AMERICAN ACADEMY OF
NEUROLOGY®

Summary of comprehensive systematic review: Rehabilitation in multiple sclerosis

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

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ABSTRACT

Objective: To systematically review the evidence regarding rehabilitation treatments in multiple sclerosis (MS).

Methods: We systematically searched the literature (1970–2013) and classified articles using 2004 American Academy of Neurology criteria.

Results: This systematic review highlights the paucity of well-designed studies, which are needed to evaluate the available MS rehabilitative therapies. Weekly home/outpatient physical therapy (8 weeks) probably is effective for improving balance, disability, and gait (MS type unspecified, participants able to walk ≥5 meters) but probably is ineffective for improving upper extremity dexterity (1 Class I). Inpatient exercises (3 weeks) followed by home exercises (15 weeks) possibly are effective for improving disability (relapsing-remitting MS [RRMS], primary progressive MS [PPMS], secondary progressive MS [SPMS], Expanded Disability Status Scale [EDSS] 3.0–6.5) (1 Class II). Six weeks' worth of comprehensive multidisciplinary outpatient rehabilitation possibly is effective for improving disability/function (PPMS, SPMS, EDSS 4.0–8.0) (1 Class II). Motor and sensory balance training or motor balance training (3 weeks) possibly is effective for improving static and dynamic balance, and motor balance training (3 weeks) possibly is effective for improving static balance (RRMS, SPMS, PPMS) (1 Class II). Breathing-enhanced upper extremity exercises (6 weeks) possibly are effective for improving timed gait and forced expiratory volume in 1 second (RRMS, SPMS, PPMS, mean EDSS 4.5); this change is of unclear clinical significance. This technique possibly is ineffective for improving disability (1 Class II). Inspiratory muscle training (10 weeks) possibly improves maximal inspiratory pressure (RRMS, SPMS, PPMS, EDSS 2–6.5) (1 Class II). *Neurology*® 2015;85:1896–1903

GLOSSARY

6MW = 6-meter walk; **AAN** = American Academy of Neurology; **BBS** = Berg Balance Scale; **BBTW** = balance-based torso weighting; **CI** = confidence interval; **CWT** = conventional walking training; **DGI** = Dynamic Gait Index; **EDSS** = Expanded Disability Status Scale; **ES** = effect size; **FEV$_1$** = forced expiratory volume in 1 second; **FIM** = Functional Independence Measure; **FVC** = forced vital capacity; **HRQL** = health-related quality of life; **MS** = multiple sclerosis; **PDI** = Pulmonary Dysfunction Index; **PI$_{max}$** = maximal inspiratory pressure; **PPMS** = primary progressive multiple sclerosis; **PT** = physical therapy; **RAGT** = robot-assisted gait training; **RD** = risk difference; **RPE** = Rate of Perceived Exertion; **RRMS** = relapsing-remitting multiple sclerosis; **SF-36** = Short Form 36 Health Survey; **SPMS** = secondary progressive multiple sclerosis; **SWP** = standard weight placement; **TUG** = Timed Up and Go test; **VAS** = visual analog scale.

Multiple sclerosis (MS) affects approximately 400,000 individuals in the United States and is a leading cause of disability in young adults.[1–5] Rehabilitation interventions are frequently used clinical strategies for improving or maintaining functional status.[6]

This systematic review addresses the following questions in MS:

1. Does outpatient or inpatient comprehensive multidisciplinary rehabilitation minimize impairment, reduce disability, or improve health-related quality of life (HRQL)?
2. Do supervised outpatient or inpatient physical therapy (PT), physical training, or physical exercise programs minimize impairments, reduce disability, or improve HRQL?

3. Do other specific therapy techniques minimize impairment, reduce disability, or improve HRQL?
4. Do energy efficiency/conservation techniques, specialty devices, or educational programs affect function or HRQL?

DESCRIPTION OF THE ANALYTIC PROCESS

The American Academy of Neurology (AAN) assembled an expert panel after review of conflict of interest statements to develop this document, following the processes documented in the 2004 AAN manual.[7] A medical research librarian helped perform a comprehensive literature search, and the authors selected articles. At least 2 authors rated each article independently of each other (AAN therapeutic classification scheme). Panelists reviewed 5,464 abstracts and selected 491 articles for full-text review. Ultimately, we rated 142 articles according to the 2004 AAN scheme for classifying therapeutic articles (appendix e-4 on the *Neurology*® Web site at Neurology.org).[7] We excluded studies lacking a control group (because of a resulting high risk of bias), involving fewer than 20 participants, or evaluating pharmaceutical efficacy, electrical simulation, pain as the sole outcome, or an instrument's psychometrics. We classified each of the outcome measure scales as an objective measure or a patient-reported measure (table e-1). Several studies evaluated multiple outcome measures, some objective and others not, with or without a blinded evaluator. Thus, a single study could have different classifications depending on the outcome measure considered. We have clarified this by adding the study class in parenthesis for each outcome. When multiple studies used the same data, we analyzed the studies together. Except for the specified primary outcome in the first publication, we considered all outcomes as secondary, unless the authors specified multiple primary outcomes in successive publications; in this latter case, we analyzed the studies as lacking a specified primary outcome. Unless subgroup analyses were available for specific MS subtypes, we restricted conclusions to the overall MS group. We applied Bonferroni corrections as needed. Tables e-2 and e-3 summarize the evidence.

ANALYSIS OF EVIDENCE

Does outpatient or inpatient comprehensive multidisciplinary rehabilitation minimize impairment, reduce disability, and improve HRQL? One study, reported in 2 articles,[8,9] evaluated the effects of comprehensive outpatient rehabilitation (n = 111, 12 weeks, primary progressive MS [PPMS], secondary progressive MS [SPMS], Expanded Disability Status Scale [EDSS][10] 4.0–8.0). The authors reported different primary outcomes in the 2 publications, using the same dataset. Both studies therefore were treated in this review as lacking a primary outcome (Class II for

objective measures of disability, Functional Independence Measure [FIM][11] and EDSS; Class III for self-reported outcomes of fatigue,[12] depression,[13] and quality of life).[14] Participants were randomized to comprehensive multidisciplinary outpatient therapy 6 days/week for 6 weeks, followed by 6 weeks (n = 58) or 12 weeks (n = 53) of home self-exercise. No change occurred in EDSS (treatment mean change −0.1, control mean change +0.1, other data not provided). HRQL (Short Form 36 Health Survey [SF-36]) results improved at 6 and 12 weeks on the following subscales: physical functioning (treatment mean ± SD 6.91 ± 18.1, control −0.1 ± 0.3, risk difference [RD] 7.01, 95% confidence interval [CI] 2.08–11.94), physical role functioning (treatment mean ± SD 14 ± 24.3, control −0.2 ± 0.5, RD 14.2, 95% CI 7.58–20.82), bodily pain (treatment mean ± SD 14.9 ± 20.0, control −0.1 ± 0.6 RD 14.1, 95% CI 8.65–19.55), general health (treatment mean ± SD 5.8 ± 10.5, control −0.2 ± 0.5 RD 6, 95% CI 3.14–8.86), and social functioning (treatment mean ± SD 11.5 ± 14.6, control −0.1 ± 0.3 RD 12.5, 95% CI 7.44–17.56). Improvements were seen at 12 weeks in Fatigue Impact Scale scores (RD 19.4, 95% CI 15.5–23.3, Kazis effect size [ES] −0.77),[15] social function (Social Experience Checklist of Tempelaar, RD 2.3, 95% CI 0.65–3.95, ES −0.46),[16] and Beck Depression Inventory[13] (RD 2.3, 95% CI 1.34–3.26, ES −0.50).[8] The second analysis, using the same data (Class II),[9] found that 55% of the treatment group improved by ≥2 steps on the FIM relative to 4% of the controls at 12 weeks (RD 10.2, 95% CI 6.98–13.42). The authors calculated Kazis ES as mean change/SD of the initial score distribution.[15] By Cohen criteria,[17] ES values were interpreted as small (0.2), moderate (0.5), or large (≥0.8). FIM subscale score changes[10] were as follows: locomotion (RD 1.6, 95% CI 0.94–2.26, Kazis ES 0.76), self-care (RD 4.3, 95% CI 3.64–4.96, ES 0.73), and transfers (RD 2.7, 95% CI 1.96–3.44, ES 0.65); sphincter function (RD 0.9, 95% CI 0.52–1.28, Kazis ES 0.40); and cognition (RD 0.9, 95% CI 0.21–1.59, ES 0.03). The inconsistency between the 2 disability measures, EDSS and FIM, is probably because they measure different disability aspects and may be affected differentially by study duration.

Conclusions.
1. Six weeks' worth of comprehensive multidisciplinary outpatient rehabilitation possibly is effective for improving disability/function as measured by FIM (PPMS, SPMS, EDSS 4.0–8.0) (1 Class II study).[9]
2. Data are inadequate to support/refute the effectiveness of the following interventions (1 Class III study each unless otherwise stated):

a. Comprehensive multidisciplinary outpatient rehabilitation for self-efficacy, fatigue, depression, or HRQL (1 Class II study with insufficient precision, 1 Class III study).[8,18]

b. Comprehensive multidisciplinary inpatient rehabilitation (2 Class III studies examining different populations and time frames).[19,20]

c. Three weeks of inpatient rehabilitation (1 Class III study, data for control group not provided).[21]

Do supervised outpatient or inpatient PT, physical training, or physical exercise programs minimize impairments, reduce disability, or improve HRQL? *Outpatient and inpatient PT and home PT.* One study (Class I for objective outcomes, Class III for patient-reported outcomes) (n = 40, 48 weeks) examined home PT, outpatient PT, and no therapy in participants with MS (type unspecified, EDSS 4–6.5) able to walk ≥5 meters with or without aid in a crossover study.[22] All participants were randomly allocated to 1 of the study groups for 8 weeks and then to the other 2 study groups for 8 weeks each. Each crossover arm was separated by an 8-week washout period. The primary outcome of disability, Rivermead Mobility Index, improved[23,24] for both the outpatient clinic and home PT groups (ES [95% CI], outpatient relative to none 1.4 [0.62–2.14], home relative to none 1.5 [0.73–2.26], $p < 0.001$). No differences were noted between the 2 PT groups. All secondary outcomes improved but did not reach significance after correction for multiple outcomes because the study was not powered for these outcomes. Mean balance time improved (ES [95% CI], hospital PT to none 4.82 [1.57–8.07], home PT to none 5.49 [2.19–8.8], $p = 0.001$). Six-meter walk (6MW) also improved (ES [95% CI], hospital PT to none −14 seconds [−23 to −5], $p = 0.003$; home PT to none −14 [−23 to −6]). Dexterity (9-hole peg test)[25] also improved (ES [95% CI], outpatient to none −18 seconds [−32 to −4], home PT to none −13 seconds [−27 to 1]). Improvements also were seen in assessor's perception of mobility (ES [95% CI], hospital to none 19.8 [14–25.7], home PT to none 22.4 [16.6–28.3], home to hospital none), participant visual analog scale (VAS) for mobility (ES [95% CI], hospital to none 25.2 [18.3–32], home PT to none 24.2 [17.3–31]), and VAS for caregiver assessment of mobility (ES [95% CI], hospital to none 16 [6.7–25.3], home to none 17.6 [8.1–27.1]). Finally, improvements also occurred in VAS for falls (ES [95% CI], hospital to none 18.3 [9–27.6], home to none 20.7 [11.2–30.2]) and Hospital Anxiety and Depression Score[26] depression scores (anxiety scores ES [95% CI], hospital to none −1.48 [−2.44 to −0.51], home to none −1.24 [−2.23 to −0.26]; depression scores ES [95% CI], hospital to none −2.22 [−3.25 to −1.18], home to none −1.7 [−2.73 to −0.66]).

One study (Class II for objective outcomes, Class III for patient-reported outcomes, n = 50, 3 weeks, relapsing-remitting MS [RRMS], SPMS, PPMS, EDSS 3–6.5) randomized participants either to twice-daily individualized inpatient physical exercise followed by home exercises or home exercises only.[27] The coprimary disability outcomes (EDSS and FIM motor domain) and HRQL (SF-36) were assessed at baseline and 3, 9, and 15 weeks. EDSS results (impairment/disability) did not change. The changes in EDSS scores clustered closely around zero in both groups at all time points (data not provided). FIM motor scores (disability, measured as a composite of the FIM self-care, locomotion, and transfer subscales) improved (3 weeks: intervention group and control group improved ≥2 steps by 48% and 9%, respectively, $p = 0.004$; 9 weeks: intervention group and control group retained the 3-week gains by 44% and 4.5%, respectively, $p = 0.001$; 15 weeks: no difference) (EDSS and FIM may have been inconsistent because of differences in sensitivity to short-term functional changes). After Bonferroni adjustment, the improvement in the FIM motor domain subscale scores was significant at 3 weeks (mean change 0.62, 95% CI 0.28–0.96). The SF-36 mental composite improved at 9 weeks (mean change 10.1, 95% CI 3.05–17.2).

Resistance training and aerobic exercise programs. No Class I or Class II studies were available.

Gait and balance training. A Class I study (n = 35, 3 weeks, RRMS, SPMS, PPMS, EDSS 6–7.5) examined the effect of robot-assisted gait training (RAGT).[28] Participants admitted for multimodal inpatient rehabilitation were randomized to receive an additional 15 sessions of RAGT (n = 19) or conventional walking training (CWT) over 3 weeks. The primary outcome was 20-meter timed walking velocity. The mean change in the RAGT group was 0.11 (95% CI 0.02–0.28), and in the CWT group, 0.07 (95% CI 0.0–0.14). ES difference between groups was 0.7 (95% CI −0.089 to 1.489). Other outcomes were 6-minute walking distance, stride length, and knee extensor strength. After 3 weeks, no statistical difference was seen between groups for these outcome measures, but the study lacked precision to detect a difference (wide CIs for the ES change in the primary outcome, the 20-minute timed walk).

A Class II study evaluated balance training (n = 44, RRMS, SPMS, PPMS, 3 weeks).[29] Participants were randomized to receive motor and sensory balance training (group 1), motor balance training only (group 2), or conventional therapy (group 3). After treatment, the relative frequencies of participants who had one or more falls were 1 (5%) in group 1, 1 (10%) in group 2, and 3 (25%) in group 3 (corrected $p < 0.005$). The small number of events in each group made

interpretation difficult. Static balance, measured by the Berg Balance Scale (BBS),[30] improved in both balance training groups post-treatment (mean change [95% CI], group 1 6.65 [3.59–9.71], group 2 4.6 [0.81–8.39], group 3 0.85 [−1.29 to 2.98], p for group effect 0.0008, post hoc p for between-group differences 0.01 for groups 1:3, 0.03 for groups 2:3, nonsignificant when corrected for multiple outcomes). Dynamic balance (Dynamic Gait Index [DGI])[31] improved in group 1 but not in groups 2 and 3 (mean change [95% CI], group 1 3.85 [2.1–5.6], group 2 1.06 [−0.91 to 3.03], group 3 1.75 [−0.52 to 4.02], p for group effect = 0.14). A clinically significant improvement was defined as a 4-point increment in the BBS score and a 3-point increase in the DGI score. Subjective reports of disability (Modified Dizziness Handicap Inventory)[32] and self-confidence (Activities-specific Balance Confidence Scale)[33] did not change, but the study lacked precision for detecting a benefit for these outcomes (wide CIs).

Community/group programs. No Class I or Class II studies were available.

Conclusions.

1. Weekly home or outpatient PT for 8 weeks probably is effective for improving balance, disability, and gait in individuals with MS (type unspecified) who are able to walk ≥5 meters with/without an assistive device (1 Class I study).[22] These programs probably are ineffective for improving upper extremity dexterity (1 Class I study).[22] Data are inadequate to support/refute the use of these programs for improving self-reported falls/mobility, depression, or anxiety (1 study rated Class III for subjective outcomes).[22]

2. Three weeks' worth of individualized inpatient exercise followed by home exercises for 15 weeks possibly is effective for reducing disability (RRMS, PPMS, SPMS, EDSS 3.0–6.5) (1 Class II study).[27] Data are inadequate to support/refute the use of this regimen for improving HRQL (1 study rated Class III for subjective outcomes).[27]

3. Three weeks' worth of motor and sensory balance training or motor balance training possibly is effective for improving static and dynamic balance, and motor balance training possibly is effective for improving static balance (RRMS, SPMS, PPMS) (1 Class II study).[29] Data are inadequate to support/refute the use of this regimen for reducing falls or self-reported disability and handicap, or for improving confidence in balance skills (small numbers of falls in each group, making interpretation difficult; insufficient precision for subjective outcomes).[29]

4. Data are inadequate to support/refute the use of the following (1 Class III study each unless otherwise stated):

   a. Home PT (1 Class III study with insufficient precision)[34]
   b. Long-term benefit (6 months) of an outpatient exercise program combined with home exercises[35]
   c. American College of Sports Medicine–based resistance training with/without electrostimulation[36]
   d. Lower-extremity progressive resistance training[37,38]
   e. Progressive bicycle ergometry resistance training combined with balance exercises[39]
   f. Three weeks of inpatient strength and aerobic training followed by a 23-week home exercise program[40,e1,e2]
   g. Short-term (3–15 weeks) aerobic exercise programs (1 Class III study lacking statistical precision; 3 Class III studies, different durations and study populations)[e3−e5]
   h. RAGT (1 imprecise Class I study)[28]
   i. Group exercise therapy (2 Class III studies, different durations and interventions)[e6,e7]
   j. An individualized physical rehabilitation program or group wellness intervention[e8]

Clinical context. Although evidence that exercise programs improve MS-related outcomes is unavailable, the benefits of exercise in the general population and the extent of MS-related disability are useful for clinicians to consider when counseling patients with MS regarding exercise.

Do other specific therapy techniques minimize impairment, reduce disability, or improve HRQL? A Class II randomized trial conducted in 2 phases compared balance-based torso weighting (BBTW, involving the addition of weights to the torso or extremities to assist in coordinated movement) with no intervention and then randomized the control group to receive BBTW or standard weight placement (SWP, 1.5% body weight). Thirty-six of 38 patients (RRMS, SPMS, PPMS, MS type unknown, EDSS 2–5) completed phase 1, and 18 patients completed phase 2.[e9] Although the BBTW group improved on most measures as compared with baseline, the only significant difference between the BBTW group and the controls (no weight, phase 1) was in timed gait: Timed 25-Foot Walk (mean change [95% CI], BBTW group −0.6 [−1.83 to 0.63], control group 0 [−1.49 to 1.49], corrected $p < 0.02$). It is uncertain whether this difference is clinically meaningful. In phase 2, 3 patients had Timed Up and Go test (TUG) scores[e10] of less than 8 seconds and were excluded from analysis in accordance with the study inclusion criteria, leaving 6 patients receiving BBTW and 9 receiving SWP. Only the mean change on the TUG differed between groups (mean change [95% CI], BBTW group −1.2 [−5.32

to 2.92], SWP group −0.2 [−4.1 to 3.7], corrected $p = 0.2$), but the study was underpowered to detect a significant difference, and the degree of change is of uncertain clinical significance. All other analyses showed no difference between groups but lacked sufficient precision to exclude an effect.

One study[e11] assessed the effect of a home program of breathing-enhanced upper extremity exercises (as compared with no intervention[e8]) on respiratory function (n = 40, RRMS, PPMS, SPMS, EDSS 4.51 ± 1.55, 6 weeks). This study is Class II for the objective outcomes of walking speed (6MW), disability (EDSS), and spirometry measures and Class III for patient-reported outcomes (Pulmonary Dysfunction Index [PDI],[e12] a subjective clinical assessment of respiratory function, and Borg Rate of Perceived Exertion [RPE][e13]). With Bonferroni correction, the following outcomes improved (differences in means [95% CI], forced expiratory volume in 1 second [FEV_1] 10.3 [3.48–17.11], PDI −0.43 [−0.66 to −0.19], and 6MW 8 [4.2 to 11.8]). EDSS did not change (mean change −0.31 [−0.56 to −0.05]); there was no change (differences in means [95% CI]) in FEV_1/forced vital capacity (FVC) (7.2 [−0.47 to 13.93], estimate imprecise), the Borg RPE (0.64 [−0.13 to 1.41]), FVC (4.7 [−0.53 to 9.93], estimate imprecise), maximal inspiratory pressure (PI_{max}) (4.1 [−2.74 to 10.95], estimate imprecise), or maximal expiratory pressure (4.6 [−0.99 to 10.19], estimate imprecise).

Another study evaluated the effect of an inspiratory muscle training program as compared with no intervention (n = 46, 10 weeks, RRMS, SPMS, PPMS, EDSS 2–6.5). The outcomes were multiple pulmonary function variables (Class II, objective) and fatigue (Fatigue Severity Scale) (Class III, patient-reported). PI_{max} improved (mean change [95% CI], treatment group 23.5 [8.92–38.08], control −0.7 [−17.08 to 15.68], corrected $p < 0.008$), but precision for the other outcomes was insufficient to exclude a possible benefit.[e14]

Conclusions.
1. Breathing-enhanced upper extremity exercises for 6 weeks possibly are effective for improving timed gait and FEV_1 in MS with moderate disability (RRMS, PPMS, SPMS, mean EDSS 4.51 ± 1.55) (1 Class II study).[e11] This regimen possibly is ineffective for improving disability (1 Class II study).[e11] The isolated improvement in FEV_1 is of uncertain clinical significance.
2. A 10-week inspiratory muscle training program possibly is effective for improving PI_{max} as measured by pulmonary function testing in RRMS, SPMS, and PPMS, EDSS 2–6.5 (1 study, Class II objective measures).[e14]

3. Data are inadequate to support/refute the use of the following (1 Class III study each unless otherwise stated):
   a. BBTW (1 Class II study with inconsistent results between sham-weight and no-weight groups)[e9]
   b. Inspiratory muscle training for fatigue[e14]
   c. Expiratory muscle training[e15]
   d. Grimaldi PT method[e16]
   e. Johnstone pressure splints[e17]
   f. Feldenkrais bodywork therapy[e18]
   g. The relative efficacy of 3 cycling-intensity protocols[e19]
   h. A whole-body vibration exercise protocol[e20]
   i. Aquatic exercise training[e21]
   j. Low-level cardiovascular endurance exercise[e22]
   k. Intermittent transcranial magnetic theta burst stimulation with/without exercise therapy[e23]
   l. A home telerehabilitation program[e24]

Do energy efficiency/conservation techniques, specialty devices, or educational programs affect function and HRQL? No Class I or Class II studies were available.

Conclusion.
1. Data are inadequate to support/refute use of the following (1 Class III study each unless otherwise stated):
   a. The short-term use of cooling garments (2 imprecise Class III studies)[e25,e26]
   b. One-month use (1 hour/day) of cooling garments[e26]
   c. Group fatigue program (Fatigue: Take Control Program)[e27]
   d. Packer energy conservation program[e28] over 6 weeks (1 Class III study)[e29] or 1 year (1 Class III study)[e30]
   e. An outpatient health promotion education program (OPTIMISE)[e31]

RECOMMENDATIONS FOR FUTURE RESEARCH The most important conclusion of this extensive systematic review is the need for well-designed trials of rehabilitation therapies and techniques. These therapies and techniques should be described in detail to permit comparison between studies and meta-analyses, if needed. Many studies were ineligible for inclusion because of methodologic flaws. Researchers need to develop and evaluate meaningful protocols with established intensity, duration, and frequency of interventions. Studies of rehabilitation need to be held to the same strict standards as drug therapies. Protocols need to enhance participant and assessor blinding. Sham interventions may be useful for participant blinding. Objective assessments are needed that measure

impairment. Researchers must select outcome measures that are most sensitive to the specific intervention and must select the meaningful, plausible primary outcome carefully. For instance, short-term programs may not be able to detect changes in EDSS scores. Outcomes should be assessed immediately postintervention, and at subsequent relevant time points, to evaluate the duration of response to interventions. In order to reduce bias, these comparisons should be performed in both treatment and control groups rather than over time in treatment groups alone.

The available evidence as judged by the criteria applied here precludes formulation of recommendations with regard to the effectiveness of rehabilitation therapy in specific MS subtypes, or in milder disability from progressive MS, or immediately after MS relapse. The benefit is unknown beyond 12 weeks in moderate disability from progressive MS. Studies either excluded individuals who had a recent exacerbation or failed to mention timing of relapse in relation to the rehabilitation technique.

Studies are needed on long-term maintenance therapy and therapies to improve upper extremity function. Strategies to reinforce comprehensive rehabilitation from the facility to the community setting need to be developed. We need more knowledge about how to integrate rehabilitation efficiently across the MS continuum in order to promote independence and social participation. Clinicians need to know when to intervene and how to reinforce positive outcomes in the community. Promising strategies need to be studied in representative groups with adequate sample sizes powered to measure change, using multicenter trials.

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AUTHOR CONTRIBUTIONS

Jodie K. Haselkorn: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript. Christina Hughes: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript. Alex Rae-Grant: acquisition of data, analysis or interpretation of data, drafting/revising the manuscript. Lily Jung Henson: 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. Christopher T. Bever: 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. Albert C. Lo: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript. Theodore R. Brown: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript. George H. Kraft: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript. Thomas Getchius: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript. Gary Gronseth: 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. Melissa J. Armstrong: analysis or interpretation of data, drafting/revising the manuscript, 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.

DISCLOSURE

J. Haselkorn is a full-time employee of the US Department of Veterans Affairs and has received funding for travel from the Paralyzed Veterans of America Summit and the Consortium of Multiple Sclerosis Centers (CMSC). C. Hughes received funding from TEVA Neuroscience for the MS Scholars Conference. A. Rae-Grant has received royalties from multiple books published by Demos Publishing and Wolters Kluwer on multiple sclerosis and neurology, and assists in editing neurology chapters for an online textbook of medicine for Dynamed. L. Henson serves on advisory boards for Biogen, Genzyme, Novartis, and sanofi-aventis; has received funding for travel from Genzyme; has received financial compensation for work on speakers bureaus for Biogen, Genzyme, Novartis, Pfizer, Serono, and Teva; and has received research support from Biogen, Genzyme, the NIH, Novartis, Opexa Therapeutics, and sanofi-aventis. C. Bever received funding for travel from the American Academy of Neurology (AAN), Americas Committee on Research and Treatment of Multiple Sclerosis, the CMSC, and the University of Maryland; and has received research support from the US Department of Veterans Affairs and the National Multiple Sclerosis Society (NMSS). His spouse has received travel support from Johns Hopkins University, royalties from publishing from Elsevier and Johns Hopkins University Press, and honoraria from Harvard University and New York University. A. Lo has received honoraria from Acorda Therapeutics; funding for travel and honoraria from the Shepherd Center in Atlanta, GA; and research support from the US Department of Veterans Affairs, Harvard University, and St. Francis Hospital in Hartford, CT. T. Brown serves on the clinical advisory committee of the NMSS; has received compensation for serving on the scientific advisory boards of Acorda and Teva, and on the editorial board of the *International Journal of MS Care*; has received honoraria from and served on speakers bureaus for Acorda, Genzyme, Pfizer, and Teva; and has received research support from Astellas, Biogen, Gallen, and Teva. G. Kraft serves on the advisory board

DISCLAIMER

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CONFLICT OF INTEREST

The American Academy of Neurology is committed to producing independent, critical, and truthful systematic reviews (SRs) and clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the conclusions of this SR. 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 SRs and CPGs and the developers of the SRs and CPGs. 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, SR and CPG projects. Drafts of the SR have been reviewed by at least 3 AAN committees, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com. For complete information on this process, access the 2004 AAN process manual.[7]

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