vitamin B12 did not show benefit in MS treatment. While the majority of MS patients who use CAM report benefit from diet, polyunsaturated fats and antioxidant supplements, these treatments have not been investigated with the rigor required to determine whether or not they are effective. Ginseng extract may reduce fatigue and improve quality of life but further studies are needed to shed light on the efficacy of ginseng in this field. A recent study has shown that *Ginkgo biloba*

does not improve cognitive performance in people with MS. Cannabis may improve spasticity in MS, although most trials show improvements in patient self-report and not in the objective measures of spasticity, and no overall effect on the progression of MS in the progressive phase. A low dose naltrexone may have a positive effect of reducing spasticity but larger trials are needed. Therapeutic effects of cooling in patients with MS have not been convincingly demonstrated, but may have some efficacy in fatigue. Studies have repeatedly demonstrated that hyperbaric oxygen is not an effective treatment for MS. Nutritional support in MS patients is necessary only if the patient has malnutrition, otherwise healthy nutrition is recommended. Herbs should be used with caution by people with MS because some may actually worsen MS or interact with MS medications. Other CAM therapies like manipulative and body-based therapy, mind-body therapies, energy therapy and alternative medical systems can improve some MS symptoms like fatigue, depression, anxiety, sleep disorders, stress, pain, and improve the quality of life with limited evidence. It is very important to follow evidence based facts when choosing complementary and alternative treatments, but also to be aware of the placebo or nocebo effects and the costs of that kind of therapy.

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Je li komplementarna i alternativna terapija u multiploj sklerozi zasnovana na dokazima?

SAŽETAK – Primjena komplementarne i alternativne terapije je učestala u bolesnika s multiplom sklerozom. To uključuje terapiju koja nije dio konvencionalne medicine. Istraživanja sigurnosti i učinkovitosti komplementarne i alternativne terapije u multiploj sklerozi su vrlo ograničena. Ako se u obzir uzmu rizici i dobit pojedinih metoda komplementarne i alternativne medicine u multiploj sklerozi, postoji širok raspon: neke su moguće korisne, druge su neučinkovite i potencijalno štetne, a najveći broj zahtijeva randomizirana kontrolirana klinička ispitivanja. Međutim, u posljednjih nekoliko godina je mnogo truda uloženo u istraživanja u ovom važnom području. Zdravstveni radnici koji pružaju objektivne, znanstveno utemeljene i praktične informacije o rizicima i prednostima komplementarne i alternativne terapije mogu poboljšati kvalitetu skrbi za osobe s multiplom sklerozom.

Ključne riječi: alternativna terapija, komplementarna terapija, multipla skleroza