

Considerations for Therapy in Patients with MS

We're pleased to introduce a new entry to our Consult series: *MS Consult*. This column will appear four times a year, posing questions from primary care practitioners answered by expert NP/PA members of the IOMSN.

Q How is complementary and alternative medicine used in multiple sclerosis, and how can I safely recommend it to my patients?

Complementary and alternative medicine (CAM) is a non-mainstream practice used in conjunction with conventional medicine.¹ Its use is prevalent among people with and without chronic illnesses, including those living with multiple sclerosis (MS). Up to 70% of Americans with MS have used some type of CAM therapy, compared with 36% of the general population.^{1,2} CAM use is higher in women than in men and is highest among persons ages 35 to 49—two demographics also associated with MS.³

CAM practices include a myriad of therapies from different disciplines (see Table 1).³ Because most people who use CAM do not discuss it with their health care providers, it is important that providers inquire about patient use

TABLE 1
Types of CAM Therapies Used in MS

Alternative medicine practices	Chinese medicine, Ayurveda, homeopathy
Bioelectromagnetics	Magnets, electromagnetic fields
Biofield medicine	Therapeutic touch, Reiki
Biologically based	Diets, herbs, vitamins, bee venom, hyperbaric oxygen, homeopathic supplements
Lifestyle and disease prevention	Exercise
Manipulative systems	Chiropractic, massage, reflexology
Mind-body medicine	Relaxation, meditation, biofeedback, tai chi, yoga, prayer

Source: Bowling. *Demos*. 2001.³

and are armed with basic safety and efficacy information.

Office visits for MS should include safety and efficacy discussions about *all* therapeutic treatments (disease modifying, relapse, and symptom management). Some issues—such as adverse effects—are obvious, while others, such as cost, are less so. A patient with MS may pursue an extremely expensive CAM therapy that lacks substantial evidence for the condition. Providers should therefore consider cost as part of the safety equation and be aware that while some CAM ther-

apies have been studied in MS, most have not (or the research has been of poor quality).⁴

For many commonly used therapies, there is insufficient scientific evidence to support their usefulness in MS. These include acupuncture, biofeedback, Chinese medicine, chiropractic care, replacing amalgam dental fillings, equine therapy, hyperbaric oxygen treatment, low-dose naltrexone, massage therapy, tai chi, and yoga. While many of these practices are relatively safe and inexpensive, others may cause financial harm. Conversely, something considered safe and inexpensive (eg, a low-fat diet with omega-3 supplementation) may be found to be ineffective. Although recommending this type of diet for a person with MS is safe, realistic expectations must be discussed

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TABLE 2

Questions to Aid in CAM Recommendations

1. Is there evidence that this therapy is helpful for an MS symptom?	If yes , proceed to next question. If no , proceed to question 3.
2. Does that evidence outweigh risks, including that of financial harm?	If yes , recommend. If no , proceed to question 3.
3. If there is no evidence, and the patient wants to try it anyway, is it harmful or costly?	If yes , proceed to question 4. If no , recommend a trial of appropriate duration and revisit.
4. If a certain CAM therapy cannot be recommended, are there others that may meet the needs of the patient?	If yes , initiate algorithm again.
5. Does the patient have realistic expectations of CAM?	Always provide a directive to the patient regarding this question.

regarding its effect (or lack thereof) on the condition.⁴

The effectiveness of medical marijuana for MS is another popular deliberation. While data suggest that several administration methods of oral cannabinoids may be effective for spasticity and pain reduction, there is inadequate evidence to support the use of smoked cannabis. The deleterious effects of cannabis on cognition also need to be considered.⁵

Dietary supplements (eg, vitamins, minerals, botanicals, dietary substances) are often regarded as safe by patients because they are “natural.” As clinicians, we must be direct in asking patients about *everything* they are taking—many dietary supplements have drug interactions and/or toxic effects and may adversely stimulate the immune system. Vitamin D, for example, is one supplement that has been heavily studied in MS; lower levels of vitamin D have been shown to increase the risk for MS, and

higher levels may be associated with lower relapse and disability rates. Therefore, standard of practice is to monitor vitamin D levels and supplement accordingly.

CAM can be safely and effectively recommended to people living with MS with due diligence. A question guide to aid recommendations is listed in Table 2.

Currently, no CAM therapies have been shown to *modify* MS, and CAM should not be recommended in place of disease-modifying treatment. However, if the proper questions are addressed, many CAM therapies can be safely recommended for common MS symptoms. Insurance coverage varies significantly among policies, but some treatments (eg, acupuncture and chiropractic care) are gaining coverage.

Finally, it is safe and a good standard of care to recommend a healthy anti-inflammatory diet, such as the Mediterranean diet, to people living with MS in order to improve general health. —MW

Q What are the considerations and recommendations for pregnancy and breastfeeding in women with multiple sclerosis? When should women discontinue their disease-modifying therapies?

Multiple sclerosis (MS) is an inflammatory, demyelinating, degenerative disease. Three times more common in women than men, it may affect pregnancy planning and childbearing experiences.⁶ Evidence demonstrates a reduction in annualized relapse rate during pregnancy and the postpartum period with exclusive breastfeeding. Therefore, pregnancy and exclusive breastfeeding provide a favorable immunomodulatory effect in women with MS, which combats the increased relapse risk associated with the postpartum period.^{7,8}

Reproductive education—including conception, pregnancy, and breastfeeding—is critical for patients with MS and their partners during a woman’s childbearing years. However, women with MS do not require special considerations during pregnancy unless they have remarkable disability. As soon as these women and their partners decide upon pregnancy, a plan should be established that includes a discussion about potential risks to the fetus due to drug exposure, as well as risks to the mother. The goal should be to minimize risk for disease activity and optimize the health of the baby.

Use of DMTs during conception, pregnancy, and breastfeeding. All disease-modifying therapies (DMTs) are usually discontinued during pregnancy and breastfeeding. Common practice

TABLE 3

Pregnancy Categories: Old and New Guidelines

New Pregnancy Guidelines	Old Pregnancy Categories
<p>These new guidelines took effect on June 30, 2015. The labeling of new medications will reflect the changes; for medications approved after June 30, 2001, labeling will be reformatted within the next three years.</p> <p>Subsections are as follows:</p> <p>Pregnancy: Information relevant to the use of the drug in pregnant women; dosing and potential risks to the developing fetus; required information about a pregnancy registry. Includes risk summary, clinical considerations, and data.</p> <p>Lactation: Information about using the drug while breastfeeding (eg, the amount of drug in breast milk and potential effects on the breastfed child). Includes risk summary, clinical considerations, and data.</p> <p>Females and Males of Reproductive Potential: Information about pregnancy testing, contraception, and infertility as it relates to the drug.</p>	<p>A: Adequate and well-controlled (AWC) studies in pregnant women have been conducted and demonstrated no fetal risk in the first and later trimesters.</p> <p>B: Animal studies failed to demonstrate fetal risk; no AWC studies in pregnant women.</p> <p>C: Animal studies showed adverse effects on the fetus; no AWC studies in pregnant women. The benefits of the product for pregnant women may be acceptable despite the potential risks.</p> <p>D: Data from human investigations, marketing experience, or human studies have demonstrated evidence of fetal risk. However, the potential benefits of the drug for pregnant women may make its use acceptable despite potential risks.</p> <p>X: Animal studies and human studies have demonstrated fetal abnormalities; or there is evidence of fetal risk based on data from human investigations, marketing experience, studies; or both. The risk to the fetus outweighs any possible benefit to the use of the drug during pregnancy.</p>

Sources: FDA. 2016¹³; Whyte. *Am Fam Physician*. 2016.¹⁴

among MS experts is to discontinue DMTs prior to conception, with a few exceptions. There is no consensus about timing of discontinuation and washout period for each DMT. The decision is based on the half-life of each DMT, the opinions of the woman and her partner, and risk tolerance. Note: For the purposes of this discussion, the old pregnancy category designations are used, since they are familiar to clinicians. New guidelines took effect in June 2015; Table 3 outlines the change in format.

Injectables. Glatiramer acetate (GA) is the safest drug in relation to pregnancy and breastfeeding (category B). There is no evidence of congenital malformation or spontaneous abortion.

The common recommendation is to discontinue the drug one to two months before conception, although some clinicians allow continuation of the injections throughout pregnancy and into breastfeeding.

Interferon- β s are category C and therefore pose minimal risk for the fetus. The washout period before conception is two to three months, varying among clinicians. Although there is no evidence of spontaneous abortion or birth defects in humans, animal data show increased risk for abortion.⁹

Both GA and interferon- β s are large molecules; there is a very minimal chance that the medication will transmit to the baby via breast milk. Thus, both DMTs are

considered safe during lactation.⁷

Oral MS medications. The three approved MS oral medications are fingolimod, dimethyl fumarate (DMF), and teriflunomide. Fingolimod and DMF are both category C. Women on DMF must discontinue use of the medication one month prior to conception due to its short half-life. There are no reports of birth defects or spontaneous abortion in women taking DMF. Fingolimod needs to be discontinued two months prior to conception. Animal data show evidence for teratogenicity and embryolethality at lower doses of fingolimod than those used in humans.⁷

Teriflunomide is category X, posing high risk for the health of the fetus. It stays in the blood for



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approximately eight months after discontinuation of use. Animal data show teratogenicity and embryotoxicity; therefore, teriflunomide is contraindicated in pregnancy. Women on teriflunomide who plan to become pregnant need to undergo an elimination procedure with cholestyramine or charcoal.

Infusions and injections (monoclonal antibodies). The approved monoclonal antibodies include natalizumab, alemtuzumab, and daclizumab. (Currently, use of rituximab in MS is off label, and the FDA is reviewing the efficacy and safety data for ocrelizumab.) The monoclonal antibodies are category C. The recommendation is to discontinue natalizumab one to two months prior to conception and discontinue alemtuzumab four months preconception.¹⁰ There is no evidence of spontaneous abortion or birth defects in women on alemtuzumab, but there is potentially increased risk for spontaneous abortion in those on natalizumab.

The spontaneous abortion rate

in daclizumab-exposed women is consistent with early pregnancy loss in the general population (12% to 26%). Data on a small number of pregnancies exposed to daclizumab did not suggest an increased risk for adverse fetal or maternal outcomes.¹¹ However, the recommendation is to discontinue daclizumab four months prior to conception. Rituximab should be discontinued 12 months prior to conception, based on the manufacturer recommendation, although it is potentially safe to conceive when the B cell counts return to normal.

Chemotherapy agents. Mitoxantrone is the only FDA-approved chemotherapeutic drug used in MS. However, a few chemotherapy drugs—among them, azathioprine, methotrexate, and cyclophosphamide—are used off label. Chemotherapeutic agents are category D, except methotrexate (category X). Women on category D medications must use a method of birth control for three months after stopping the DMT. Often, clinicians will recommend women initiate GA or interferon during this period, in the hope of minimizing disease activity. Women on mitoxantrone and methotrexate need to use birth control for six months after stopping these immunosuppressive medications, before conceiving.¹² These women likely need to switch to a safer pregnancy DMT during the long washout period.

Pregnancy and breastfeeding among women with MS require planning and decision making. The recommendations differ among clinicians and MS experts since there is no definitive evidence about the risks of the DMTs

on the mother and/or the fetus. Clinicians should discuss the potential risks with women based on their knowledge and experience, and the data available based on animal research and the pregnancy registries. —**ABB-Z CR**

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