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


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 non-standardized cannabis extracts and overall CAM quality control/nonregulation. Safety/efficacy of other CAM/CAM interaction with MS disease-modifying therapies is unknown.

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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; GDNS = Guy's Neurological Disability Scale; HRQL = 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, particularly among those who are female, have higher education levels, and report poorer health.

This document summarizes extensive information provided in the complete...
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. 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. Because studies were 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, hypotheraphy, 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), lipoemuls plus phenylalanine with B12 (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 III18–21). A large Class I study15 (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 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,15 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 study14 (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 study13 (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 study13 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>
<thead>
<tr>
<th>CAM intervention</th>
<th>Description</th>
<th>Evidence</th>
<th>MS types studied</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mind–body medicine</strong></td>
<td></td>
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<tr>
<td>Biofeedback</td>
<td>Active physiologic monitoring of a body system (e.g., EMG activity). The results of the monitoring are provided to the patient in real time.</td>
<td>1 Class III&lt;sup&gt;48&lt;/sup&gt;</td>
<td>MSU</td>
<td></td>
</tr>
<tr>
<td>Music therapy</td>
<td>Uses music prescribed in a skilled manner by a music therapist.</td>
<td>2 underpowered Class II&lt;sup&gt;13,49,50&lt;/sup&gt;</td>
<td>RRMS, PPMS, SPMS</td>
<td></td>
</tr>
<tr>
<td>Mindfulness-based training</td>
<td>Mental training by nonjudgmental awareness of moment-to-moment experience by mindfulness exercises including observation of sensory, affective, and cognitive domains of perceptible experience</td>
<td>1 Class III&lt;sup&gt;41&lt;/sup&gt;</td>
<td>RRMS, SPMS</td>
<td>None described</td>
</tr>
<tr>
<td>Hypnosis</td>
<td>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.</td>
<td>1 Class III&lt;sup&gt;42&lt;/sup&gt;</td>
<td>Unspecified</td>
<td>None described</td>
</tr>
<tr>
<td><strong>Biologically based practices</strong></td>
<td></td>
<td></td>
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<tr>
<td>Padma 28</td>
<td>Ayurvedic mixture of 22 herbs&lt;sup&gt;43&lt;/sup&gt; with presumed immunologic effects on the suppressor lymphocytes and the endogenous interferon production&lt;sup&gt;44&lt;/sup&gt;</td>
<td>1 Class III&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Progressive MS, type unclear</td>
<td></td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>An unsaturated omega-6 fatty acid</td>
<td>2 underpowered Class II&lt;sup&gt;66,47&lt;/sup&gt;</td>
<td>MSU</td>
<td></td>
</tr>
<tr>
<td>Creatine monohydrate</td>
<td>A naturally occurring nitrogenous organic compound involved in energy metabolism (phosphocreatine)</td>
<td>1 underpowered Class II&lt;sup&gt;60&lt;/sup&gt;</td>
<td>RRMS, MSU</td>
<td></td>
</tr>
<tr>
<td>Acetyl-L-carnitine</td>
<td>A naturally occurring compound that is the acetylated form of L-carnitine (synthesized from lysine and methionine)</td>
<td>1 underpowered Class II&lt;sup&gt;62&lt;/sup&gt;</td>
<td>RRMS, SPMS</td>
<td></td>
</tr>
<tr>
<td>Inosine</td>
<td>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.</td>
<td>1 underpowered Class II&lt;sup&gt;63&lt;/sup&gt;</td>
<td>RRMS, SPMS</td>
<td>4/18 patients in 1 Class III study developed kidney stones&lt;sup&gt;66&lt;/sup&gt;</td>
</tr>
<tr>
<td>Threonine</td>
<td>Naturally occurring amino acid observed to increase glycine in rat spinal cord and therefore proposed as a treatment of spasticity</td>
<td>1 Class III&lt;sup&gt;67&lt;/sup&gt;</td>
<td>Progressive MS, type unspecified</td>
<td></td>
</tr>
<tr>
<td>Glucosamine sulfate</td>
<td>An amino sugar and a prominent precursor in the biochemical synthesis of glycosylated proteins and lipids, with potential immunoregulatory effects</td>
<td>1 Class III&lt;sup&gt;68&lt;/sup&gt;</td>
<td>RRMS</td>
<td></td>
</tr>
<tr>
<td>Low-dose naltrexone</td>
<td>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</td>
<td>1 underpowered Class II&lt;sup&gt;69&lt;/sup&gt;</td>
<td>All MS subtypes</td>
<td></td>
</tr>
<tr>
<td>Transdermal histamine with caffeine</td>
<td>Histamine is a neurotransmitter</td>
<td>1 Class III&lt;sup&gt;61&lt;/sup&gt;</td>
<td>RRMS and progressive MS, type unspecified</td>
<td></td>
</tr>
<tr>
<td>Hyperbaric oxygen therapy</td>
<td></td>
<td></td>
<td>MS type unspecified</td>
<td></td>
</tr>
<tr>
<td><strong>Manipulative and body-based practices</strong></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Hippotherapy</td>
<td>Therapeutic horseback riding where the subject is described as being passive</td>
<td>3 Class III&lt;sup&gt;70,71,72&lt;/sup&gt;, 1 underpowered, 2 noninterpretable statistically evaluating effect on gait, balance, and mood</td>
<td>RRMS, SPMS&lt;sup&gt;66&lt;/sup&gt; MS type unspecified&lt;sup&gt;66&lt;/sup&gt; All MS subtypes&lt;sup&gt;70&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Yoga</td>
<td>Mind–body approach that has components of meditation, breathing, and postures</td>
<td>4 Class III&lt;sup&gt;73,74&lt;/sup&gt;, 3 underpowered&lt;sup&gt;75&lt;/sup&gt;,&lt;sup&gt;76,77&lt;/sup&gt; evaluating effect on disability, spasticity, fatigue, cognition, mood, balance, and walking speed</td>
<td>MS types unspecified&lt;sup&gt;73,75&lt;/sup&gt; All MS subtypes&lt;sup&gt;73,74&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

Continued
(12–15 weeks; 2 Class I,13,14 1 Class III15). This subjective benefit is possibly maintained for 1 year (1 Class II15).

THC is probably effective for reducing patient-reported symptoms of spasticity and pain (15 weeks, 1 Class I15). This subjective benefit is possibly maintained for 1 year (1 Class II15).

OCE and THC are probably ineffective for reducing both objective spasticity measures and MS-related tremor symptoms (15 weeks, 1 Class I15). OCE and THC are possibly effective for reducing symptoms and objective measures of spasticity over 1 year (1 Class II15).

Sativex oromucosal cannabinoid spray. The search identified 3 Class I,23–25 2 Class II,26–27 and 3 Class III28–30 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 RCT24 (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 RCT25 (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 I23), pain (5 weeks, 1 Class I23), and urinary frequency (10 weeks, 1 Class I25).

Sativex oromucosal cannabinoid spray is probably ineffective for reducing objective spasticity measures over 6 weeks (1 Class I25) or bladder incontinence episodes over 10 weeks (1 Class I25).

Sativex oromucosal spray is possibly ineffective for reducing MS-related tremor over 15 weeks (1 Class II9).

Smoked cannabis. We reviewed 2 Class III studies.11,32

One Class III crossover study22 (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 study32 (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 III15), balance/posture (1 Class III22), and cognition (1 Class III15).
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):

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

<table>
<thead>
<tr>
<th>CAM intervention</th>
<th>Number and class of studies</th>
<th>MS types studied</th>
<th>Outcome</th>
<th>Recommendation level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cannabinoids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCE</td>
<td>2 Class I,13,14 1 Class II,17 1 Class III,18</td>
<td>RRMS, SPMS, PPMS, MSU</td>
<td>Symptoms of spasticity, pain</td>
<td>A Effective</td>
</tr>
<tr>
<td></td>
<td>1 Class I,13</td>
<td>RRMS, SPMS, PPMS</td>
<td>Signs of spasticity (short-term), tremor (short-term)</td>
<td>B Ineffective</td>
</tr>
<tr>
<td></td>
<td>1 Class II,17</td>
<td>MSU</td>
<td>Signs and symptoms of spasticity (long-term)</td>
<td>C Effective</td>
</tr>
<tr>
<td></td>
<td>2 Class I,13 1 Class II,16</td>
<td>RRMS, SPMS, PPMS, MSU</td>
<td>Bladder symptoms, urge incontinence</td>
<td>U</td>
</tr>
<tr>
<td>Synthetic THC</td>
<td>1 Class I,13 1 Class II,17</td>
<td>RRMS, SPMS, PPMS</td>
<td>Symptoms of spasticity, pain</td>
<td>B Effective</td>
</tr>
<tr>
<td></td>
<td>1 Class I,13</td>
<td>RRMS, SPMS, PPMS</td>
<td>Signs of spasticity (short-term), tremor (short-term)</td>
<td>B Ineffective</td>
</tr>
<tr>
<td></td>
<td>1 Class II,17</td>
<td>MSU</td>
<td>Signs and symptoms of spasticity (long-term)</td>
<td>C Effective</td>
</tr>
<tr>
<td></td>
<td>1 Class I,13 1 Class II,16 1 Class III,19</td>
<td>RRMS, SPMS, PPMS, MSU</td>
<td>Bladder symptoms, urge incontinence, central neuropathic pain</td>
<td>U</td>
</tr>
<tr>
<td>Sativex oromucosal spray</td>
<td>3 Class I,19-25 3 Class III,28-30</td>
<td>MSG</td>
<td>Symptoms of spasticity, pain, urinary frequency</td>
<td>B Effective</td>
</tr>
<tr>
<td></td>
<td>1 Class II,17</td>
<td>MSU</td>
<td>Signs of spasticity, incontinence episodes</td>
<td>B Ineffective</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tremor</td>
<td>C Ineffective</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anxiety/sleep, cognition, QOL, fatigue</td>
<td>U</td>
</tr>
<tr>
<td>Smoked cannabis</td>
<td>2 Class III,31,32</td>
<td>RRMS, SPMS, MSU</td>
<td>Spasticity, pain, balance and posture, cognition</td>
<td>U</td>
</tr>
<tr>
<td><strong>Other CAM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>2 Class I,17 2 Class II,18 3 Class III,19</td>
<td>RRMS, SPMS, PPMS</td>
<td>Fatigue, Cognitive function</td>
<td>C Effective A Ineffective</td>
</tr>
<tr>
<td></td>
<td>1 Class II,18</td>
<td>RRMS, SPMS, PPMS</td>
<td>Disability, symptoms, depression, fatigue</td>
<td>C Ineffective</td>
</tr>
<tr>
<td>Lofepramine plus phenylalanine with B12 (Carl Loder regimen)</td>
<td>1 Class II,19</td>
<td>RRMS, SPMS, PPMS</td>
<td>Paresthesia</td>
<td>C Effective</td>
</tr>
<tr>
<td>Reflexology</td>
<td>1 Class I,18 1 Class II,20 1 Class III,22</td>
<td>MSU</td>
<td>Paresthesia</td>
<td>C Effective</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pain, HRQOL, disability, spasticity, fatigue, cognition, bowel/bladder function, depression, anxiety, insomnia</td>
<td>U</td>
</tr>
<tr>
<td>Bee venom</td>
<td>1 Class II,19</td>
<td>RRMS, SPMS</td>
<td>MRI lesion number and volume, relapses, disability, fatigue, HRQOL</td>
<td>C Ineffective</td>
</tr>
<tr>
<td>Magnetic therapy</td>
<td>1 Class I,18 2 Class II,20 3 Class III,22-24</td>
<td>RRMS, SPMS, PPMS</td>
<td>Fatigue, Depression</td>
<td>B Effective B Ineffective</td>
</tr>
<tr>
<td>Low-fat diet with omega-3 supplementation</td>
<td>1 Class I,18 1 Class II,19 1 Class III,20</td>
<td>RRMS</td>
<td>Relapses, disability, MRI lesions, fatigue, QOL</td>
<td>B Ineffective</td>
</tr>
</tbody>
</table>

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).
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/deep 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, 1 to seizure-related aspiration pneumonia, and 2 to cancer, presumed unrelated). 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). Gastrointestinal AEs, including increased appetite, nausea, vomiting, constipation, and dry/sore mouth, occurred in about 10% of subjects receiving cannabinoids and were more common in those receiving cannabinoids than placebo. Other less common AEs included myalgia, increased spasticity, seizures (4/137 subjects had seizures), lower limb weakness, hemorrhagic cystitis, dehydration, temporary psychosis (1 rated as severe), hallucinations, and oral ulceration.

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 predisposition to psychosis have been reported with long-term cannabis exposure. Development of marijuana addiction is controversial; however, long-term heavy marijuana use has been associated with tolerance and dependence. 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. 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.

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, 2 Class II) 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 = 0.9, nonsignificant) improvement in the Stroop Color Word test compared with those taking placebo.

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]; baseline: GB 37.8 ± 14.7, placebo 39.8 ± 15.1; postintervention: GB 27.3 ± 11.2, placebo 29.7 ± 12.2, p = 0.008).
A Class II follow-up analysis\textsuperscript{10} 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\textsuperscript{7-8}).

GB is possibly effective over 4 weeks for reducing fatigue in MS (1 Class II\textsuperscript{8}).

**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,\textsuperscript{11,12} 1 Class II,\textsuperscript{13} and 1 Class III\textsuperscript{14}). 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.\textsuperscript{12}

The Class II study (1-year underpowered RCT, N = 27, RRMS)\textsuperscript{13} 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.\textsuperscript{13}

**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).\textsuperscript{12}

**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\textsubscript{12} is known as the Cari Loder regimen.\textsuperscript{47,48} One 24-week Class II RCT (N = 138, all MS subtypes) compared the Cari Loder regimen with placebo pills and IM vitamin B\textsubscript{12} (1 mg weekly).\textsuperscript{48} The primary outcome measures of disability did not change significantly (Guy’s Neurological Disability Scale [GNDS]\textsuperscript{47} −1.16 [95% CI −2.75 to 0.43], Expanded Disability Status Scale [EDSS]\textsuperscript{48} −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\textsuperscript{47}).

**Lofepramine practice recommendation.** Clinicians might counsel patients with MS that lofepramine plus L-phenylalanine with vitamin B\textsubscript{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,\textsuperscript{1,19} 2 Class II,\textsuperscript{20-21} and 1 Class III\textsuperscript{22}).

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.\textsuperscript{49} Both groups showed reductions in pain (VAS), disability (Roland Morris Disability Questionnaire\textsuperscript{50}), spasticity (VAS), fatigue (Multiple Sclerosis Impact Scale [MSIS]\textsuperscript{51}), Fatigue Severity Scale [FSS], MPIS), and depression (Beck Depression Inventory\textsuperscript{52}). Differences between groups were nonsignificant.\textsuperscript{19}

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.\textsuperscript{20} 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.\textsuperscript{21}

**Conclusions.** Reflexology is possibly effective for reducing MS-associated paresthesia over 11 weeks (MS type unspecified, 1 Class II\textsuperscript{20}).

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\textsuperscript{26} 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, GNDS), fatigue (Shortened Fatigue Questionnaire, Fatigue Impact Scale), or HRQOL (Short Form-36).

AEs included tenderness, swelling, and redness at the sting sites; itching (4 subjects); and flu-like symptoms (5 subjects).

**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).

**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, 2 Class II, and 3 Class III).

The Class I 12-week RCT (N = 41, RRMS) reported significantly less fatigue (MFIS) with low-frequency pulsed electromagnetic field therapy (bioelectromagnetic-energy-regulation device, in the form of a metal mat upon which subjects lay for 8 minutes twice a day) (active 26.84 ± 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). 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 (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 (Enemed 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). Magnetic therapy was generally well tolerated; most studies reported no AEs.

**Conclusions.** Magnetic therapy is probably effective for reducing fatigue in RRMS (1 Class I, 1 Class III) and probably ineffective for reducing depression in RRMS over 15 weeks (1 Class I).

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

**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) 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.

**AUTHOR CONTRIBUTIONS**

Vijaysheer Yadav: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision. Allen Bowling: study concept and design, analysis or interpretation of data, critical revision of the manuscript for important intellectual content. Dennis Bourdette: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision. Michelle Cameron: analysis or interpretation of data, critical revision of the manuscript for important intellectual content. Gary Gronseth: study concept and design, acquisition of the data, analysis and interpretation of the data, review of the manuscript for important intellectual content. Peter Bever, Jr.: study concept and design, analysis or interpretation of data, critical revision of the manuscript for important intellectual content. Michelle Cameron: analysis or interpretation of data, critical revision of the manuscript for important intellectual content. Dennis Bourdette: study concept and design, acquisition of data, analysis or interpretation of data, critical revision of the manuscript for important intellectual content, study supervision. Gary Gronseth: study concept and design, acquisition of data, analysis or interpretation of data, critical revision of the manuscript for important intellectual content, study supervision. Pushpa Narayanaswami: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision.

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