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Summary of evidence-based guideline: Complementary and alternative medicine in multiple sclerosis

Report of the Guideline Development Subcommittee of the American Academy of Neurology

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ABSTRACT

Objective: To develop evidence-based recommendations for complementary and alternative medicine (CAM) in multiple sclerosis (MS).

Methods: We searched the literature (1970–March 2011; March 2011–September 2013 MEDLINE search), classified articles, and linked recommendations to evidence.

Results and recommendations: Clinicians might offer oral cannabis extract for spasticity symptoms and pain (excluding central neuropathic pain) (Level A). Clinicians might offer tetrahydrocannabinol for spasticity symptoms and pain (excluding central neuropathic pain) (Level B). Clinicians should counsel patients that these agents are probably ineffective for objective spasticity (short-term)/tremor (Level B) and possibly effective for spasticity and pain (long-term) (Level C). Clinicians might offer Sativex oromucosal cannabinoid spray (nabiximols) for spasticity symptoms, pain, and urinary frequency (Level B). Clinicians should counsel patients that these agents are probably ineffective for objective spasticity/urinary incontinence (Level B). Clinicians might choose not to offer these agents for tremor (Level C). Clinicians might counsel patients that magnetic therapy is probably effective for fatigue and probably ineffective for depression (Level B); fish oil is probably ineffective for relapses, disability, fatigue, MRI lesions, and quality of life (QOL) (Level B); ginkgo biloba is ineffective for cognition (Level A) and possibly effective for fatigue (Level C); reflexology is possibly effective for paresthesia (Level C); Cari Loder regimen is possibly ineffective for disability, symptoms, depression, and fatigue (Level C); and bee sting therapy is possibly ineffective for relapses, disability, fatigue, lesion burden/volume, and health-related QOL (Level C). Cannabinoids may cause adverse effects. Clinicians should exercise caution regarding standardized vs nonstandardized cannabis extracts and overall CAM quality control/nonregulation. Safety/efficacy of other CAM/CAM interaction with MS disease-modifying therapies is unknown. *Neurology*® 2014;82:1083–1092

GLOSSARY

AAN = American Academy of Neurology; **AE** = adverse effect; **CAM** = complementary and alternative medicine; **CBD** = cannabidiol; **CI** = confidence interval; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; **EDSS** = Expanded Disability Status Scale; **FDA** = US Food and Drug Administration; **FSS** = Fatigue Severity Scale; **GB** = ginkgo biloba; **GNDS** = Guy's Neurological Disability Scale; **HRQOL** = health-related QOL; **MFIS** = Modified Fatigue Impact Scale; **MS** = multiple sclerosis; **MSIS** = Multiple Sclerosis Impact Scale; **OCE** = oral cannabis extract; **PPMS** = primary progressive MS; **QOL** = quality of life; **RCT** = randomized controlled trial; **RRMS** = relapsing-remitting MS; **SAE** = serious adverse effect; **SPMS** = secondary progressive MS; **THC** = tetrahydrocannabinol; **VAS** = visual analog scale.

Complementary and alternative medicine (CAM) therapies are nonconventional therapies used in addition to or instead of physician-recommended therapies. CAM use is prevalent in 33%–80% of patients with MS,[1-10] particularly among those who are female, have higher education levels, and report poorer health.[1-4,11] This document summarizes extensive information provided in the complete

Supplemental data at Neurology.org

guideline, available as a data supplement on the *Neurology*® Web site at Neurology.org. Tables e-1 through e-3 and appendices e-1 through e-6, cited in the full guideline (data supplement), as well as references e1–e84, cited in this summary, are available at Neurology.org.

This guideline addresses the following questions: In patients with MS,

1. do CAM therapies reduce specific symptoms and prevent relapses or disability?
2. can CAM use worsen MS or cause serious adverse effects (SAEs)?
3. can CAM use interfere with MS disease-modifying therapies?

DESCRIPTION OF THE ANALYTIC PROCESS This guideline was developed in accordance with the 2004 American Academy of Neurology (AAN) process manual.[12] After review of conflict of interest statements, the AAN selected a panel of experts. A medical research librarian helped perform a comprehensive literature search, and the authors selected articles. At least 2 authors independently rated each article (AAN therapeutic classification scheme). We linked recommendation strength to the evidence quality. With regard to cannabis for pain, we reviewed studies evaluating pain associated with spasticity separately from those evaluating pain specified to be of central neuropathic origin and made separate recommendations. We performed Bonferroni correction for multiple comparisons when necessary.

ANALYSIS OF EVIDENCE Because studies were unavailable or, where available, had a high risk of bias, were in conflict, or lacked statistical precision, we found the evidence insufficient to support or refute the effectiveness of the following therapies in MS (table 1): acetyl-L-carnitine, acupuncture, biofeedback, carnitine, chelation therapy, Chinese medicine, chiropractic medicine, creatine monohydrate, dental amalgam replacement, glucosamine sulfate, hippotherapy, hyperbaric oxygen, inosine, linoleic acid, low-dose naltrexone, massage therapy, mindfulness training, music therapy, naturopathic medicine, neural therapy, Padma 28, progressive muscle relaxation therapy, tai chi, threonine, transdermal histamine, and yoga. Data also were insufficient to determine whether any CAM therapies worsen MS or interfere with disease-modifying therapies.

Evidence was available to develop practice recommendations for use of bee venom therapy, cannabinoids, ginkgo biloba (GB), lofepramine plus phenylalanine with B_{12} (Cari Loder regimen), low-fat diet with omega-3 supplementation, magnetic therapy, and reflexology (table 2). This evidence is discussed herein and includes only the studies that inform the conclusions and recommendations. We selected the final level of obligation for compliance with a recommendation (*might/may*, *should*, or *must*) after taking into consideration the quality of evidence (Level A, B, or C) and other factors (e.g., limited generalizability of the studies, safety/side effect concerns, availability of alternative treatments).

Cannabinoids. Cannabinoids are a group of compounds with psychoactive properties. Tetrahydrocannabinol (THC) and cannabidiol (CBD) are the major cannabinoids of cannabis. Synthetic cannabinoids are chemically related to THC. Orally administered cannabinoids (cannabis extract, synthetic THC), mucosally delivered cannabinoids (cannabis extract oral spray, nabiximols [trade name Sativex]), and smoked cannabis have all been studied for therapeutic effects in MS.

Oral cannabinoids (cannabis extract and THC). The search identified 9 studies (3 Class I,[13-15] 2 Class II,[16,17] and 4 Class III[18-21]).

A large Class I study[13] (N = 630; patients with relapsing-remitting MS [RRMS], primary progressive MS [PPMS], and secondary progressive MS [SPMS]; 15 weeks) found that neither oral cannabis extract (OCE, THC with CBD) nor synthetic THC (Marinol) had greater effect than placebo on the primary outcome measure of spasticity as measured by total Ashworth scale[22] change from baseline (mean change ± SD: OCE: 1.24 [6.60], THC: 1.86 [7.95], placebo: 0.92 [6.56], $p = 0.40$). However, in this same study,[13] significantly more patients reported reduced spasticity symptoms in the treatment groups (secondary outcomes spasticity/pain: OCE [52/46%], THC [51/50%], placebo [37/30%]). Sleep and muscle spasms also improved in the treatment groups.

In a second Class I study[14] (N = 249; "stable MS," type unspecified; 12 weeks) the proportion of patients achieving relief of muscle stiffness was 29.4% in the OCE group compared with 15.7% in the placebo group (odds ratio 2.26, 95% confidence interval [CI] CI 1.24–4.13). Secondary outcomes (muscle stiffness and spasms, pain, sleep) also improved in the cannabis group.

A third Class I study[15] (N = 57; RRMS, SPMS, PPMS), insufficiently powered, found no significant difference in objective spasticity (Ashworth scale) or patient-reported spasm frequency.

In both adequately powered Class I studies,[13,14] significantly more patients treated with cannabinoids reported reduced pain, whereas disability measures and health questionnaire results were not significantly different between groups. One Class I study[13] assessed tremor and bladder symptoms and noted no significant difference in outcomes between patients treated with cannabinoids and placebo.

Conclusions. OCE is established as effective for reducing patient-reported spasticity symptoms and pain

Table 1	CAM therapies with insufficient evidence to support specific practice recommendations for their use in multiple sclerosis			
CAM intervention	Description	Evidence	MS types studied	Adverse effects
Mind–body medicine				
Biofeedback	Active physiologic monitoring of a body system (e.g., EMG activity). The results of the monitoring are provided to the patient in real time.	1 Class III[e38]	MSU	
Music therapy	Uses music prescribed in a skilled manner by a music therapist	2 underpowered Class III[e39,e40]	RRMS, PPMS, SPMS	
Mindfulness-based training	Mental training by nonjudgmental awareness of moment-to-moment experience by mindfulness exercises including observation of sensory, affective, and cognitive domains of perceptible experience	1 Class III[e41]	RRMS, SPMS	None described
Hypnosis	Induction followed by a series of suggestions for analgesia and comfort. Patients practiced the skills by listening to an audio recording and using a cue to re-experience hypnotic effects.	1 Class III[e42]	Unspecified	None described
Biologically based practices				
Padma 28	Ayurvedic mixture of 22 herbs[e43] with presumed immunologic effects on the suppressor lymphocytes and the endogenous interferon production[e44]	1 Class III[e45]	Progressive MS, type unclear	
Linoleic acid	An unsaturated omega-6 fatty acid	2 underpowered Class II[e46,e47] 2 Class III[e48,e49]	MSU	
Creatine monohydrate	A naturally occurring nitrogenous organic compound involved in energy metabolism (phosphocreatine)	1 underpowered Class II[e50] 1 underpowered Class III[e51]	RRMS, MSU	
Acetyl-L-carnitine	A naturally occurring compound that is the acetylated form of L-carnitine (synthesized from lysine and methione)	1 underpowered Class II[e52]	RRMS, SPMS	
Inosine	Ribosylated precursor of uric acid, which raises uric acid levels. Uric acid is a scavenger of peroxynitrate, a highly reactive compound postulated to cause potentially toxic changes in MS plaques, including nitration of tyrosine residues.	1 underpowered Class II[e53] 3 conflicting Class III[e54-e56]	RRMS, SPMS	4/16 patients in 1 Class III study developed kidney stones[e56]
Threonine	Naturally occurring amino acid observed to increase glycine in rat spinal cord and therefore proposed as a treatment of spasticity	1 Class III[e57]	Progressive MS, type unspecified	
Glucosamine sulfate	An amino sugar and a prominent precursor in the biochemical synthesis of glycosylated proteins and lipids, with potential immunoregulatory effects	1 Class I[e58]	RRMS	
Low-dose naltrexone	Long-lasting opiate receptor antagonist; may intermittently block opiate receptors resulting in increased endogenous production of endorphins and opiate receptors, promoting psychological well-being and general health	1 underpowered Class I[e59] 1 underpowered Class II[e60]	All MS subtypes	
Transdermal histamine with caffeine	Histamine is a neurotransmitter	1 Class III[e61]	RRMS and progressive MS, type unspecified	
Hyperbaric oxygen therapy		1 Class I noninterpretable due to suboptimal control intervention (10% oxygen with nitrogen)[e62] 5 underpowered Class II[e63-e67]	MS type unspecified	
Manipulative and body-based practices				
Hippotherapy	Therapeutic horseback riding where the subject is described as being passive	3 Class III[e68-e70]; 1 underpowered, 2 noninterpretable statistically evaluating effect on gait, balance, and mood	RRMS, SPMS[e68] MS type unspecified[e69] All MS subtypes[e70]	
Yoga	Mind–body approach that has components of meditation, breathing, and postures	4 Class III[e71-e74]; 3 underpowered[e71, e73,e74] evaluating effect on disability, spasticity, fatigue, cognition, mood, balance, and walking speed	MS types unspecified[e71,e72] All MS subtypes[e73,e74]	

Continued

CAM intervention	Description	Evidence	MS types studied	Adverse effects
Massage therapy		4 Class III; mood[e75]; self-efficacy[e76]; constipation[e77]; pain, fatigue, balance, gait, and spasticity[e78]	MS type unspecified[e75] MS all types[e76,e77] RRMS, SPMS, PPMS[e78]	
Chinese acupuncture	Procedures involving penetration of the skin with needles in order to stimulate certain points on the body	1 Class III[e79] evaluating effect on QOL in SPMS	SPMS	
Electroacupuncture	Insertion of metallic needles into specific points and stimulating them electrically	1 Class III evaluating effect on disability, QOL, and pain[e80]	RRMS	
Progressive muscle relaxation therapy	Therapist instructs patients to contract and release different muscle groups	1 Class III evaluating effect on pain, disability, spasms, fatigue, cognition, and depression[e81] 1 Class III evaluating QOL[e82]	RRMS, SPMS[e81]; RRMS, SPMS, PPMS[e82]	
Energy medicine				
Neural therapy	A modified form of acupuncture with local anesthetic injections	1 Class III[e83] evaluating effect on disability	All MS subtypes	
Naturopathic medicine	Multimodal therapy including diet, herbs, nutritional supplements, homeopathy, physical medicine, and counseling	1 Class III[e84] evaluating effect on QOL, cognition, disability, depression, and fatigue	RRMS	

Abbreviations: CAM = complementary and alternative medicine; MS = multiple sclerosis; MSU = MS type unspecified; PPMS = primary progressive MS; QOL = quality of life; RRMS = relapsing-remitting MS; SPMS = secondary progressive MS.
Studies cited using reference list in summary guideline article (appearing in print).

(12–15 weeks; 2 Class I,[13,14] 1 Class III[18]). This subjective benefit is possibly maintained for 1 year (1 Class II[17]).

THC is probably effective for reducing patient-reported symptoms of spasticity and pain (15 weeks, 1 Class I[13]). This subjective benefit is possibly maintained for 1 year (1 Class II[17]).

OCE and THC are probably ineffective for reducing both objective spasticity measures and MS-related tremor symptoms (15 weeks, 1 Class I[13]). OCE and THC are possibly effective for reducing symptoms and objective measures of spasticity over 1 year (1 Class II[17]).

Sativex oromucosal cannabinoid spray. The search identified 3 Class I,[23-25] 2 Class II,[26,27] and 3 Class III[28-30] studies in patients with MS, type unspecified.

A Class I study, a randomized controlled trial (RCT)[23] (N = 160, 6 weeks), evaluated the effect of Sativex spray (GW Pharmaceuticals, Salisbury, UK) delivering THC 2.7 mg and CBD 2.5 mg. Spasticity visual analog scale (VAS) was the only outcome measure on which scores improved significantly after Bonferroni correction (active −31.2, placebo −8.4, difference −22.79, 95% CI −35.52 to −10.07, p = 0.001). Scores on physician-evaluated spasticity measures (Ashworth) did not change between groups.

A Class I RCT[24] (N = 66, MS type unspecified, 5 weeks) in MS-related central neuropathic pain found that oromucosal cannabinoids were superior for reducing mean pain intensity (number needed to treat to reduce pain by 50%: 3.7 [95% CI 2.2–13]). Another Class I RCT[25] (N = 135, 10 weeks, MS type unspecified) did not find improvement in the number of incontinence episodes with Sativex. However, the daily number of bladder voids (change

from baseline: treatment −1.95, placebo −0.9; p = 0.049) decreased significantly.[25] A Class II RCT (N = 337, all MS types, 15 weeks)[26] observed that tremor did not improve with Sativex.

Conclusions. Sativex oromucosal cannabinoid spray is probably effective for improving subjective spasticity symptoms (6 weeks, 1 Class I[23]), pain (5 weeks, 1 Class I[24]), and urinary frequency (10 weeks, 1 Class I[25]).

Sativex oromucosal cannabinoid spray is probably ineffective for reducing objective spasticity measures over 6 weeks (1 Class I[23]) or bladder incontinence episodes over 10 weeks (1 Class I[25]).

Sativex oromucosal spray is possibly ineffective for reducing MS-related tremor over 15 weeks (1 Class II[26]).

Smoked cannabis. We reviewed 2 Class III studies.[31,32]

One Class III crossover study[31] (37 patients, RRMS and SPMS, 2 weeks), reported spasticity reduction (modified Ashworth scale) in the cannabis group (standardized effect size 2.74, 2.2–3.14). Pain, the secondary outcome measure, also improved. After cannabis treatment, the subjects consistently showed reduced cognitive performance (Paced Auditory Serial Addition Test).[33]

A second Class III study[32] (N = 20, MS type unspecified) found that both normal subjects and patients with MS fared worse on measures of posture and balance 10 minutes after smoking 1 marijuana cigarette. After Bonferroni correction, the effect was significant only for patients with MS (p = 0.018).

Conclusions. Data are inadequate to determine the safety or efficacy of smoked cannabis used for spasticity/pain (1 Class III[31]), balance/posture (1 Class III[32]), and cognition (1 Class III[31]).

Table 2 CAM therapies with sufficient evidence to support practice recommendations in multiple sclerosis

CAM intervention	Number and class of studies	MS types studied	Outcome	Recommendation level
Cannabinoids				
OCE	2 Class I,[13,14] 1 Class II,[17] 1 Class III[18]	RRMS, SPMS, PPMS, MSU	Symptoms of spasticity, pain	A Effective
	1 Class I[13]	RRMS, SPMS, PPMS	Signs of spasticity (short-term), tremor (short-term)	B Ineffective
	1 Class II[17]	MSU	Signs and symptoms of spasticity (long-term)	C Effective
	2 Class I,[13] 1 Class II[16]	RRMS, SPMS, PPMS, MSU	Bladder symptoms, urge incontinence	U
Synthetic THC	1 Class I,[13] 1 Class II[17]	RRMS, SPMS, PPMS	Symptoms of spasticity, pain	B Effective
	1 Class I[13]	RRMS, SPMS, PPMS	Signs of spasticity (short-term), tremor (short-term)	B Ineffective
	1 Class II[17]	MSU	Signs and symptoms of spasticity (long-term)	C Effective
	1 Class I,[13] 1 Class II,[16] 1 Class III[19]	RRMS, SPMS, PPMS, MSU	Bladder symptoms, urge incontinence, central neuropathic pain	U
Sativex oromucosal spray	3 Class I,[23-25] 2 Class II,[26,27] 3 Class III[28-30]	MSU	Symptoms of spasticity, pain, urinary frequency	B Effective
			Signs of spasticity, incontinence episodes	B Ineffective
			Tremor	C Ineffective
			Anxiety/sleep, cognition, QOL, fatigue	U
Smoked cannabis	2 Class III[31,32]	RRMS, SPMS, MSU	Spasticity, pain, balance and posture, cognition	U
Other CAM				
Ginkgo biloba	2 Class I,[e7,e8] 2 Class II[e9,e10]	RRMS, SPMS, PPMS	Fatigue Cognitive function	C Effective A Ineffective
Lofepramine plus phenylalanine with B₁₂ (Cari Loder regimen)	1 Class II[e16]	RRMS, SPMS, PPMS	Disability, symptoms, depression, fatigue	C Ineffective
Reflexology	1 Class I,[e19] 2 Class II,[e20,e21] 1 Class III[e22]	MSU	Paresthesia	C Effective
			Pain, HRQOL, disability, spasticity, fatigue, cognition, bowel/bladder function, depression, anxiety, insomnia	U
Bee venom	1 Class II[e26]	RRMS, SPMS	MRI lesion number and volume, relapses, disability, fatigue, HRQOL	C Ineffective
Magnetic therapy	1 Class I,[e31] 2 Class II,[e32,e33] 3 Class III[e34-e36]	RRMS, SPMS, PPMS	Fatigue Depression	B Effective B Ineffective
Low-fat diet with omega-3 supplementation	1 Class I,[e12] 1 Class II,[e13] 1 Class III[e14]	RRMS	Relapses, disability, MRI lesions, fatigue, QOL	B Ineffective

Abbreviations: CAM = complementary and alternative medicine; HRQOL = health-related QOL; MS = multiple sclerosis; MSU = MS type unspecified; OCE = oral cannabis extract; PPMS = primary progressive MS; QOL = quality of life; RRMS = relapsing-remitting MS; SPMS = secondary progressive MS; THC = tetrahydrocannabinol. A = established as effective or ineffective; B = probably effective or ineffective; C = possibly effective or ineffective; U = insufficient evidence to determine effectiveness or ineffectiveness.
Studies cited using reference list in summary guideline article (appearing in print) and e-references for print article (online data supplement).

Cannabinoid practice recommendations. Clinicians might offer OCE to patients with MS to reduce patient-reported symptoms of spasticity and pain (excluding central neuropathic pain) (Level A) and might counsel patients that this symptomatic benefit is possibly maintained for 1 year (Level C), although OCE is probably ineffective for improving objective spasticity measures (short-term) or tremor (Level B).

Clinicians might offer THC to patients with MS to reduce patient-reported symptoms of spasticity and pain (excluding central neuropathic pain) (Level B). Clinicians might counsel patients that this symptomatic benefit is possibly maintained for 1 year (Level C), although THC is probably ineffective for improving objective spasticity measures (short-term) or tremor (Level B).

Clinicians might offer Sativex oromucosal cannabinoid spray (nabiximols), where available, to reduce symptoms of spasticity, pain, or urinary frequency, although it is probably ineffective for improving objective spasticity measures or number of urinary incontinence episodes (Level B).

Clinicians might choose not to offer Sativex oromucosal cannabinoid spray to reduce MS-related tremor (Level C).

Data are inadequate to support or refute use of the following in MS (Level U):

1. OCE/THC for bladder urge incontinence and overall symptoms
2. Synthetic THC (Marinol) for central neuropathic pain
3. Sativex oromucosal cannabinoid spray for overall bladder symptoms, anxiety symptoms/sleep problems, cognitive symptoms, quality of life (QOL), and fatigue
4. Smoked cannabis for spasticity, pain, balance/posture, and cognition

Data are inadequate to determine the abuse potential or effect on psychopathologic symptoms of Sativex cannabinoid spray (Level U).

Clinical context. The cannabinoid studies have limitations that physicians and patients must be aware of. Most studies were of short duration (6–15 weeks). Another limitation was the potential for central side effects to unmask patients to treatment assignment—a concern with regard to all masked trials involving treatments with prominent side effects. It is also important to recognize that the Ashworth scale used for objective measurement may be insensitive to spasticity changes. These factors may contribute to the discordant effects of cannabinoids on subjective and objective spasticity measures.

Adverse effects. Cannabinoids were generally well tolerated, although some SAEs were reported. Few studies reported deaths in the cannabinoid-treated groups (1 due to pneumonia,[13] 1 to seizure-related aspiration pneumonia, and 2 to cancer, presumed unrelated[16]). Mild/moderate adverse effects (AEs) were common (approximately 50%–80% of subjects) and appeared to be equally prevalent in subjects receiving cannabinoids or placebo. No significant laboratory, hematologic, urologic, or cardiac changes, or differences in vital signs, were noted. CNS AEs (e.g., dizziness, somnolence, drowsiness, lightheadedness, memory disturbance, difficulty concentrating) were more common in subjects receiving cannabinoids vs placebo. Dizziness was most common (15%–50% of subjects).[13,15,17,20,21,24-26,28,30] Gastrointestinal AEs, including increased appetite, nausea, vomiting, constipation, and dry/sore mouth, occurred in about 10% of subjects receiving cannabinoids[15] and were more common in those receiving cannabinoids than placebo. Other less common AEs included myalgia, increased spasticity, seizures (4/137 subjects had seizures),[23] lower limb weakness, hemorrhagic cystitis, dehydration, temporary psychosis (1 rated as severe),[21] hallucinations,[24] and oral ulceration.[23]

Because cannabinoids have known psychoactive properties, their potential for psychopathologic and neurocognitive AEs is a concern, especially in a patient population that may be vulnerable due to underlying disorders. Depression and predisposal to psychosis have been reported with long-term cannabis exposure.[34-36] Development of marijuana addiction is controversial; however, long-term heavy marijuana use has been associated with tolerance and dependence.[37-39] Evidence is also available, albeit inconsistent, for impairments in memory, concentration, and executive functions in chronic cannabis users, although it remains unclear how long these deficits persist after abstinence and whether there is permanent neurotoxicity.[40,e1-e3] In 1 study, patients with MS and prolonged use of "street" cannabis had cognitive function impairments relative to patients with MS who did not use cannabis.[e4] Patients with MS who smoked cannabis regularly had more extensive cognitive abnormalities and were more likely to meet criteria for a lifetime *DSM-IV* psychiatric diagnosis.[e5] Although not generalizable to medical cannabis, the associations from these studies of street cannabis raise concerns. A substudy of the large Class I study reviewed here,[13] available only in abstract form, reported a significant reduction in verbal learning and memory in patients with MS receiving cannabis extracts vs those receiving placebo.[e6] Several of the reviewed studies assessed psychopathology and cognition as secondary outcomes without significant AEs; however, these studies were short-term and inadequately powered to exclude an effect.[15,21,24,28]

Clinicians should therefore counsel patients about the potential for psychopathologic/cognitive and other AEs associated with cannabinoids. Sativex oromucosal cannabinoid spray is not US Food and Drug Administration (FDA) approved and is unavailable in the United States. In the United States, caution should be exercised with regard to extrapolation of results of trials of standardized OCEs (which are unavailable commercially) to other nonstandardized, nonregulated cannabis extracts (which may be commercially available in states with medical marijuana laws).

Ginkgo biloba. We reviewed 4 studies (2 Class I,[e7,e8] 2 Class II[e9,e10]). A Class I RCT evaluating cognitive function (N = 39; RRMS, SPMS, PPMS) found that subjects taking GB 120 mg twice a day for 12 weeks had a 4.5-second greater (95% CI −7.6–0.9, p = 0.015, nonsignificant [$p < 0.008$ significant per authors] after Bonferroni correction) improvement in the Stroop Color Word test than those taking placebo.[e7] A second Class I study (N = 121; RRMS, PPMS, SPMS, relapsing-progressive MS; 12 weeks) also found no difference in cognition measures with GB 120-mg administration twice a day compared with placebo, confirming the pilot study results.[e8]

The Class II study (N = 22, all MS types) found significantly greater fatigue reduction with GB 240 mg/day for 4 weeks relative to placebo (Modified Fatigue Impact Scale [MFIS][e11] baseline: GB 37.8 ± 14.7, placebo 39.8 ± 15.1; postintervention: GB

35.5 ± 13.9, placebo 42.4 ± 15.6; $p = 0.024$).[e9] A Class II follow-up analysis[e10] of the data from this study did not reveal a difference between the GB and placebo groups on visual–spatial memory and attention/concentration.

GB was well tolerated in all studies. No hemorrhagic AEs were reported.

Conclusions. GB is established as ineffective for improving cognitive function in MS (12 weeks, 2 Class I[e7,e8]).

GB is possibly effective over 4 weeks for reducing fatigue in MS (1 Class II[e9]).

GB practice recommendations. Clinicians might counsel patients with MS that GB is established as ineffective for improving cognitive function (Level A).

Clinicians might counsel patients with MS that GB is possibly effective for reducing fatigue (Level C).

Clinical context. GB and other supplements are not FDA regulated. Their quality control may play a role in their effectiveness and AE risk. Moreover, interactions of supplements with other medications, especially disease-modifying therapies for MS, are a clinical concern.

Low-fat diet with omega-3 fatty acid supplementation (omega-3). We reviewed 3 studies (1 Class I,[e12] 1 Class II,[e13] and 1 Class III[e14]). The Class I study (RRMS, N = 92) of omega-3 fatty acids (1,350 mg eicosapentaenoic acid and 850 mg docosahexaenoic acid daily) revealed no difference in the cumulative number of gadolinium-enhancing MRI lesions at 6 months, relapse rates at 6 and 24 months, disability progression, fatigue, or QOL.[e12]

The Class II study (1-year underpowered RCT, N = 27, RRMS)[e13] evaluated a low-fat diet supplemented with either omega-3 fatty acid (fish oil) or olive oil. There was no significant difference in health-related QOL (HRQOL), relapse rates, or disability.[e13]

Conclusion. A low-fat diet with fish oil supplementation is probably ineffective for reducing MS-related relapse, disability, or MRI lesions, or for improving fatigue or QOL (RRMS, 1 Class I).[e12]

Omega-3 practice recommendation. Clinicians might counsel patients that a low-fat diet with fish oil supplementation is probably ineffective for reducing relapses, disability, or MRI lesions, or for improving fatigue or QOL in MS (Level B).

Lofepramine. Lofepramine (a tricyclic antidepressant structurally related to imipramine and desipramine) combined with L-phenylalanine and IM vitamin B_{12} is known as the Cari Loder regimen.[e15] One 24-week Class II RCT (N = 138, all MS subtypes) compared the Cari Loder regimen with placebo pills and IM vitamin B_{12} (1 mg weekly).[e16] The primary outcome measures of disability did not change significantly (Guy's

Neurological Disability Scale [GNDS][e17] −1.16 [95% CI −2.75 to 0.43], Expanded Disability Status Scale [EDSS][e18] −0.17 [95% CI −0.39 to 0.05]). There was a small improvement in fatigue and symptoms, nonsignificant with Bonferroni correction. Depression did not improve.

Conclusion. The Cari Loder regimen is possibly ineffective for reducing MS-related disability, symptoms, depression, or fatigue (all MS subtypes, 1 Class II[e16]).

Lofepramine practice recommendation. Clinicians might counsel patients with MS that lofepramine plus L-phenylalanine with vitamin B_{12} (Cari Loder regimen) is possibly ineffective for treating disability, symptoms, depression, or fatigue (Level C).

Reflexology. Reflexology involves applying manual pressure to points on the feet. We evaluated 4 studies (1 Class I,[e19] 2 Class II,[e20,e21] and 1 Class III[e22]).

The Class I study (underpowered RCT; N = 71; RRMS, SPMS, PPMS) compared 10 weekly 45-minute sessions of sham reflexology (foot massages) with precision reflexology.[e19] Both groups showed reductions in pain (VAS), disability (Roland Morris Disability Questionnaire[e23]), spasticity (VAS), fatigue (Multiple Sclerosis Impact Scale [MSIS],[e24] Fatigue Severity Scale [FSS], MFIS), and depression (Beck Depression Inventory[e25]). Differences between groups were nonsignificant.[e19]

One Class II RCT (MS type unspecified, N = 71) found significantly greater reductions in paresthesia, urinary symptoms, and spasticity (Ashworth Scale) with 11 weekly reflexology treatments plus calf massage relative to calf massage alone.[e20] After Bonferroni correction, only the difference in paresthesia reduction remained significant (mean ± SD difference pre-/posttreatment in treated group −1.49 ± 2.1, controls 0.16 ± 2.1; $p = 0.04$).

Another Class II RCT (underpowered; SPMS, PPMS; N = 20; 16 weeks) of reflexology compared with sham treatments did not reveal improvement in the primary outcome of HRQOL (change in MSIS: 17; 95% CI −4.121 to 40.21, $p = 0.112$). Secondary outcomes of pain, spasticity, sleep, mood, and bowel/bladder function also did not change.[e21]

Conclusions. Reflexology is possibly effective for reducing MS-associated paresthesia over 11 weeks (MS type unspecified, 1 Class II[e20]).

Data are inadequate to support or refute the use of reflexology for pain, HRQOL, disability, spasticity, fatigue, cognition, bowel/bladder function, depression, anxiety, or insomnia in MS.

Reflexology practice recommendation. Clinicians might counsel patients with MS that reflexology is possibly effective for reducing paresthesia (Level C).

Bee venom. One Class II crossover study[e26] of bee venom (20 stings from live bees 3 times weekly for 24 weeks) (N = 26; RRMS, SPMS) found no

significant effect on the number of new gadolinium-enhancing lesions on MRI, volume of enhancing lesions, total lesion volume, relapses, disability (EDSS, Multiple Sclerosis Functional Composite,[e27] GNDS), fatigue (Shortened Fatigue Questionnaire,[e28] Fatigue Impact Scale[e29]), or HRQOL (Short Form-36[e30]). AEs included tenderness, swelling, and redness at the sting sites; itching (4 subjects); and flu-like symptoms (5 subjects).[e26]

Conclusion. Bee sting therapy is possibly ineffective for reducing MS-related relapses, disability, fatigue, total MRI lesion burden, new gadolinium-enhancing lesion volume, or HRQOL (RRMS, SPMS; 1 Class II).[e26]

Bee venom practice recommendation. Clinicians might counsel patients with MS that bee sting therapy is possibly ineffective for reducing relapses, disability, fatigue, total MRI lesion burden, new gadolinium-enhancing lesion volume, or HRQOL (Level C).

Clinical context. Bee stings can be associated with anaphylactic reaction and possible death.

Magnetic therapy. The search identified 6 studies (1 Class I,[e31] 2 Class II,[e32,e33] and 3 Class III[e34-e36]).

The Class I 12-week RCT (N = 41, RRMS) reported significantly less fatigue (MFIS) with low-frequency pulsed electromagnetic field therapy (bio-electromagnetic-energy-regulation device, in the form of a metal mat upon which subjects lay for 8 minutes twice a day) (active $26.84 \pm SE\ 12.061$, placebo 36.67 ± 13.253; $p = 0.024$). Fatigue, measured by FSS, a secondary outcome measure, also decreased in the treated group (FSS mean [SD]: placebo 4.7 [1.6], treatment 3.5 [1.3], $t = -2.53$; $p = 0.016$). There was no change in depression or disability (EDSS).[e31] However, an EDSS change may not have been detected because of the study's short duration (EDSS may be insensitive to change in short-term disability).

A Class II underpowered RCT[e32] (N = 30, RRMS/progressive MS) found no significant change after Bonferroni correction in disability (EDSS) or patient-reported performance scale related to bladder control, cognition, fatigue, mobility, sensation, spasticity, vision, total performance, or hand function between subjects wearing wristwatch-size magnetic pulsing devices (Enermed device) (10–24 hours/day for 2 months) or inactive devices.

Another Class II underpowered RCT (N = 50; RRMS, SPMS, PPMS) found no significant difference in fatigue (MFIS, FSS) with low-frequency magnetic stimulation 3 sessions per week for 8 weeks (intensity 37.5 mT and a sequence of pulses at 4–7 Hz).[e33] Magnetic therapy was generally well tolerated; most studies reported no AEs.[e34,e36] One study reported headache, spasms, and burning sensation.[e32]

Conclusions. Magnetic therapy is probably effective for reducing fatigue in RRMS (1 Class I,[e31] 1 Class II[e34]) and probably ineffective for reducing depression in RRMS over 15 weeks (1 Class I[e31]).

Data are inadequate to support or refute the effect of magnetic therapy on reducing MS-related disability (1 Class I[e31] with insensitive outcome measure; 1 underpowered Class II[e32]), bladder control problems, or spasticity, or on improving cognition, mobility, sensation, or vision (1 underpowered Class II,[e32] 3 underpowered/inconsistent Class III[e34-e36]).

Magnetic therapy practice recommendation. Clinicians might counsel patients with MS that magnetic therapy is probably effective for reducing fatigue (Level B) and probably ineffective for reducing depression (Level B).

Other CAM therapies practice recommendation. Clinicians should counsel patients with MS that the safety and efficacy of other reviewed CAM, or the interaction of CAM with disease-modifying therapies for MS, are unknown Level U).

LIMITATIONS This review has several limitations. Because the search strategy is limited only to MS, some potentially important AEs (e.g., bleeding risk with GB)[e37] of the reviewed therapies noted when they were evaluated in other diseases were not apparent in the MS population. Therapies that have received much press attention (e.g., dental amalgam removal, transdermal histamine) have little evidence to support recommendations.

DISCLAIMER

This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. Formal practice recommendations are not intended to replace clinical judgment.

CONFLICT OF INTEREST

The American Academy of Neurology is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least 3 AAN committees, a network of neurologists, *Neurology* peer reviewers and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com. For complete information on this process, access the 2004 AAN process manual.[12]

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