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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ABBREVIATIONS

9-HPT = 9-Hole Peg Test
AAN = American Academy of Neurology
ADL = activities of daily living
AE = adverse effect
ALCAR = Acetyl-L-carnitine
BBS = Berg Balance Scale
BDI = Beck Depression Inventory
CAM = complementary and alternative medicine
CBD = cannabidiol
CI = confidence interval
CES-D = Center for Epidemiologic Studies Depression Scale
CPG = clinical practice guideline
CR = cognitive restructuring
CRS = category rating scale
CSS = Constipation Scoring System
EDSS = Kurtzke Expanded Disability Status Scale
FAMS = Functional Assessment of Multiple Sclerosis
FDA = Food and Drug Administration
FIS = Fatigue Impact Scale
FS = Functional Systems
FSS = Functional System Scores
FSS = Fatigue Severity Scale
GB = ginkgo biloba
GDS = guideline development subcommittee
GHQ-30 = General Health Questionnaire-30
GNDS = UK Guy's Neurological Disability Scale
HADS = Hospital Anxiety and Depression Scale
HAQUAMS = Hamburg Quality of Life Questionnaire for Multiple Sclerosis
HBO = hyperbaric oxygen
HRQOL = health related quality of life
HYP = self-hypnosis
HYP-CR = combined self-hypnosis and cognitive restructuring
LDN = low-dose naltrexone
MBI = mindfulness-based intervention
MCS-8 = Mental Component Score-8
MFIS = Modified Fatigue Impact Scale
MS = multiple sclerosis
MSFC = Multiple Sclerosis Functional Composite
MSIS-29 = Multiple Sclerosis Impact Scale
MSQLI = Multiple Sclerosis Quality of Life Inventory
NMSS = National Multiple Sclerosis Society
NRS = numeric rating scale
OCE = oral cannabis extract
PASAT = Paced Auditory Serial Addition Test

PMRT = progressive muscle relaxation therapy
PPMS = primary progressive MS
PQOLC = Profile of Quality of Life for the Chronically Ill
PSS = primary symptom score
QOL = quality of life
RCT = randomized, controlled trial
RMDQ = Roland Morris Disability Questionnaire
RMI = Rivermead Mobility Index
RRMS = relapsing-remitting MS
SAE = serious adverse effect
SF-36= Short Form-36
SFQ = Shortened Fatigue Questionnaire
SPMS = secondary progressive MS
STAI = Spielberger State-Trait Anxiety Inventory
THC = tetrahydrocannabinol
TUG = Timed Up and Go Test
VAS = visual analog scale

ABSTRACT

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

Methods: We searched the literature (1970–March 2011, with second, pragmatic, search of Medline March 2011–September 2013) on CAM therapies in MS. We reviewed and classified articles according to the American Academy of Neurology therapeutic scheme and linked recommendations to evidence strength.

Results and recommendations: Clinicians might offer **oral cannabis extract** for spasticity symptoms, pain (excluding central neuropathic pain) (Level A). Clinicians might offer tetrahydrocannabinol for spasticity symptoms, pain (excluding central neuropathic pain) (Level B). Clinicians should counsel patients that these agents are probably ineffective for objective spasticity measures (short-term) and tremor (Level B); possibly effective for spasticity and pain (long-term) (Level C). Clinicians might offer **Sativex oromucosal cannabinoid spray (nabiximols)** for spasticity symptoms, pain, urinary frequency (Level B). Clinicians should counsel patients that these agents are probably ineffective for objective spasticity measures and urinary incontinence episodes (Level B). Clinicians might choose not to offer these agents to reduce tremor (Level C). Clinicians might counsel patients that **magnetic therapy** is probably effective for reducing fatigue, probably ineffective for reducing depression (Level B); a low-fat diet with **fish oil** supplementation is probably ineffective for relapses, disability, fatigue, MRI lesions, or quality of life (Level B); **ginkgo biloba** is ineffective for cognition (Level A), possibly effective for fatigue (Level C); **reflexology** is possibly effective for paresthesia (Level C); **Cari Loder regimen** is possibly ineffective for MS-related disability, symptoms, depression, fatigue (Level C); **bee sting therapy** is possibly ineffective for relapses, disability, fatigue, total MRI lesion burden, new gadolinium-enhancing lesion volume, health-related quality of life (all Level C). Clinicians should counsel patients with MS considering cannabinoids about the potential for psychopathologic/cognitive and other adverse effects; caution should be exercised in extrapolation of results of trials with standardized cannabis extracts that are not available in the United States to nonstandardized cannabis extracts, and with regard to quality control and lack of US Food and Drug Administration regulation of CAM in general.
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). Further research is warranted.

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 multiple sclerosis (MS),[e1–e10] particularly among those who are female, have higher education levels, and report poorer health.[e1–e4,e11] However, few patients (< 7%–18%) discuss CAM use with their neurologists.[e8,e12]

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?

CAM modalities have been classified as mind–body medicine, biologically based practices, manipulative and body-based practices, and energy medicine (National Center for Complementary and Alternative Medicine).[e13] The guideline author panel considers vitamin D supplementation to be a conventional intervention and hence did not include it in this review. Several validated scales, listed next, were used to assess outcomes (see table e-1). Outcome measures considered objective include the Kurtzke Expanded Disability Status Scale (EDSS)[e14] which quantifies disability in eight Functional Systems (FSs) and allows neurologists to assign Functional System Scores (FSSs) to each of these[e14]; the Multiple Sclerosis Functional Composite (MSFC)[e15] which comprises the Timed 25-foot Walk, the 9-Hole Peg Test (9-HPT), and the Paced Auditory Serial Addition Test (PASAT)[e15]; the UK Guy's Neurological Disability Scale (GNDS)[e16]; the Berg Balance Scale (BBS)[e17] to assess postural stability; the Timed Up and Go (TUG) test[e17,e18] to assess mobility; and the Ashworth Scale or modified Ashworth Scale[e19] to assess spasticity. Self-reported measures evaluating subjective outcomes include the Multiple Sclerosis Impact Scale (MSIS-29),[e20] which measures physical and psychological impact of MS; the Fatigue Severity Scale (FSS),[e21] Fatigue Impact Scale (FIS),[e22] and Modified Fatigue Impact Scale (MFIS),[e23] and Shortened Fatigue Questionnaire (SFQ),[e24] questionnaires to assess fatigue; the Short Form-36 (SF-36),[e25] Hamburg Quality of Life Questionnaire for Multiple Sclerosis (HAQUAMS),[e26] Multiple Sclerosis Quality of Life Inventory (MSQLI),[e27] Functional Assessment of Multiple Sclerosis (FAMS),[e28] and Profile of Quality of Life for the Chronically Ill (PQoLC)[e29] for assessing quality of life (QOL); the Center for Epidemiologic Studies Depression Scale (CES-D)[e30] questionnaire, Beck Depression Inventory (BDI),[e31] Hospital Anxiety and Depression Scale (HADS),[e32] and Spielberger State-Trait Anxiety Inventory (STAI),[e33] for assessing mood; the General Health Questionnaire-30 (GHQ-30)[e34] for assessing mental health; the Roland Morris Disability Questionnaire (RMDQ)[e35] for assessing back pain; the Constipation Scoring System (CSS)[e36] for assessing constipation; and the Rivermead Mobility Index (RMI)[e37,e38] for assessing disability. Where ordinal scales that were not well validated were used, we interpreted results cautiously, in concert with results from other validated scales. When evaluating studies of cannabis on pain, we graded separately the evidence for pain associated with spasticity and the evidence for pain specified to be of central, neuropathic origin, and made separate recommendations. Where necessary, we performed a Bonferroni correction for multiple comparisons for studies reporting multiple secondary outcomes.

DESCRIPTION OF THE ANALYTIC PROCESS

This guideline was developed according to the processes described in the 2004 American Academy of Neurology (AAN) guideline development process manual.[e39] The American Academy of Neurology (AAN) Guideline Development Subcommittee (appendices e-1 and e-2) convened a panel of experts to develop the guideline. The panel searched Medline, Web of Science, EMBASE, Cochrane, and Allied and Complementary Medicine Database (1970–March 2011) using the terms listed in appendices e-3 and e-4. From March 2011 to September 2013, we performed a pragmatic search of Medline, using the clinical queries filters, which allowed us to identify, with high sensitivity, high-quality articles that would potentially change conclusions and recommendations. The pragmatic search may have missed lower-quality studies, but any such studies that may have been found would be unlikely to change conclusions and recommendations. At least 2 panelists reviewed all abstracts for relevance. A third reviewer arbitrated any disagreements. We included all human randomized, controlled trials (RCTs); cohort studies; case-control studies; and case series (those with $N \geq 10$ or addressing AEs) of MS and CAM therapies that evaluated outcomes pertaining to specific MS symptoms, relapses, progression, or AEs. We rated articles for quality of evidence using the AAN classification scheme for therapeutic articles (appendix e-5). Conclusions and recommendations were linked to the strength of evidence (appendix e-6). The authors 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) as well as other factors, including limitations in the generalizability of the studies, safety/side effect concerns, and the availability of alternative treatments. Appendices e-1, e-2, e-5, and e-6 are available herein; appendices e-3 and e-4 are available on the *Neurology*® Web site at www.neurology.org.

ANALYSIS OF EVIDENCE

We identified 2,608 citations, 291 of which met our inclusion criteria for initial review. Two panelists reviewed the full text of these articles. Cooling and Feldenkrais therapies were excluded because they are included in a guideline in development that evaluates rehabilitation in MS. Of the 291 articles, 115 were deemed relevant and underwent data extraction, with 10 rated as Class I, 23 as Class II, 41 as Class III, and 25 as Class IV. Class I, II, and III studies are described herein (table e-2 summarizes all reviewed articles). Table e-3 summarizes CAM therapies with no evidence from studies in MS subjects. This guidelines addresses questions 1 and 2 together because most studies looked at all or some of these outcomes together. No evidence was available to evaluate the effect of CAM on disease-modifying therapies (question 3).

Mind–body medicine.

Biofeedback.

One Class III[e40] RCT (N = 20, MS type unspecified) found that biofeedback was not associated with improvement in bladder dysfunction.

Conclusion. Data are inadequate to evaluate the role of biofeedback in MS (1 Class III study[e40]).

Hypnosis.

A Class III study (MS type unspecified, N = 23) evaluating the effects of self-hypnosis (HYP), cognitive restructuring (CR), and combined HYP-CR on pain and catastrophizing found pre- to

postsession decreases in pain intensity for both the HYP and HYP-CR groups. After Bonferroni correction, other outcomes did not improve. The number of dropouts (32%) and missing data on the analyzed subjects make interpretation of these results difficult.[e41]

Conclusion.
Data are inadequate to assess the effect of HYP, CR, or HYP-CR on pain or mood (1 Class III study[e41])

Music therapy.
We identified 2 Class III studies.[e42,e43] The first study[e42] (N = 20, relapsing-remitting MS [RRMS], primary progressive MS [PPMS], and secondary progressive MS [SPMS]) found that 1 year of music therapy (Nordoff Robbins technique)[e44] did not improve self-acceptance (Scale for Self-Acceptance) or reduce depression (BDI), anxiety (HADS), or disability (MSFC, EDSS) after Bonferroni correction. The study is underpowered to exclude benefit.
The second study[e43] (N = 20, chronic progressive MS, type unspecified), also inadequately powered, found no significant difference in respiratory muscle strength (maximum inspiratory and expiratory pressures) after music therapy.

Conclusion.
Data are inadequate to assess the effect of music therapy on mood (RRMS, PPMS, SPMS; 1 underpowered Class III study[e42]) or respiratory muscle function (chronic progressive MS, 1 underpowered Class III study[e43]).

Mindfulness training.
Mindfulness-based intervention (MBI) is a form of mental training by nonjudgmental awareness of moment-to-moment experience that involves mindfulness exercises including observation of sensory, affective, and cognitive domains of perceptible experience. One Class III RCT (N = 150, RRMS, SPMS) found that relative to usual care, 8 weeks of MBI improved health-related QOL (HRQOL; PQOLC, HAQUAMS) and decreased depression (CES-D), anxiety (STAI), and fatigue (MFIS).[e45]

Conclusion.
Data are inadequate to evaluate the effects of MBI on QOL, depression, or fatigue (RRMS, SPMS, 1 Class III study[e45]).

Biologically based practices.
Herbs.
Padma 28.
Padma 28 is an Ayurvedic mixture of 22 herbs[e46] with presumed immunologic effects on the suppressor lymphocytes and the endogenous interferon production.[e47–e49]
One Class III study (N = 100, progressive MS, type unclear) compared the effects of oral Padma 28 (2 tablets 3 times a day) and symptomatic therapy ("drugs to reduce pain, spasticity and cramps and inhibit detrusor contractions," drug type and dose unspecified) on relapses, progression, and symptoms over 1 year.[e50] Twenty-two of 50 (44%) treated subjects improved in strength and sphincter function vs 0 of 50 controls. The study did not mention criteria for MS diagnosis. The therapeutic efficacy was determined using a numeric scale that combines attack

frequency, disease progression, and improvement in individual symptoms, making the interpretation of results difficult.

Conclusion.
Data are inadequate to assess the effect of Padma 28 on relapse, disability, and symptoms in MS (progressive MS, type unclear; 1 Class III study[e50]).

Ginkgo biloba.
The search identified 4 studies (2 Class I,[e51,e52] 2 Class II[e53,e54] examining ginkgo biloba (GB) use. The first Class I study (RCT), evaluating cognitive function (N = 39, RRMS, SPMS, PPMS), found that subjects taking GB 120 mg twice daily for 12 weeks had a 4.5-second greater (95% confidence interval [CI]: -7.6–0.9, $p = 0.015$, not significant, as $p < 0.008$ was significant per authors after Bonferroni correction) improvement in the Stroop color word test than those taking placebo.[e51] The second Class I study (N = 121, RRMS, PPMS, SPMS and relapsing-progressive MS, 12 weeks) also found no difference in cognition measures with GB 120-mg administration twice daily as compared with placebo, confirming the results of the pilot study.[e52] One Class II study (N = 22, all MS types) found significantly greater fatigue reduction with GB administration 240 mg/day for 4 weeks relative to that from placebo (MFIS baseline: GB 37.8± 14.7, placebo 39.8±15.1; post-intervention: GB 35.5 ± 13.9, placebo 42.4±15.6; F = 6.05, $p = 0.024$).[e53] A Class II follow-up analysis of the data from this study (12 patients in the GB group and 9 in the placebo group) did not reveal a difference between the GB and placebo groups on visual–spatial memory and attention/concentration. Pre- and post-treatment comparisons between the GB-treated group and placebo group did not show enhanced processing speed after Bonferroni correction but were underpowered to detect a difference.[e54]

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

Conclusion.
GB is established as ineffective for improving cognitive function in MS (2 Class I studies[e51,e52]). GB is possibly effective for reducing fatigue in MS (1 Class II study[e53]).

Cannabis.
The search of cannabis use identified 19 studies: 6 Class I,[e55–e60] ~~4~~ Class II,[e61–e64] and 9 Class III.[e65–e73] The studies evaluated 4 major forms of cannabis: oral cannabis extract (OCE) containing tetrahydrocannabinol (THC) and cannabidiol (CBD), synthetic THC, Sativex oromucosal cannabinoid spray (nabiximols), and smoked cannabis.

OCE (containing THC and CBD) and synthetic THC.
The search identified 3 Class I,[e55,e56,e58] 2 Class II,[e61,e64] and 4 Class III[e66,e67,e70,e71] studies that evaluated the efficacy of oral cannabinoid use in patients with RRMS, SPMS, PPMS, or MS type unspecified.
The largest Class I study, an RCT[e55] (N = 630, RRMS, PPMS, SPMS), found that neither OCE (THC with CBD) nor synthetic THC (Marinol) for 15 weeks had greater effect than placebo on the primary outcome measure of spasticity (total Ashworth scale change from baseline to 13 weeks) in patients with MS (mean change +/- SD: cannabis extract: 1.24 [6.60], THC: 1.86 [7.95], placebo: 0.92 [6.56], $p = 0.40$). Likewise, upper-body or lower-body scores did not

change significantly between groups. The secondary outcome measure of median timed 10-meter walk time decreased in the THC group as compared with the placebo group (percentage, 95% CI): THC 12% (6%–21%), cannabis extract 4% (0%–10%), and placebo 4% (-2% to 7%). However, data were available only for 278/630 treated patients, making interpretation difficult. Scores on other secondary outcome measures, including the RMI, 4 self-completion questionnaires, the GNDS, Barthel Activities of Daily Living [ADL] Index, and the GHQ-30, did not change between groups. Patients' perceptions of reduction in tremor or bladder symptoms also did not change between groups. Significantly more patients reported reduced spasticity and pain in the treatment groups (spasticity/pain: cannabis extract [52/46%], THC [51/50%], placebo [37/30%], $p = 0.01/0.002$). Sleep and muscle spasms also improved in the treatment groups (sleep/spasms: cannabis extract 50/53%, THC 47/43%, placebo 36/39%, $p = 0.025/0.038$).

A second Class I (crossover) study (N = 57, RRMS, SPMS, PPMS)[e56] found no significant difference in spasticity, spasm frequency and symptoms, mobility, hand function, and cognition (Ashworth, EDSS, RMI, MSFC) between cannabis plant extract (3–11 capsules/day of 2.5 mg THC + 0.9 mg CBD) and placebo for 14 days. Patient-reported outcomes related to spasm frequency, micturition, tremor, and sleep problems also did not change. The study was underpowered to detect a benefit.

In a third Class I study, a double-blind RCT (N = 249, "stable MS," type unspecified, 12 weeks), patients received either cannabis extracts containing THC and CBD (titrated to maximum daily dose of 25 mg THC) or placebo.[e58] A 2-week titration period was followed by a 10-week maintenance phase, with assessments at 2, 4, 8, and 12 weeks. The primary outcome measure was an 11-point category rating scale (CRS) wherein 0 indicates very much better, 5 signifies no difference, and 10 indicates very much worse. CRS scores in categories 0 to 3 were classified as signifying a clinically relevant response with "relief of muscle stiffness." The proportion of patients achieving relief of muscle stiffness was 29.4% in the cannabis group and 15.7% in the placebo group at 12 weeks (odds ratio 2.26, 95% CI: 1.24–4.13, $p = 0.004$). Secondary outcomes, including improvement in muscle stiffness at 4 and 8 weeks, body pain at 4 and 8 weeks, and muscle spasms and poor sleep quality at 4, 8, and 12 weeks, improved in the cannabis group. Body pain was not reduced at the 12-week time point. AEs were more common in the cannabis group (93%) relative to those in the placebo group (74.6%). AEs that were > 3% higher in the cannabis group were dizziness, disturbance in attention, balance disorder, somnolence, dry mouth, nausea, diarrhea, fatigue, "feeling abnormal," urinary tract infection, disorientation, confusional state, and falling.

In the first Class II study,[e61] a follow-up from the first Class I study,[e55] treatment was continued, double-blinded, for 12 months in 80% (502/630) of the initially enrolled patients. Significantly greater spasticity reduction (Ashworth scale) was found at 12 months in the treated group (mean reduction: synthetic THC 1.82 [n = 154, 95% CI: 0.53–3.12], cannabis extract 0.10 [n =172, 95% CI: 0.99–1.19], placebo -0.23 [n = 176, 95% CI: -1.41–0.94]; $p = 0.04$ unadjusted for ambulatory status and center, $p = 0.01$ adjusted). Disability (GNDS, Barthel ADL Index) did not change. Patient-reported outcomes (pain, spasticity, and spasms) continued to improve significantly in the treatment group just as in the main study.

A second Class II study,[e64] a secondary analysis of the largest Class I study,[e55] evaluated the efficacy of cannabis extract and oral THC in urinary urge incontinence (N = 522, RRMS, PPMS, and SPMS). Only 255 subjects (49%) were available for analysis. All 3 groups (THC, cannabis extract, and placebo) showed a significant reduction in the primary outcome, episode rate for urinary urge incontinence. However, both treatment groups improved significantly relative to placebo (cannabis extract 25%, $p = 0.005$; THC 19%, $p = 0.039$). Urodynamics and QOL did not change, and reductions in pad weight were not significant (the latter corrected for multiple outcomes). There was baseline imbalance between groups, with more patients in the THC group reporting baseline urge incontinence and higher rates of urinary incontinence episodes, making the interpretation of results difficult.

A Class III (randomized, crossover) study[e66] (N = 24; RRMS, PPMS, and SPMS; 9 weeks) evaluated the effect on central neuropathic pain of 2.5 mg of oral dronabinol THC (Marinol, Banner Pharmacaps, USA; IPC-Nordic, Denmark) which was escalated to a final dose of 10 mg daily. The median spontaneous pain intensity was lower in the treated group (intensity score, [25th–75th percentiles]: drug 4 [2.3–6.0], placebo 5 [4–6.4], $p = 0.02$). Multiple secondary outcome measures did not change with Bonferroni correction.

A second Class III (crossover) study[e67] (N = 13, MS type unclear, escalating 2.5–15 mg THC for 5 days) found no significant differences in objective measures (physician-rated limb weakness, spasticity, gait, coordination, reflexes) between the periods on and off THC treatment, although subjects reported significant spasticity reductions on an ordinal scale with increasing THC doses (placebo 3.40±0.73, THC 2.23±0.90; t = 2.73, $p = 0.03$).

A third Class III study, a small (N = 14, MS type unspecified) crossover study,[e70] found no significant difference in arm tremor (tremor index) between 2 weeks of cannabis extract and placebo, but the study was underpowered to detect an effect.

A fourth Class III study[e71] (N = 16, SPMS, PPMS) evaluating the safety and tolerability of THC and cannabis extract found that THC was generally well tolerated. Overall, AEs were more common in the treatment group (5–10 mg/day of cannabis plant extract or THC, odds ratio 1.9, $p = 0.01$). Significantly, 5/13 patients reported increased spasticity with treatment, and 1 patient had an acute psychotic episode. Other AEs were dizziness (6/16), headache (5/16), ataxia (3/16), dry mouth (3/16), and emotional lability (3/16). No significant differences in spasticity (Ashworth scale) or disability (EDSS, MSFC) were noted over 4 weeks. The study found improvement in the THC and plant-extract treatment groups on the "mental health" subscale score of the Medical Outcomes Study Short Form 36 ($F = 8.1$, $p = 0.02$) and "psychological status" domain of the HRQOL questionnaire ($F = 8.1$, $p = 0.02$) during THC treatment, not significant when corrected for multiple outcomes. In addition, these findings were contradicted by worsening of the visual analog scale (VAS) "subject's global impression" score (THC: $F = 9.2$, $p = 0.01$; plant extract: $F = 7.1$, $p = 0.02$). Statistical precision could not be determined because of the method of data presentation.

Conclusions.
OCE is established as effective for reducing patient-reported spasticity symptoms and pain (12–15 weeks, 2 Class I studies,[e55,e58] 1 Class III study[e67]) but is probably ineffective for

reducing objective spasticity measures short-term (15 weeks, 1 Class I study[e55]). THC is probably effective for reducing patient-reported spasticity symptoms and pain over a period of 15 weeks (1 Class I study,[e55] 1 Class III study[e67]) but is probably ineffective for reducing objective spasticity measures short-term (15 weeks, 1 Class I study[e55]). OCE and THC are possibly effective for reducing spasticity symptoms and objective spasticity measures over a 12-month period (1 Class II study[e61]). OCE and THC are probably ineffective for reducing symptoms of MS-related tremor (15 weeks, 1 Class I study[e55]). Data are inadequate to support or refute the use of OCE/oral THC for overall bladder symptom severity (conflicting Class I[e55] and II studies[e64]), urinary urge incontinence (1 Class II study,[e64] noninterpretable due to baseline imbalance between treatment groups), or the use of synthetic THC (Marinol) for central neuropathic pain (1 Class III study[e66]).

Sativex oromucosal cannabinoid spray (nabiximols).

A Class I study, an RCT,[e57] evaluated the effect of Sativex oromucosal cannabinoid spray delivering THC 2.7 mg and CBD 2.5 mg (GW Pharmaceuticals, Salisbury, United Kingdom, approved for use outside of the United States) on 5 target symptoms: spasticity, spasms, bladder problems, tremor, and pain that was not obviously musculoskeletal (N = 160, MS unspecified type, 6 weeks). The primary outcome measure was the VAS for each patient's most troublesome symptom (the primary symptom, measured as the primary symptom score [PSS]). This included any of the target symptoms the subjects mentioned as being the primary symptoms. The PSS improved in both placebo and treatment groups. A subgroup analysis found a large effect for patients for whom pain was the primary symptom in both placebo and treatment groups. However, even when the PSS for pain was excluded from the analysis, the difference was not significant after Bonferroni correction. Spasticity 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 measures such as Ashworth, GNDS, and Barthel ADL Index did not change between groups.

A second Class I study,[e59] an RCT (N = 135, 10 weeks, MS type unspecified), did not find significant improvement in the primary outcome measure of change in the number of urinary incontinence episodes over 10 weeks with Sativex relative to that with placebo (Incontinence Quality of Life, a 0–10 numeric rating scale [NRS] of overall bladder condition [0 = no problems, 10 = intolerable problems]). Daily number of voids (change from baseline: treatment -1.95, placebo -0.9, $p = 0.049$) and bladder symptom severity (patient NRS) (change from baseline treatment -2.21, placebo -1.05, $p = 0.008$) decreased significantly, and the Patient Global Impression of Change score (treatment 84% improved, placebo 58% improved, $p = 0.04$) improved significantly after correction for multiple outcomes.[e59]

A third Class I study (RCT)[e60] (N = 66, MS type unspecified, 5 weeks) evaluated the effect of Sativex oromucosal spray for MS-related central pain. The primary outcome measure was an 11-point NRS completed by the patient. Oromucosal cannabinoids were significantly superior for reducing the mean pain intensity (mean change, 95% CI: cannabis 2.7, 3.4–2.0; placebo –1.4, 2.0–0.8; $p = 0.005$). Scores on the Neuropathic Pain Scale, a secondary measure of pain, also decreased significantly in the treated group ($p = 0.044$). However, the proportion of patients rating themselves "much" or "very much" improved did not differ between groups. Anxiety, depression, and disability did not change, and sleep disturbance did not change when corrected

for multiple outcomes. More treated subjects developed AEs; 88.2% on cannabis developed at least one AE relative to 22 patients (68.8%) on placebo. Dizziness was the most common AE; at least 1 occurrence each of confusion, disorientation, hallucination, and low mood was seen. Cognitive effects on long-term storage memory could not be excluded. The number needed to treat to reduce pain by 50% was 3.7 (95% CI: 2.2–13), and the numbers needed to harm were 5.13 for any AE and 2.68 for dizziness in particular (cannabis vs placebo 0.19, 95% CI: 0.00–0.39; $p = 0.053$).

Two Class II studies (RCTs)[e62,e63] reported on use of cannabinoid oromucosal spray (Sativex) for spasticity in MS. The first of these 2 RCTs (N = 189, MS type unspecified, 6 weeks) found significant patient-reported reduction in spasticity (NRS, a daily diary assessment on a 0- to 10-point scale) (Sativex mean decrease 1.18 points, placebo decrease 0.63, mean treatment difference 0.52, 95% CI: -1.029–0.004; $p = 0.048$).[e62] Forty-eight (40%) subjects showed a $\geq$ 30% reduction in NRS spasticity over the study course as compared with 14 (21.9%) on placebo (difference 18.1%; 95% CI: 4.73–31.52; $p = 0.014$). Physician-rated outcomes (Ashworth, Motricity Index) did not change. The second of these 2 studies, a larger Class II RCT (N = 337, all MS types, 15 weeks) by the same authors, found no significant improvement in the patient-reported primary outcome of spasticity (NRS) with Sativex.[e63] The responder rate (> 30% reduction in mean spasticity on NRS) was also nonsignificant. Other secondary outcomes, including results of the 10-meter walk, caregiver's global impression of change, Barthel ADL Index, Ashworth scale, and QOL indices, did not change. NRS results for the secondary outcome measures of tremor and bladder symptoms, pain, fatigue, and sleep quality also did not improve with Sativex.

A Class III open-label study,[e65] a follow-up to a Class I study,[e57] enrolled 137/160 patients who had perceived benefit with Sativex oromucosal spray with regard to pain, spasms, spasticity, and bladder symptoms and found that the subjective improvement on VAS was maintained over 1 year of treatment. However, because the study had a large number of dropouts (42.3%), conclusions could not be drawn. The SAEs considered as being related to Sativex included 2 patients who developed seizures, 1 of whom died of seizure-related aspiration pneumonia, and a third patient for whom loss of balance resulted in a fall and ankle fracture.

The second Class III study,[e68] underpowered (N = 17, 8-weeks, unspecified MS type), found no significant differences in psychopathologic symptoms (Symptom Checklist-90 Revised and the Self-rating Anxiety Scale), cognition (PASAT), general tolerability, abuse potential, QOL (VAS on HRQOL, MSIS-29), and fatigue (FSS) between Sativex and placebo.

A third Class III (crossover) study[e69] (N = 20, type unspecified, 6 weeks) found no difference in the VAS for pain or patient-/physician-reported reduction in spasticity (NRS and Ashworth scale, respectively) over a 6-week period before and after treatment with Sativex oromucosal spray. Because of the method of presentation of the results, the study's precision could not be calculated.

Conclusions.
Sativex oromucosal cannabinoid spray is probably effective for improving subjective symptoms of spasticity over 6 weeks (1 Class I study[e57]), central neuropathic pain over 5 weeks (1 Class I

study[e60]), and total number of bladder voids in 24 hours over 10 weeks (1 Class I study[e59]). Sativex oromucosal cannabinoid spray is probably ineffective for improving objective measures of spasticity over 6 weeks (1 Class I study[e57]) or the number of bladder incontinence episodes over 10 weeks (1 Class I study[e59]). Sativex oromucosal cannabinoid spray is possibly ineffective for reducing symptoms of MS-related tremor over 15 weeks (1 Class II study[e63]). Data are inadequate to support or refute the use of Sativex oromucosal cannabinoid spray for reducing overall bladder symptoms (conflicting Class I studies[e57,e59,e63]), anxiety symptoms or sleep problems (1 Class I study underpowered to detect benefit[e60]), or symptoms related to cognition, QOL, or fatigue (1 Class III study[e68]). Data are inadequate to assess psychopathologic symptoms or abuse potential due to Sativex (1 Class III study[e68]).

Smoked cannabis.
A Class III study, a double-blind, crossover RCT of smoked cannabis[e72] (37 patients, RRMS and SPMS, 2 weeks), reported a decrease in spasticity (modified Ashworth scale) in the cannabis group (mean difference before and after treatment, 95% CI: cannabis 2.95, 2.49–3.38; placebo 0.21, -0.09–0.51; effect 2.74, 2.2–3.14; $p < 0.001$). The clinically meaningful effect was a 2-point change in Ashworth scale. The secondary outcome measure of pain as measured by VAS also improved in the treated group (mean difference before and after treatment, 95% CI: cannabis 8.27, 4.51–13.49, and placebo 2.99, 0.64–6.55; effect 5.28, 2.48–10.01; $p = 0.008$). No differences were noted in timed walk tests between groups. Of note, patient perception of "highness" was greater by 5.04 points in the cannabis group than in the placebo group ($p < 0.001$). Seventeen of the 30 participants who completed the study guessed their treatment allocation correctly for all 6 visits; the other participants guessed their cannabis treatments correctly on 33/35 visits and their placebo treatments on 21/36 visits. Cognition as tested by the PASAT improved post-treatment with each session as compared with baseline, consistent with practice effects. However, within groups, the subjects consistently showed reduced performance on the PASAT after cannabis as compared with baseline (treatment scores, 95% CI: placebo pretreatment 138.08, 123.76–147.74; placebo post-treatment 138.43, 123.37–150.38; cannabis pretreatment 140.78, 127.31–151.52; cannabis post-treatment 132.46, 116.38–144.07; difference between groups 8.67, 4.10–14.31 in favor of placebo; $p = 0.003$, not significant when corrected for multiple outcomes). Patient perception of fatigue was not affected by cannabis. The timed walk was worse in the cannabis group post-treatment as compared with that in the placebo group post-treatment (pretreatment–post-treatment comparison), but the difference was not significant. Differences in timed walk between the 2 groups, cannabis and placebo, were also not significant. AEs were similar to those reported in other reported studies and included dizziness, headache, fatigue, nausea, and feeling "too high."

Another Class III study,[e73] evaluating the safety of smoked marijuana (N = 20, MS type unspecified), found that both normal subjects and patients with MS did worse on measures of posture and balance 10 minutes after smoking 1 marijuana cigarette, but 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 and pain (1 Class III study[e72]), balance/posture (1 Class III study[e73]), and cognition (1 Class III study[e72]).

Dietary supplementation.

Low-fat diet with omega-3 fatty acid supplementation.

We reviewed 3 studies (1 Class I,[e74] 1 Class II,[e75] and 1 Class III[e76]). The Class I study (RRMS, N = 92) of omega-3 fatty acids (1,350 mg of eicosapentaenoic acid and 850 mg of 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. The sample size too small to exclude a moderate benefit.[e74]

The Class II study, a 1-year underpowered RCT[e75] (N = 27, RRMS), evaluated a low-fat diet supplemented with either omega-3 fatty acid (fish oil) or olive oil. There was no significant difference in HRQOL, relapse rates, or disability.[e75] The Class III study, examining effects of omega-3 fatty acids (RRMS, N = 312), did not show improvement in disability (EDSS), relapse rate, severity, or duration as compared with olive oil supplementation.[e76]

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 symptoms (RRMS; 1 Class I study,[e74] 1 Class III study[e76]).

Linoleic acid.

We reviewed 2 Class II[e77,e78] and 2 Class III[e79,e80] studies. The 2 Class II (N = 75, 96, MS type unspecified) studies found no significant difference in disability progression (EDSS)[e77,e78] or relapse rate (patient-reported relapses)[e77] between linoleic acid (sunflower seed oil) and oleic acid (olive oil) supplementation over 2 years and 30 months, respectively. One study was underpowered,[e77] and statistical precision could not be calculated for the other.[e78] The first Class III[e79] study (RCT), which compared linoleic and oleic acids (N = 152, chronic progressive MS), also found no significant difference in relapses or disability progression (EDSS, record of relapses) over 2 years. The second Class III trial (N = 36, 18 months, MS type unspecified) found significant reduction in relapse rates and disability (EDSS) between high- (14 g/day) and low-dose (5 g/day) γ-linoleic acid–rich borage oil.[e80]

Conclusion.

Data are insufficient to support or refute the use of linoleic acid for reducing MS-related disability or relapse (MS type unspecified, 2 Class II studies,[e77,e78] 2 conflicting Class III studies[e79,e80]).

Creatine monohydrate.

One Class II underpowered RCT[e81] (N = 16, RRMS) found no significant increase in isokinetic knee extension and flexion strength between oral creatine 20 g or placebo for 5 days. Another Class III trial (N = 12, MS type unspecified, 14 days), also underpowered, found no significant improvement in knee flexion and extension power and work with creatine.[e82]

Conclusion:

Data are inadequate to support or refute the use of creatine monohydrate for improving exercise

capacity short-term (5 days) in RRMS (1 underpowered Class II study[e81]) or in MS, type unspecified (1 underpowered Class III study[e82]).

Acetyl-L-carnitine (ALCAR).
One Class II crossover RCT[e83] (N = 36; RRMS, SPMS; 3 months) found no significant reduction in fatigue (FSS) with 2 g/day of ALCAR relative to 200 mg/day of amantadine for 3 months, but lacked precision to exclude a benefit (ALCAR 21/30, 70% with reduced FSS, amantadine 13/30, 43%, $p = 0.073$). When an FSS score decrease of 0.5 was considered a clinically significant effect, 29 patients improved after ALCAR treatment and 21 after amantadine treatment ($p = 0.549$). This amantadine dose was similar to that used in other studies of MS-related fatigue.
Conclusion.
Data are inadequate to support or refute the use of ALCAR 2 g/day for reducing MS-related fatigue (RRMS, SPMS; 1 underpowered Class II study[e83]).

Inosine.
We evaluated 1 Class II study[e84] and 3 Class III studies.[e85–e87]
The 2-year Class II study, underpowered to detect a modest benefit (N = 159, RRMS), found no significant change in disability or time to sustained progression with inosine relative to placebo.[e84]

The first Class III study (N = 11, SPMS) found that oral administration of uric acid or inosine did not significantly change disability (EDSS). All patients were non-ambulatory and hence may have been too disabled for improvement to be measured by the EDSS.[e85] The second Class III study (N = 64, 32/group, RRMS, 36 months) noted a lower relapse rate with inosine 2–4 g daily for 36 months relative to no intervention (16 relapses in treated patients vs 56 in controls, $p < 0.0001$).[e86] Disability progression (EDSS) was significantly slower in the treated group (EDSS change: treated 2.62+/- 1.48 to 3.03+/- 1.66, control: 1.84+/-1.05 to 3.28+/1 1.01, $p = 0.025$). The third Class III study, an RCT (N = 16, RRMS), had 2 arms: a group given placebo with crossover at 6 months to inosine (or vice versa) and a group given inosine alone for 12 months.[e87] Significant reduction in disability (EDSS) was seen with inosine in the crossover arm and in the inosine-only arm from baseline to 6 months, which was maintained but nonsignificant at 1 year.[e87] Four patients (25%) developed kidney stones.

Conclusion.
Data are inadequate for assessing the effect of inosine on MS-related relapse rate and disability (RRMS, SPMS; conflicting Class II and III studies[e84–e86]).

Lofepramine plus L-phenylalanine with vitamin B_{12}.
Lofepramine (a tricyclic antidepressant structurally related to imipramine and desipramine) combined with L-phenylalanine and intramuscular vitamin B_{12} is also known as the Cari Loder regimen.[e88] A 24-week Class II RCT (N = 138, all MS subtypes) compared the Cari Loder regimen (oral lofepramine 10 mg bid, oral l-phenylalanine 500 mg bid, and intramuscular vitamin B_{12} 1 mg weekly) with placebo pills and intramuscular vitamin B_{12} (1 mg weekly).[e89] The primary outcome measures of disability did not change significantly (GNDS, -1.16 [95% CI: -2.75–0.43], EDSS [-0.17, 95% CI: -0.39–0.05]). There was a small improvement in fatigue (Chalder Fatigue Scale) and symptoms (Gulick Multiple Sclerosis Specific Symptom Scale).

Depression (BDI) did not improve. None of the improvements was significant when corrected for multiple outcomes. AEs included constipation, dry mouth, nausea, and insomnia.

Conclusion.
The Cari Loder regimen is possibly ineffective for reducing MS-related disability, symptoms, depression, or fatigue (all MS subtypes, 1 Class II study[e89]).

Threonine.
One Class III crossover study (N = 26, progressive MS, type unspecified) found improvement in signs of spasticity (Clinician Spasticity Scale) with threonine (7.5 mg/day for 8 weeks), nonsignificant after Bonferroni correction, but no improvement on the Ashworth Scale. No effect was seen on disability (EDSS), patient-reported spasticity symptoms, or global neurologic function (Global Assessment Scale).[e90]

Conclusion.
Data are inadequate to evaluate the effect of threonine on MS-related spasticity and disability (progressive MS, type unspecified, 1 Class III study[e90]).

Glucosamine sulfate.
One 6-month Class I RCT (N = 97, RRMS) found no significant difference in disability (EDSS) or the number of relapses at 6 months between subjects taking glucosamine sulfate (1,000 mg oral/day) or placebo.[e91] The AEs included abdominal pain, dyspepsia, fatigue, and headache but were not different between intervention and placebo. The study was underpowered to exclude a benefit.

Conclusion.
Data are inadequate to support or refute the use of glucosamine sulfate for reducing relapse rate or disability in RRMS (1 underpowered Class I study[e91]).

Low-dose naltrexone.
We evaluated 1 Class I RCT[e92] and 1 Class II study[e93] on low-dose naltrexone (LDN) use. Both studies were underpowered to exclude a meaningful clinical effect.

The Class I RCT (N = 106, RRMS or SPMS, 17 weeks) found no significant difference in QOL between subjects taking LDN (4.5 mg daily) or placebo.[e92] The Class II crossover (N = 80, all MS subtypes, 8 weeks) study found no significant effect of LDN on HRQOL (MSQLI) after correction for multiple outcomes. Only 75% of patients completed the trial.[e93]

Conclusion.
Data are inadequate to support or refute the use of LDN for improving QOL in RRMS and SPMS (1 Class I study,[e92] 1 Class II study,[e93] both underpowered).

Other biologically based practices.
Bee venom.
One Class II crossover study[e94] of bee venom (20 stings from live bees 3 times weekly for 24 weeks) in MS (N = 26, 13 RRMS, 13 SPMS) found no significant effect on the number of new

gadolinium-enhancing lesions on MRI or volume of enhancing lesions, total lesion volume, relapse number, disability (EDSS, MSFC, GNDS), fatigue (Abbreviated Fatigue Questionnaire, FIS), or HRQOL (SF-36). AEs included tenderness, swelling, and redness at the sting sites; itching (4 subjects); and flu-like symptoms (5 subjects).[e94]

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 study).[e94]

Transdermal histamine with caffeine.
One Class III RCT[e95] found reduced patient-reported fatigue with 4 weeks of transdermal histamine combined with caffeine in a patch/cream (Prokarin, EDMS LLC, USA) relative to placebo in 29 patients with MS (RRMS and progressive MS, type unspecified). The small sample size and the presence of caffeine limit interpretation of results. Headaches and skin irritation were reported.

Conclusion.
Data are inadequate to assess the effect of transdermal histamine cream on MS-related fatigue (1 Class III study).[e95]

Hyperbaric oxygen.
We evaluated 1 Class I study,[e96] 5 Class II studies,[e97–e101] and 5 Class III[e102–e106] studies. The Class I RCT (N = 40, 29 chronic progressive MS, type unspecified, 11 chronic stable MS, type unspecified) found that 100% oxygen at 2 atmospheres reduced symptoms in more subjects than did the control intervention (10% oxygen and 90% nitrogen) (90 minutes daily for 20 days).[e96] The study showed significant improvements on objectively measured mobility, fatigue, and coordination (10/17 active treatment vs 1/20 placebo, $p < 0.0005$); tremor (3/8 vs 0/15, $p < 0.031$); bladder control (5/13 vs 1/17, $p < 0.039$); nystagmus (8/13 vs 0/10, $p < 0.003$); and Romberg sign (3/5 vs 0/7, $p < 0.045$). Overall improvement at treatment end was better in the treated group ($p < 0.0001$).[e96] Interpretation of results is confounded by the control intervention, with only 10% oxygen and possible relative hypoxemia or nitrogen narcosis.
The first Class II study randomized 120 patients (MS type unspecified) to either 100% oxygen in a hyperbaric oxygen (HBO) chamber at 2 atmospheres or normal air at normal pressure (daily 90-minute sessions for 20 exposures).[e97] Although significant improvement in some EDSS functional scores favoring HBO was noted, attributed largely to reduced bowel and bladder symptoms, this was nonsignificant when corrected for multiple outcomes. The overall EDSS scores did not improve. The study was underpowered to exclude a benefit.
The second Class II study (N = 84, MS type unspecified), which was underpowered, found no significant difference in EDSS, timed walk, or subjective measures, immediately or 1 month post-treatment, between 20 sessions of HBO at 2 atmospheres or placebo.[e98] AEs included ear discomfort/pain, deafness, nausea, and vision disturbance.

The third Class II study,[e99] an RCT (N = 44, MS type unspecified) (N = 44), reported a significant reduction in mean EDSS and in pyramidal and cerebellar FSSs with HBO (100% oxygen) relative to room air for 1 year. The number of subjects with improved EDSS scores at 1

year was higher in the HBO group (12/22 [55%] vs 4/22 [18%], $p < 0.05$). None of these outcomes was significant when corrected for multiple outcomes.

The fourth Class II study (N = 41, chronic stable MS, type unspecified, 6 months) found no significant difference in disability (EDSS or individual FSSs), brain MRI, or functional independence between HBO and placebo but was underpowered to detect a difference.[e100] The final, underpowered, Class II study (N = 19, chronic progressive MS, type unspecified) found no significant difference in EDSS and FSSs between HBO (N = 10) and placebo (N = 9).[e101]

Conclusion.
Data are inadequate to assess the effect of HBO on MS-related disability or symptoms (chronic MS, type unspecified; 1 Class 1 study[e96] [control intervention made results noninterpretable], 5 Class II studies,[e97–e101] with inadequate power).

Manipulative and body-based practices.

Hippotherapy.
Three Class III studies of hippotherapy (therapeutic horseback riding) were identified.[e107–e109] The first study[e107] (N = 11, RRMS or SPMS) found improvements in individual patients on balance, gait velocity, and role-emotional assessment on the SF-36 after 10 weekly 30-minute hippotherapy sessions. No summary statistics were provided. The second study[e108] (N = 10, MS type unspecified) found increased walking velocity and decreased depression (corrected for multiple outcomes) in patients receiving twice-weekly hippotherapy for 9 weeks. Three subjects reported increased spasticity. In a third, underpowered, study (N = 15, all MS subtypes, 14 weeks; 9 treatment, 6 controls with no intervention) the hippotherapy (one 30-minute weekly session) group showed significant improvement in balance in pretreatment–post-treatment comparisons, but between-group comparisons showed no difference.[e109]

Conclusion.
Data are inadequate to assess the effect of hippotherapy on MS-related problems with gait, balance, or mood (3 Class III studies,[e107–e109] 2 of which were noninterpretable statistically[e107,e109]).

Reflexology.
Reflexology involves applying manual pressure to points on the feet. We evaluated 4 RCTs (1 Class I,[e110] 2 Class II,[e111,e112] and 1 Class III[e113]).

The Class I underpowered RCT (N = 71, RRMS, SPMS, PPMS) compared 10 weekly 45-minute sessions of sham reflexology (foot massages) to precision reflexology.[e110] Both groups showed improvement in pain (VAS), disability (RMDQ), spasticity (VAS), fatigue (MSIS-29, FSS, MFIS), cognition (MFIS cognitive subscale) and depression (BDI). Differences between groups were not significant. No AEs were reported.[e110]

The first Class II RCT (MS type unspecified, N = 71) found significantly greater reductions in paresthesia, urinary symptoms (American Urologic Association symptom score), and spasticity (Ashworth Scale) with 11 weekly reflexology treatments plus calf massage relative to calf

massage alone.[e111] After correction for multiple outcomes, only the difference in paresthesia reduction remained significant (mean +/- SD difference pre-/post-treatment in treated group -1.49+/- 2.1, controls 0.16+/- 2.1, $p = 0.04$). The difference persisted at the 3-month mark.[e111]
The second Class II RCT, underpowered (SPMS, PPMS N = 20, 16 weeks), examined reflexology as compared with sham treatments and did not reveal improvement in the primary outcome of HRQOL (change in MSIS-29 at end of study: 17; 95% CI: -4.121 to 40.21, $p = 0.112$). Secondary outcomes of pain, spasticity, sleep, mood, or bowel/bladder function also did not change.[112]
The Class III RCT (N = 53, all MS subtypes) randomized subjects to progressive muscle relaxation therapy (PMRT) or reflexology for 6 weeks followed by a 4-week washout period and crossover to the other treatment.[e113] Mood, insomnia, and HRQOL improved in both groups, but there was no significant difference between groups. The study was confounded by residual effects of the first treatment despite the washout period.[e113]

Conclusion.
Reflexology is possibly effective for reducing MS-associated paresthesia (MS type unspecified, 1 Class II study[e111]). 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.

Yoga.
We evaluated 4 Class III studies[e114–e117] of yoga in MS.
The first study (RCT) (N = 69, 6 months, MS type unspecified) found no change in cognition or alertness between weekly Iyengar yoga class and home practice (n = 26), weekly exercise (stationary bicycle) and home exercise (n = 21), or wait-list controls who were told that they could enroll at no cost in a yoga or exercise class after the 6-month study period (n = 22). Both active-intervention groups reported significantly reduced fatigue and increased energy (yoga: baseline 45.7 ± 22.7, study end 52.8 ± 18.8, $p < 0.03$; exercise: baseline 43.1 ± 17.7, study end 51.2 ± 16.7, $p < 0.03$) after correction for multiple outcomes. The study was underpowered to detect benefit.[e114]
The second study (RCT) (N = 21, MS type unspecified, 8 weeks) evaluating the effect of Hatha yoga (three 60- to 70-minute sessions weekly) found a significant difference between yoga-assigned subjects and wait-list controls after Bonferroni correction in balance score (BBS), walk distance, and mental health composite and cognitive function subscales of Multiple Sclerosis Quality of Life-54 at 4 weeks, and in balance score and walk distance at 8 weeks.[e115] The third study (N = 20, all MS subtypes, once/week for 10 weeks) evaluated the effects on disease progression (EDSS), spasticity (Ashworth), cognitive function (executive function, evaluated by Mazes subtest of Executive Functions Module from the Neuropsychological Assessment Battery, Tower of London Test, and d2 Test of Attention by Brickenkamp), mood (CES-D), and fatigue (MFIS) pre– and post–sports climbing (active) as compared with Hatha yoga (control).[e116] No significant effect was found for either intervention after correction for multiple outcomes. The study was underpowered to detect a benefit.[e116] No AEs were reported.
The final, also underpowered, Class III study (RRMS, SPMS, PPMS, N = 312, 12 weeks) of yoga, physical therapist–led exercise, and fitness instructor–led exercise as compared with no

intervention revealed no benefit of yoga on the primary outcome, the physical impact of MS (physical component of the Multiple Sclerosis Impact Scale-29, version 2 [MSIS-29v2]).[e20,e117]

Conclusion.
Data are inadequate to assess the effect of yoga on MS-related disability, spasticity, or fatigue, or on problems with cognition, mood, balance, or walking speed (MS type unspecified, 4 Class III studies,[e114–e117] 3 underpowered[e114,e117]).

Massage therapy.
We evaluated 4 Class III studies.[e118–e121]
The first study (N = 24, MS type unspecified) found improvements in mood (POMS F [1, 22] = 14.04, $p = 0.001$), social engagement (Inventory of Functional Status-Multiple Sclerosis, group-by-days interaction F [1, 22] = 7.83, $p = 0.01$), self-esteem (F [1,22] = 5.47, $p = 0.03$), and body satisfaction (F [1,22] = 7.72, $p = 0.011$), and decreases in anxiety (STAI, F [1, 22] = 4.45, $p = 0.05$) and negative outlook on disease progression (F [1,22] = 5.47, $p = 0.03$), with ten 45-minute massage sessions over 5 weeks relative to standard medical treatment.[e118] The second study (N = 23, all MS subtypes), examining the changes in Multiple Sclerosis Self-Efficacy scores following massage therapy (1 weekly massage for 16 weeks), found significant improvement (mean [SD]: baseline 1233.5 [346.8], post-intervention 1381.3 [310.4]; $p < 0.002$). Only 60% of patients completed the study, and it is unclear at what point post-intervention the survey was performed.[e119] A third study, an RCT (N = 30, MS all types) evaluating abdominal massage for constipation, demonstrated significant reductions in constipation for both groups, as measured by the Constipation Scoring System, with the massage group performing better than controls at 4 weeks (mean difference between groups in score change -5.0 [SD 1.5], 95% CI: -8.1 to -1.8; $p = 0.003$) but not at 8 weeks. However, MSIS-29 scores and QOL as measured by the Qualiveen questionnaire, a 30-item questionnaire assessing bladder-related QOL (subscale domains are bother with limitations, frequency of limitations, fears and feelings) in patients with neurologic conditions, did not change significantly in either group.[e120] The final study, a Class III study (RRMS, SPMS, N = 48) comparing exercise, swedish massage, exercise plus swedish massage, and standard care, found no difference in pain (VAS), fatigue (FSS), balance (BBS and Timed Up and Go tests), gait (10-meter timed walk, 2-minute walk), and spasticity (Modified Ashworth scale) before and after massage sessions, or combined exercise/massage sessions, when corrected for multiple comparisons by the author panel. The study authors used a $p > 0.01$ to correct for multiple comparisons, but this was thought to be inadequate given the number of comparisons performed.[e121]
Conclusion.
Data are inadequate to evaluate the effect of massage therapy on mood, self-efficacy, constipation, pain, fatigue, balance, gait, or spasticity in MS (1 Class III study for each[e118–e121]

Acupuncture.
Two Class III studies were reviewed.[e122,e123] The first Class III RCT (N = 14, SPMS) of Chinese medical acupuncture (active intervention) and minimal acupuncture (superficial form of acupuncture designed to be less effective)[e122] evaluating quality of life showed significant improvement only in the MSIS-29 psychological subscore in the control group (minimal acupuncture) as compared with Chinese acupuncture, but this was not significant after Bonferroni correction.

The second Class III study (RRMS, N = 31) compared electroacupuncture with sham treatments (30-minute sessions weekly for 6 months) and did not reveal improvements in disability (EDSS), QOL (FAMS), or pain when corrected for multiple outcomes; however, the study was underpowered to detect a benefit.[e123]

Conclusion.

Data are inadequate to evaluate the effect of Chinese acupuncture on QOL in SPMS or disability, QOL, or pain in RRMS (1 Class III study each,[e122,e123] 1 underpowered[e123]).

Progressive muscle relaxation therapy.

In PMRT, patients are instructed by a therapist to contract and release different muscle groups. We found 2 Class III studies.[e113,e124] The first study, described in the reflexology section, showed no differences in pain (VAS), disability, spasms, fatigue, cognition, and depression between subjects randomized to PMRT or reflexology.[e113] The second study (N = 66; RRMS, SPMS; 2 months), evaluating the effectiveness of PMRT relative to no intervention for improving HRQOL, found significant improvement in the Mental Component Score-8 (MCS-8) and total SF-36 score between groups, and in the Physical Component Score-8, MCS-8, and total score at 1 and 2 months within groups, after correction for multiple outcomes.[e113]

Conclusion.

Data are inadequate to evaluate the effect of PMRT on pain, disability, spasms, fatigue, cognition, depression (1 Class III study[e113]), or QOL (1 Class III study[e124]) in MS.

Energy medicine.

Magnetic therapy.

We evaluated 1 Class I study,[e125] 2 Class II studies,[e126,e127] and 3 Class III studies.[e128–e130] The Class I study, a 12-week RCT (N = 41, RRMS), evaluated the effect on fatigue (MFIS) of low-frequency, pulsed electromagnetic field therapy (bio-electric-magnetic-energy-regulation device, in the form of a metal mat upon which subjects lay for 8 minutes twice daily for 12 weeks) and reported significantly less fatigue with active treatment (active 26.84±SE 12.061, placebo 36.67±13.253, $p = 0.024$). Fatigue (FSS) also decreased in the treated group (FSS at week 12 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).[e125] However, an EDSS change may not have been detected because of the study's short duration, as EDSS may be insensitive to change in short-term disability.

A Class II RCT[e126] (N = 30 RRMS/progressive MS) found no significant change in disability (EDSS) or FSSs related to bladder control, cognition, fatigue, mobility, sensation, spasticity, vision, total performance, or hand function, after Bonferroni correction, between subjects wearing wristwatch-size magnetic pulsing devices (Enermed device) (10–24 hours/day for 2 months) or inactive devices. The study was underpowered to detect a benefit.

Another Class II RCT (N = 50, RRMS, SPMS, PPMS) found no significant difference in fatigue (MFIS, FSS) with low-frequency magnetic stimulation at 3 sessions per week for 8 weeks (intensity 37.5 mT and a sequence of pulses at 4–7 Hz) but was underpowered to detect a difference.[e127]

The first Class III study[e128] (N = 25, RRMS/progressive MS, type unspecified) found no significant difference in fatigue (FSS) between 1 pulsed magnetic field (using magnetic field mattress and pillow) therapy session (16 min twice/day for 5 days/week for 3–4 weeks) and sham; however, the study was underpowered to detect a difference. The second Class III study, a 10-week crossover RCT[e129] (N = 117; RRMS, PPMS, SPMS), reported significant improvements in fatigue and overall QOL (MSQLI) after 4 weeks of daily (up to 24 hours/day) pulsed electromagnetic therapy (Enermed device) relative to placebo. The dropout rate in this study was high, 19%. The third Class III study[e130] (N = 12, type unspecified) showed significant improvement in spasticity (Ashworth Scale), maximal voluntary contraction of foot dorsiflexors and plantar flexors, and activities of daily living (self-scores) 24 hours after 30 minutes of magnetic stimulation (coil placed at the mid-thoracic level).

Magnetic therapy was generally well tolerated; most studies reported no AEs.[e128,e130] One study reported headache, spasms, and burning sensation.[e126]

Conclusions.
Magnetic therapy is probably effective for reducing fatigue in RRMS (1 Class I study,[e125] 1 Class III study[e128]) and probably ineffective for reducing depression in RRMS (1 Class I study[e125]). Data are inadequate to support or refute the effectiveness of magnetic therapy for reducing MS-related disability (1 Class I study[e125] with insensitive outcome measure, 1 underpowered Class II study[e126]), bladder control problems, or spasticity, or for improving cognition, mobility, sensation, or vision (1 underpowered Class II study,[e126] 3 underpowered or inconsistent Class III studies[e128–e130]).

Neural therapy.
Neural therapy is a modified form of acupuncture with local anesthetic injections. One Class III study[e131] (N = 40, all MS subtypes) in a before–after design found reduced disability (Kurtzke 26/40, 65%; EDSS 15/40, 37.5%) over 3 weeks. After this pilot the next 21 patients with MS were recruited into a Class II RCT[e131] with 2 weekly injections into acupuncture points around the ankle and skull (2 lignocaine [n = 11] or 2 saline injections [n = 10] in the first week; all 21 subjects received 2 lignocaine injections in the second week). Disability (EDSS) decreased in the neural therapy group at 1 and 2 weeks. However, this rapid change in EDSS is difficult to interpret clinically. The study lacks generalizability because of short duration.

Conclusion.
Data are inadequate to assess the effect of neural therapy on MS-related disability (1 Class II study[e131] with limited generalizability, 1 Class III study[e131]).

Naturopathic medicine.
Naturopathic medicine stimulates the self-healing capacity through diet, herbs, nutritional supplements, homeopathy, physical medicine, and counseling. One Class III RCT (N = 45, RRMS, 6 months) randomized 15 subjects into 3 groups (usual care, naturopathic medicine plus usual care, and MS education plus usual care) for 6 months. The study, which was Class III for the primary outcome of QOL and Class II for disability (EDSS, MSFC) and cognitive impairment (PASAT), found no significant improvement in QOL (SF-36), fatigue, depression, cognition, or disability; however, the study was underpowered to exclude a modest benefit.[e132]

Conclusion.
Data are inadequate to support or refute a benefit of naturopathic medicine for improving QOL, cognition, or disability, or for reducing depression or fatigue in RRMS (1 Class III study[e132]).

RECOMMENDATIONS

No evidence is available for evaluating whether CAM use worsens MS or interferes with MS disease-modifying therapies. Table e-4 summarizes the outcomes evaluated and the level of evidence available for each therapy for the respective outcome. The recommendations for cannabinoids vary depending on the preparation used, duration of the studies, and outcomes evaluated, and on whether clinician-evaluated or patient-reported outcome measures were used. All recommendations for cannabis are therefore summarized next, followed by recommendations for other CAM therapies reviewed.

Cannabis.
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).
Clinicians might offer THC to patients with MS to reduce patient-reported symptoms of spasticity and pain (excluding central neuropathic pain) (Level B), and might counsel patients that this symptomatic benefit is possibly maintained for 1 year (Level C).
Clinicians should counsel patients considering OCE or THC that, although these preparations improve spasticity-related symptoms, they are probably ineffective (short-term studies [15 weeks]) for improving objective measures of spasticity (Level B). Clinicians should counsel patients considering OCE or THC that these preparations are probably ineffective for improving tremor (Level B).

Clinicians might offer Sativex oromucosal cannabinoid spray (nabiximols), where available, to reduce symptoms of spasticity, pain, or urinary frequency (Level B). Clinicians should counsel patients considering Sativex oromucosal cannabinoid spray that although this preparation improves spasticity-related symptoms and urinary frequency, it is probably ineffective for improving objective measures of spasticity or the 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 (all Level U):

1. OCE/THC for urinary urge incontinence and overall bladder symptoms in MS
2. Synthetic THC (Marinol) for central neuropathic pain in MS
3. Sativex oromucosal cannabinoid spray for overall bladder symptoms, anxiety symptoms, or sleep problems, or symptoms related to cognition, QOL, or fatigue in MS
4. Smoked cannabis for spasticity, pain, balance/posture, or cognition in MS

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

Clinical context. It is notable that most of the cannabis studies for efficacy were of short duration, ranging from 6–15 weeks. The safety and efficacy of cannabis over a longer time frame were evaluated only in 1 Class II study,[e61] a factor physicians and patients must be aware of when considering cannabis use. In addition, no evidence was available for evaluating the safety and efficacy of smoked cannabis, although results from a single Class III study[e72] suggest that decline in cognitive performance may be an SAE. An important limitation of studies involving cannabis is the potential for the central effects of cannabis that can potentially unmask the subjects to the treatment assignment and hence influence some of the subjective outcome results. This was noted in the Class III study of smoked cannabis[e72] wherein a significant proportion of subjects guessed correctly whether they received cannabis or placebo and also reported "feeling high." It is also important to recognize that Ashworth's (or modified Ashworth's) scale, which is commonly used to measure spasticity, may also have limitations in sensitivity for assessing spasticity objectively. The discordant effects of cannabinoids on subjective and objective measures of spasticity may be due to these factors.

In the reviewed studies, cannabinoids were generally well tolerated, although some SAEs were reported. Few studies reported deaths in the cannabinoid-treated groups (1 death due to pneumonia,[e55] 1 to seizure-related aspiration pneumonia, and 2 to cancer presumed unrelated[e64]). Mild or moderate adverse effects (AEs) were common (reported in approximately 50%–80% of study subjects) and appeared to be of similar prevalence in subjects receiving cannabinoids and in those receiving a placebo control intervention. Where details of AEs were provided, no significant attributable laboratory, hematologic, urologic, or cardiac changes were noted and no significant differences were noted in vital signs. CNS AEs (e.g., dizziness, somnolence, drowsiness, lightheadedness, memory disturbance, difficulty concentrating) were more common in subjects receiving cannabinoids than in those receiving placebo. The most common of these was dizziness, which occurred in 15% to 50% of subjects.[e55,e56,e59–e62,e65,e69–e71] Gastrointestinal-related AEs, including increased appetite, nausea, vomiting, constipation, and dry or sore mouth, were also common, occurring in about 10% of subjects receiving cannabinoids[e56] and were more common in those receiving active rather than placebo interventions. Other, less-common, AEs included myalgia, increased spasticity, seizures (4/137 subjects had seizures),[e57] lower-limb weakness, hemorrhagic cystitis, dehydration, temporary psychosis (1 case rated as severe),[e71] hallucinations,[e60] and oral ulceration.

Because cannabinoids have known psychoactive properties, their potential for psychopathological and neurocognitive AEs is a concern especially in a patient population that may be vulnerable due to underlying disorders. Patients with MS have higher rates of depression and suicide than the general population.[e133–e135] Cognitive dysfunction is not uncommon in patients with MS.[e136] There are reports of depression and predisposal to psychosis with long-term cannabis exposure.[e137–e139] Although development of marijuana addiction is a controversial concept, long-term, heavy use of marijuana has been associated with development of tolerance and dependence.[e140–e142] 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 the person begins to abstain from use, and whether there is permanent neurotoxicity.[e143–e146] Although 1 study of 8-week treatment with Sativex oromucosal spray did not show treatment-induced psychopathology or impaired cognition in 17 patients with MS who were cannabis naïve, the study reported a positive correlation with blood

levels of THC and psychopathological scores.[e68] In 1 study, patients with MS who had prolonged use of "street" cannabis were found to have impairments in cognitive function as compared with patients with MS who did not use cannabis.[e147] 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.[e148] 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,[e55] available only in abstract form, reported a significant reduction in verbal learning and memory in patients with MS receiving cannabis extracts as compared with those receiving placebo.[e149] In another study,[e60] a difference in 1 secondary outcome of long-term memory storage capacity was improved in the placebo group as compared with the Sativex group; however, the study was not powered to detect a significant difference. Although several of the reviewed studies assessed psychopathology and cognition as secondary outcomes with no significant AEs, these were short-term studies and were not adequately powered to exclude an effect on these secondary outcomes.[e56,e60,e65,e71] Clinicians should therefore counsel patients about the potential for psychopathologic/cognitive AEs as well as other AEs associated with cannabinoids. Sativex oromucosal cannabinoid spray is not US Food and Drug Administration (FDA) approved and is not available in the United States. In the United States, caution should be exercised with regard to the extrapolation of the results of trials of standardized OCEs (which are not commercially available) to other, nonstandardized and nonregulated, cannabis extracts (which may be commercially available in states with medical marijuana laws).

Other CAM therapies.

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

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

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

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

Clinicians might counsel patients with MS that reflexology is possibly effective for reducing MS-associated paresthesia (Level C).

Clinicians might counsel patients with MS that bee sting therapy is possibly ineffective for reducing MS-related 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.

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).

Clinicians should counsel patients with MS that the safety and efficacy of the following agents are unknown (Level U):

1. Acupuncture for QOL, disability, or pain
2. ALCAR for MS-related fatigue
3. Biofeedback
4. Carnitine*
5. Chelation therapy*
6. Chinese medicine*
7. Chiropractic medicine*
8. Creatine monohydrate for exercise improvement short-term

   Clinical context. Although creatine is used most often for treatment of MS-related fatigue, no studies evaluated this effect.
9. Dental amalgam replacement*
10. Glucosamine sulfate for MS-related relapse rate or disability
11. HBO for MS-related disability or symptoms
12. Hippotherapy for problems with gait, balance, or mood
13. Inosine for MS-related relapse rate or disability

    Clinical context. Inosine use is associated with kidney stone formation in 25% of patients in 1 study.
14. LDN for QOL
15. Linoleic acid for reducing MS-related disability or relapse
16. Magnetic therapy for reducing disability, bladder control problems, or spasticity, or for improving cognition, mobility, sensation, or vision
17. Massage therapy for mood, self-efficacy, constipation, pain, fatigue, balance, gait, or spasticity
18. MBI for MS-related depression, fatigue, or QOL
19. Music therapy for mood or respiratory muscle function
20. Naturopathic medicine for improving QOL, cognition, or MS-related disability, or for reducing depression or fatigue
21. Neural therapy for MS-related disability
22. Padma 28 for MS-related relapse, disability, or symptoms
23. PMRT on MS-related pain, disability, spasms, fatigue, cognition, depression, or QOL
24. Reflexology for MS-related pain, HRQOL, disability, spasticity, fatigue, cognition, bowel/bladder function, depression, anxiety, or insomnia
25. Tai chi*
26. Threonine for MS-related spasticity or disability
27. Transdermal histamine cream for MS-related fatigue
28. Yoga for MS-related disability, spasticity, or fatigue, or for problems with cognition, mood, balance, or walking speed

* CAM not reviewed because only Class IV studies were available.

Clinical context. CAM therapies are not regulated by the FDA. The quality control of these supplements may play a role both in their effectiveness and in their AE risk. Moreover, interactions of CAM therapies with other medications, especially disease-modifying therapies for MS, are a clinical concern. Given the popularity of CAM therapies both in patients with MS and

in patients with other neurologic disorders (e.g., Alzheimer disease, Parkinson disease), it may be useful for patients to discuss CAM treatment with neurologists and for neurologists to ask patients routinely about their CAM use. Information resources for health professionals include the National Multiple Sclerosis Society (http://www.nmss.org), the National Institutes of Health (NIH) (http://www.nih.gov), and the NIH division of the National Center for Complementary and Alternative Medicines (http://nccam.nih.gov).

Patients should be counseled regarding applicable quality control, safety, lack of FDA regulation of CAM, potential out-of-pocket expenses (these may not be covered by insurers), and potential drug interactions with other symptomatic and disease-modifying therapies in MS.

RECOMMENDATIONS FOR FUTURE RESEARCH

This review has several limitations. Because the search strategy is limited only to MS, some potentially important AEs (e.g., bleeding risk with GB)[e150] of the reviewed therapies noted when they were evaluated in other diseases were not apparent in the MS population. Furthermore, therapies that have received much press attention (e.g., dental amalgam removal, transdermal histamine) have little evidence to support recommendations. Most clinical trials involving CAM have methodologic flaws limiting their interpretation.

There is a need for further, rigorously designed studies of appropriate durations both for evaluating the outcomes of interest sufficiently and for using appropriate outcome measures, especially for CAM therapies that show preliminary benefits. Therapies such as mind–body practices, including yoga, dietary changes, and GB and antioxidant use, hold promise as research areas. Studies of the safety and efficacy of smoked cannabis are warranted. Studies on CAM in animal models may be useful to identify potential therapies that affect disease progression or disability and that may merit large-scale human studies; however, symptomatic effects may be difficult to evaluate in animal studies.

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 three 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.[e39]

Appendix e-1: 2013–2015 Guideline Development Subcommittee (GDS) members

Cynthia Harden, MD (Chair); Steven R. Messé, MD, FAAN (Vice-Chair); Richard L. Barbano, MD, PhD, FAAN; Jane Chan, MD, FAAN; Diane Donley, MD; Terry Fife, MD, FAAN; Jeffrey Fletcher, MD; Michael Haboubi, MD; John J. Halperin, MD, FAAN; Cheryl Jaigobin, MD; Andres M. Kanner, MD; Jason Lazarou, MD; David Michelson, MD; Pushpa Narayanaswami, MD, MBBS; Maryam Oskoui, MD; Tamara Pringsheim, MD; Alexander Rae-Grant, MD; Kevin Sheth, MD, FAHA; Kelly Sullivan, PhD; Theresa A. Zesiewicz, MD, FAAN; Jonathan P. Hosey, MD, FAAN (Ex-Officio); Stephen Ashwal, MD, FAAN (Ex-Officio); Deborah Hirtz, MD, FAAN (Ex-Officio); Jacqueline French, MD, FAAN (Ex-Officio)

Appendix e-2: Mission statement of GDS

The mission of the GDS is to prioritize, develop, and publish evidence-based guidelines related to the diagnosis, treatment, and prognosis of neurological disorders.
The GDS is committed to using the most rigorous methods available within our budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

Appendices e-3 and e-4: Search strategies
See the "appendices e-3 and e-4 search strategies" pdf on the *Neurology*® Web site at www.neurology.org.

Appendix e-5: Classification of evidence scheme for therapeutic interventions

Class I: A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

The following are also required:

a. concealed allocation
b. primary outcome(s) clearly defined
c. exclusion/inclusion criteria clearly defined
d. adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias.
e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:

1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.
2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
4. The interpretation of the results of the study is based upon a per protocol analysis that takes into account dropouts or crossovers.

Class II: A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**

Class IV: Studies not meeting Class I, II, or III criteria, including consensus or expert opinion.
* Note that numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.
**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Appendix e-6: Classification of recommendations

A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).

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