

Alternative Medicine and Multiple Sclerosis

An Objective Review From an American Perspective

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Abstract

The use of complementary and alternative medicine (CAM), or unconventional medicine, may be challenging for health care providers in the United States. There are several definitions of CAM, and therapies that are considered alternative in one country may be conventional in other countries. Unconventional medical practices may be used instead of, or in addition to, conventional medical therapy. It may be difficult for people with multiple sclerosis (MS) to obtain reliable MS-relevant CAM information, and there may be conflicts between the values of patients and those of health care providers. These issues may create problems in the clinical decision-making process. The relevance to MS of some commonly used CAM therapies is discussed: herbal medicine, vitamins and minerals, marijuana, and a histamine and caffeine transdermal gel patch. Current information about the efficacy and safety of CAM therapies is extremely variable. Some therapies appear promising, others are unsafe or ineffective, and nearly all need to be studied further.

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In the United States, complementary and alternative medicine (CAM) are increasing in popularity¹ and appears to be widely used by multiple sclerosis (MS) patients.^{2,3} However, there are limitations to the MS-relevant CAM information that is currently available. In addition, addressing issues raised by patients interested in CAM may be particularly challenging for mainstream health care professionals.

This review article discusses CAM issues that are important to health professionals who are specialized in MS care. CAM therapy is defined, and the demographics of CAM users are discussed. The clinical decision-making process is considered as it applies specifically to MS patients. Differing and potentially clashing value systems of MS patients and health care providers are highlighted. Information provided in this article is limited to CAM therapies and selected MS-relevant information. More detailed

information may be found in the literature about CAM,⁴⁻⁷ CAM and MS,⁸ and dietary supplements.⁹⁻¹⁶

Definition

Controversy and confusion surround alternative medicine, and even the definition itself is controversial. Alternative medicine (also known as unconventional or unorthodox medicine) is often defined by what it is not: It generally refers to medical therapies that typically are not taught in medical schools or are not readily available in community hospitals.¹ According to this definition, the term means one thing in the United States, another in Germany, and something completely different in China. In the United States, the definition is a "moving target," since increasingly alternative medicine therapies are provided in hospitals and alternative medicine courses are offered in medical schools.¹⁷ To define alternative medicine by what it is, the National Institutes of Health (NIH) has developed a classification system for alternative medicine (Table 1).¹⁸

Table 1. Classification Scheme for CAM.

Category	Examples
Biologically based therapies	Herbs, diets, bee venom therapy
Alternative medical systems	Traditional Chinese medicine, homeopathy
Mind-body interventions	Meditation, prayer
Manipulative and body-based methods	Chiropractic medicine, massage
Energy therapies	Therapeutic touch, magnets

Unconventional medical therapies may be used in an alternative or complementary manner. Alternative use means that they are used instead of conventional medicine, while complementary use indicates that they are used in conjunction with conventional medicine. A broad term that encompasses both practices is complementary and alternative medicine (CAM).

Demographics of CAM Use

There have been many studies of CAM use in the general population. Much of the recent interest in CAM was generated by a US study conducted in 1990 and reported in 1993.¹⁹ It found that 34% of the general population used some form of CAM and that \$14 billion was spent annually on CAM professional services. A follow-up study conducted in 1997 and reported in 1998 found an increased prevalence of CAM use to 42% and an increased annual expenditure for CAM services to \$21 billion.¹ Of possible relevance to the MS population, this study found that CAM use was relatively high in people with chronic conditions, women, and people between the ages of 35 and 49.

Studies of CAM use in MS patients are more limited. A recent survey conducted in

California and Massachusetts found that nearly 60% of people with MS had used CAM; on average, individuals used two or three different forms of CAM.² A preliminary report from a study in British Columbia indicated that 67% of MS patients used CAM.²⁰ A study conducted in Colorado evaluated visits to CAM practitioners (as opposed to CAM use overall). Thirty-three percent of MS patients used CAM practitioners,³ which is approximately 40% greater than the use of CAM practitioners by the general population.¹ It is notable that these studies of CAM showed that the majority of people with MS^{2,3} and the general population¹ use CAM in a complementary manner, ie, in conjunction with conventional medicine.

Clinical Decision Making and CAM

Clinical decision making about any type of medical therapy, whether it is conventional or unconventional, involves two important components: disclosure of information about therapies and evaluation of patients' values regarding therapies.²¹ Most conventional health care providers are familiar with this decision-making process when it involves conventional therapies. However, in the area of CAM, the process may be compromised because of limited information and possible mismatches between patients' values and those of health care providers.

MS-Relevant CAM Information

Unfortunately, there are current limitations on the CAM information available to people with MS. Readily available disease-specific information may be very limited in quantity, inaccurate, or nonexistent. To evaluate the information on MS and CAM in the lay literature, we conducted an informal survey at two large bookstores in Denver, Colorado. Out of 50 popular CAM books, 33 books, or about two thirds, had sections on MS. Most books suggested five or six different therapies, and about 20% recommended 10 or more therapies. In some books, MS was incorrectly defined as a form of muscular dystrophy. In addition, no two books had the same recommendations, and it was rare for the use of any CAM therapy to be discouraged.

In addition to obtaining information from books, patients may seek CAM information from vendors of CAM products (such as supplements), CAM practitioners, or conventional health care providers. Product vendors may exaggerate claims in order to sell products. Both vendors and CAM practitioners may have limited experience and information about a specific disease process such as MS. Finally, almost by definition, most conventional health care providers have little or no knowledge or experience with CAM therapies.

Patient Values and Health Care Provider Values

From a conventional medical perspective, therapies are recommended after they have undergone rigorous clinical testing. Generally, therapies are considered "effective" when they have produced significant positive results in randomized, double-blind, placebo-controlled trials. Therapies that have not satisfied these criteria are considered "not

definitely effective" and are not generally recommended. This leads to a black-and-white view of medical therapies. Such a view ensures high standards of clinical practice and allows only definitely effective therapies to be used on a widespread basis.

However, some patients with chronic diseases such as MS may have a different perspective. Since the conventional disease-modifying and symptomatic therapies for MS may be only partially effective or may produce undesirable side effects, some MS patients may be interested in the possible benefits of CAM therapies. From this perspective, the conventional black-and-white view of medical therapies may be too rigid; some patients may be interested in "gray areas." For example, some people with MS may be interested in low-risk therapies that are scientifically rational (but have not been tested clinically) or in those that have shown promise in limited clinical trials (but have not been proven to be definitely effective).

The professional values established to advance clinical medicine may not match the personal values of individuals who are confronted with a disease that progresses or symptoms that persist despite conventional medical treatment. In some clinical situations, this creates a feeling of two cultures with very different value systems.

These differences in professional and personal standards may be especially apparent when conventional health care providers treat themselves. A survey of faculty members at a major health center in Florida found that 53% of physicians used some form of CAM to treat their own medical conditions.²² Many of the CAM therapies that were used, such as massage and dietary supplements, have not been proven to be effective. In another example, in the late 1990s, the American Heart Association did not officially recommend antioxidant supplementation for heart disease,²³ but a survey at that time showed that 44% of American cardiologists took antioxidant vitamin supplements.²⁴

The schism that can exist between professional and personal standards has been expressed by a patient at our MS center who is a mainstream clinician knowledgeable in basic science, statistics, and clinical trial methodology: "Physicians wisely require powerful evidence of efficacy before prescribing treatments. From a patient perspective, that standard may be too high." He continued, "My standard is this: If a treatment is probably safe, it is worth trying, even if evidence regarding its efficacy is equivocal. To deny patients the opportunity to make that decision is paternalistic and wrong."

A Need for Accurate Information and Understanding of Patient Values

The combination of lack of scientifically sound information for patients and a potential clash of value systems of patients and health care providers can lead to significant problems related to CAM decision making in MS patients. Due to this situation, MS patients may make decisions about CAM therapies with inadequate information and without the input of mainstream health care providers. This creates an unhelpful and potentially dangerous situation for MS patients who are interested in CAM.

Examples of MS-Relevant CAM Therapies

Herbal Medicine

Use of herbal medicine has grown extensively in the United States over the past decade. Americans spend approximately \$5 billion yearly for herbal therapies.²⁵ There are several misconceptions about herbs. One popular misconception is that herbs are "natural" and are not really drugs. In fact, herbs contain many different chemicals, some of which may, like drugs, exert therapeutic effects through receptor-based mechanisms. To emphasize this point, it has been suggested that herbs be referred to as "herbal drugs."

There are many other important issues about herbal therapies. One is that some of the chemicals in herbs may produce adverse effects or interact with prescription medications. Another is concern about the lack of regulations in the US to ensure the quality, safety, and efficacy of herbal preparations.²⁵ These and other issues may be summarized in general considerations and guidelines about herbal therapy (Table 2).

Table 2. Considerations/Guidelines For Using Herbal Medicine.

Herbs are often used as drugs.

Herbs may contain many different chemicals, some of which have not yet been identified or characterized.

These chemicals may be toxic or interact with other drugs.

The composition and quality of herbal preparations are variable.

If herbs are used, they should generally be used for a short time for benign, self-limiting conditions.

Herbs should be avoided by:

- Women who are pregnant or breast-feeding
- People with multiple medical problems
- People who take multiple medications

Herbs should be used with caution, and their use should be discussed with a physician.

Multiple herbal therapies are of potential interest to MS patients. The MS-relevance of four popular herbs will be considered: St. John's wort, valerian, cranberry, and ginkgo biloba

St. John's Wort

Patients with MS may experience depression, and St. John's wort is an herb that appears to have antidepressant effects. Its use dates back to ancient Greece.¹³ Currently, St. John's wort is one of the most popular herbs in the United States, and, in Germany, the use of St. John's wort surpasses that of fluoxetine.²⁶ Many clinical studies indicate that St. John's wort has antidepressant effects²⁶; however, its effectiveness relative to the selective serotonin reuptake inhibitors (SSRIs) is not known. To address this issue, an NIH-funded study is underway to compare St. John's wort and sertraline.

There are several important concerns about the use of St. John's wort in patients with MS. First, depression should not be treated and diagnosed without the involvement of a health care provider. St. John's wort may also produce sedation and photosensitivity.²⁷ It should not be taken with other antidepressant medications.²⁷ Finally, St. John's wort is a cytochrome P450 inducer and thus may interact with multiple medications, some of which may be used by MS patients (including amitriptyline, carbamazepine, imipramine, nortriptyline, phenytoin, phenobarbital, and primidone).²⁸

Valerian

Another popular herb is valerian. Several studies indicate that its root may be an effective treatment for insomnia.¹⁰ The active constituent is not known, but it may, like benzodiazepines, produce its effects through the GABA-ergic system.¹⁰ There have been occasional reports of hepatotoxicity, but this may be due to contaminants and not to valerian itself.¹⁰ Valerian may produce excessive sedation and therefore has the potential to worsen MS fatigue or accentuate the effects of sedating medications (eg, lioresal, tizanidine, and benzodiazepines) and alcohol.¹⁰

Cranberry and Urinary Tract Infections

Cranberry, which may be taken as juice or capsules, has a long history of use as an herbal method to treat or prevent urinary tract infections (UTIs).¹³ This is of potential relevance to MS patients who are prone to UTIs. Two constituents of cranberry, fructose and proanthocyanidins, appear to inhibit bacterial adhesion to the urinary tract.²⁹ Clinical studies indicate that cranberry may be effective for preventing UTIs, but definitive clinical studies have not been done.³⁰ There are no known adverse effects except diarrhea and other gastrointestinal symptoms with daily ingestion of more than 3 to 4 L of cranberry juice.¹⁰ For preventing UTIs, use of cranberry may be reasonable for patients interested in an herbal approach. For treating UTIs, antibiotics should be used, because the effectiveness of cranberry for treatment is unproven and UTIs may cause serious complications in MS patients.

Vitamin C is also sometimes recommended for treating UTIs. The rationale for this approach is that vitamin C may acidify the urine. However, there is not convincing evidence that vitamin C acidifies the urine^{10,31} or that vitamin C is effective for preventing or treating urinary tract infections.³²

Ginkgo Biloba

Ginkgo biloba is an especially popular herb in the United States. Much of its popularity may be due to a frequently cited 1997 article about ginkgo biloba treatment in elderly patients with dementia.³³ Ginkgolides, chemical constituents in ginkgo biloba, have antioxidant properties and also inhibit the effects of platelet activating factor (PAF), which is involved in thrombosis as well as inflammation.³⁴

Due to PAF's role in inflammation and the antagonistic effect of ginkgolides on PAF, there has been interest in the possible use of ginkgo biloba for MS. Animal studies indicate that ginkgo biloba decreases the severity of experimental allergic encephalomyelitis (EAE), the animal model for MS.³⁴ In a small clinical study of 10 MS

patients with exacerbations, eight improved with ginkgo biloba treatment.³⁵ However, a subsequent study of 104 patients found that ginkgo biloba was not effective for treating exacerbations.³⁶ Thus, ginkgo biloba does not appear to be an effective therapy for MS attacks. The effects of ginkgo biloba on disease course and on MS-related cognitive dysfunction have not been studied.

Due to its antiplatelet effects, ginkgo biloba use may occasionally lead to bleeding complications. In case reports, ginkgo biloba has been associated with spontaneous subdural hematomas,³⁷ intracerebral hemorrhage,³⁸ and ocular bleeding.³⁹ Ginkgo biloba should probably be avoided by people who take antiplatelet or anticoagulant medication, people with bleeding disorders, and people undergoing surgery.

Herbs Having Possible Risks

Several herbs are described as "immune-stimulating." One of the most common of these herbs is echinacea, which appears to stimulate macrophages and T cells.⁴⁰ This observation is based on in vitro and ex vivo studies. Whether this effect has clinical relevance for an autoimmune condition such as MS has not been investigated. As a result, using it may be viewed as a theoretical risk. Other herbs that have been shown to stimulate macrophages or T cells in experimental systems include astragalus,^{41,42} Asian ginseng,⁴³ Siberian ginseng,⁴⁴ and garlic.⁴⁵

A number of herbs that are sometimes specifically recommended for MS have been shown to produce toxic effects. Three of these herbs (borage seed oil, chaparral, and comfrey) may be hepatotoxic.¹⁵ Another herb, lobelia, may cause nausea, vomiting, tachycardia, seizures, and encephalopathy.¹⁰

Vitamins and Minerals

There is a great deal of misunderstanding about the use of vitamin and mineral supplements. Some supplements are recommended with little or no justification for MS. They may be recommended in other situations because it is mistakenly assumed that if a deficiency state of a particular vitamin or mineral impairs the function of the immune system or nervous system, an excess of that same vitamin or mineral is beneficial and, therefore, therapeutic for MS. Vitamin B₆ (pyridoxine) is a well-recognized example for which this assumption is incorrect: nervous system injury may occur if the intake of this vitamin is deficient or excessive.¹⁰

Antioxidant Vitamins

The antioxidant vitamins, including vitamins A, C, and E,⁴⁶ are sometimes claimed to be effective therapies for MS. In fact, there is suggestive evidence that free radical-induced oxidative damage is increased in MS patients⁴⁷⁻⁴⁹ and that oxidative damage plays a role in myelin injury⁵⁰ as well as axonal damage.^{51,52} However, antioxidant vitamins also stimulate T cells and macrophages; thus, they also pose a theoretical risk.^{53,54} One 5-week study of 18 people with MS found that supplementation with antioxidants was not associated with worsening of the disease.⁵⁵ However, this study was too limited to provide definitive information about the safety of antioxidants in people with MS. Due to the widespread use of antioxidant supplements and the possible

role of free radicals in MS, further studies of antioxidant safety and efficacy in MS are needed.

Nonvitamin antioxidant supplements are also sometimes recommended for MS. These include alpha lipoic acid, coenzyme Q10, grape seed extract, oligomeric proanthocyanidins (OPC), and Pycnogenol.¹⁰ These supplements are more expensive than antioxidant vitamins, and at this time it has not been established that their antioxidant activity and clinical efficacy are superior to those of antioxidant vitamins. In addition, without more information about the safety and efficacy of antioxidants in MS patients, it is not clear that any antioxidant supplement is safe or effective in this patient population.

Vitamin D and Calcium

Vitamin D and calcium play an important role in maintaining bone density, but unfortunately they may be underutilized in MS patients.⁵⁶ It is increasingly recognized that osteoporosis and osteopenia are not restricted to postmenopausal white women.⁵⁷ MS patients appear to have decreased bone density and increased fracture risk; this situation may be under-recognized.^{56,58-61} Risk factors for osteoporosis that may be common in MS patients include female gender (especially postmenopausal women), immobility, decreased weight, and steroid treatment.⁵⁶ Vitamin D and calcium supplements should be considered for these patients. For those with known osteoporosis, treatment is usually vitamin D and calcium supplements as well as osteoporosis medications and (if appropriate) hormone replacement therapy.⁵⁶

Vitamin D also has immunosuppressant effects.^{62,63} In animals with EAE, vitamin D treatment decreases the severity of the disease.^{64,65} However, in a recent preliminary study of 11 people with MS, a six-month treatment with a vitamin D analogue (19-nor) did not alter the disease course and did not decrease disease activity as assessed by MRI.⁶⁶ Further study of the possible clinical utility of vitamin D in MS is appropriate.

Vitamin B12

Some CAM literature recommends vitamin B12 treatment for MS. This is presumably due to the observation that vitamin B12 deficiency may, like MS, cause damage to the spinal cord and optic nerves and that vitamin B12 levels are decreased in some MS patients.⁶⁷⁻⁶⁹ The current scientific literature does not indicate that widespread use of vitamin B12 is indicated in MS because biologically significant vitamin B12 deficiency is rare in MS patients.⁷⁰ A small subgroup of MS patients have vitamin B12 deficiency, and for those individuals, vitamin B12 treatment is indicated.

Marijuana

In limited studies, smoked marijuana and orally administered cannabinoids have been reported to improve some MS-related symptoms.⁷¹ There were 112 respondents to a survey sent to 230 people with MS who smoke marijuana. ⁷² More than 90% stated that marijuana improved spasticity, pain, tremor, and depression. Several small clinical studies suggest that MS-related spasticity may be decreased with smoked marijuana or

oral cannabinoids.^{71,73,74} In mice with EAE, spasticity and tremor are decreased by cannabinoid agonists and increased by cannabinoid antagonists.⁷⁵ The National Academy of Sciences/Institute of Medicine (NAS/IOM) reviewed the marijuana literature in 1999. They concluded that some studies suggest that marijuana and oral cannabinoids may decrease MS-related spasticity.⁷⁶ To further investigate the area of cannabinoids and MS, large clinical trials of cannabinoid effects on spasticity and pain are under way in the United Kingdom.⁷⁷

In addition to their possible effects on MS symptoms, cannabinoids exert actions on the immune system. Cannabinoid receptors are present on macrophages and T cells, and cannabinoids appear to have an immunosuppressive effect.^{78,79} In EAE, the severity of disease is lessened by treatment with cannabinoids.^{79,80}

It is important to note that there are significant adverse effects associated with smoked marijuana.^{71,74} The risks include cancer, worsening of cardiovascular disease, and poor pregnancy outcomes. MS-relevant neurologic symptoms that may be worsened by marijuana include sedation, incoordination, and gait unsteadiness. The interaction of cannabinoids with prescription medications is poorly understood. The NAS/IOM report concluded that if cannabinoids are to be used as therapeutic agents, delivery methods must be developed that are safer than smoking.⁷⁶

Transdermal Histamine and Caffeine

Recently, there has been interest in a pharmacy-compounded transdermal gel patch containing histamine and caffeine that is claimed to improve multiple MS symptoms.⁸¹ The patch is marketed under the brand name Procarin®. The use of histamine is based on studies in the late 1940s and early 1950s that indicated that intravenous histamine produced multiple beneficial effects in MS patients.^{82,83} However, the significance of these results is not clear, because the studies lacked controls and patients were treated with tubocurarine, received physical therapy, and had allergy testing in addition to histamine therapy.

Published studies of the safety and efficacy of Procarin are limited. A study of 55 MS patients found a six-week treatment with Procarin produced improvement in 67% of patients.⁸⁴ Symptoms that improved included weakness, numbness, gait unsteadiness, pain, fatigue, and depression. This study has significant limitations, including the lack of a control group, the lack of a caffeine-only treatment group, and the use of self-assessment measures.

There are concerns about the safety of Procarin. Histamine may provoke asthmatic attacks. Also, since the effectiveness of Procarin is unproven, patients should not use Procarin instead of conventional therapies, especially disease-modifying medications (interferons and glatiramer acetate). Controlled clinical studies should be conducted to evaluate the safety and effectiveness of this therapy.

Final Considerations

Attitudes about CAM are sometimes polarized: Some individuals and organizations broadly denounce CAM, while others actively promote it. As this article documents, it is

too simplistic to hold generalized positive or negative opinions about CAM. Rather, the available

information about each specific CAM therapy must be considered with regard to a particular disease such as MS. Through this process, it becomes apparent that some CAM therapies are promising, others are unsafe or ineffective, and most need to be studied further. In addition to careful consideration of the available information, the values of patients, which may be very different from those of conventional health care providers, must be assessed and incorporated into the decision-making process about CAM.

Conventional health care providers may interact with patients in several different ways regarding CAM (Table 4). The lowest level of involvement is a "don't ask, don't tell" approach in which CAM therapies are simply not discussed by health care providers or by patients. This approach is not helpful, and it may be dangerous to patients who are considering CAM and want objective information about the possible benefits and risks of specific therapies.

Table 4. Levels of Involvement in CAM.

1. "Don't ask, don't tell"
2. Refer patients to reliable sources of CAM information
3. Provide CAM information to patients
4. Make recommendations about CAM therapies
5. Practice CAM therapies

Beyond this approach, there are progressively increasing levels of involvement for the health care provider. A simple, helpful measure is to refer patients to reliable sources of information, as there are reliable lay sources of information on MS and CAM^{8,85} and on CAM in general.^{5,6,13,86} If interested, conventional health care providers may go one step further by becoming knowledgeable and providing CAM information themselves. Finally, health care providers may become even more involved by actually recommending or providing therapies; either of these approaches must be carried out with caution, because a higher level of involvement raises potentially important licensing and liability issues.

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