Comprehensive Systematic Review: Rehabilitation in Multiple Sclerosis

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

Jodie K. Haselkorn, MD, MPH[1,2]
Christina Hughes, MD[3]
Alex Rae-Grant, MD[4,5]
Lily Jung Henson, MD, MMM[6]
Christopher T. Bever, MD, MBA[7,8]
Albert C. Lo, MD, PhD[9,10,11]
Theodore R. Brown, MD, MPH[12]
George H. Kraft, MD, MS[13]
Thomas Getchius[14]
Gary Gronseth, MD[15]
Melissa J. Armstrong, MD, MSc[7]
Pushpa Narayanaswami, MBBS, DM[16,17]

1) MS Center of Excellence West, US Veterans Health Administration, Seattle, WA
2) Departments of Rehabilitation and Epidemiology, University of Washington, Seattle
3) Rehabilitation Medicine, EvergreenHealth Rehabilitation Services, Kirkland, WA
4) Department of Neurology, Cleveland Clinic, OH
5) College of Medicine of Case Western Reserve University, Cleveland, OH
6) Swedish Neuroscience Institute, Seattle, WA
7) Department of Neurology, University of Maryland School of Medicine, Baltimore
8) Research Service, VA Maryland Health Care System, Baltimore
9) Departments of Neurology and Community Health, Brown University, Providence, RI
10) Rehabilitation Research and Development Center for Restorative and Regenerative Medicine, Providence VA Medical Center, RI
11) Mandell Center for Multiple Sclerosis, Mount Sinai Rehabilitation Hospital, Hartford, CT
12) EvergreenHealth Multiple Sclerosis Center, Evergreen Neuroscience Institute, Kirkland, WA
13) MS Rehabilitation Research and Training Center, University of Washington, Seattle
14) Center for Health Policy, American Academy of Neurology, Minneapolis, MN
15) Department of Neurology, University of Kansas School of Medicine, Kansas City, KS
16) Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA
17) Department of Neurology**,** Harvard Medical School, Boston, MA

Address correspondence and reprint requests to
American Academy of Neurology:
guidelines@aan.com

Approved by the Guideline Development, Dissemination, and Implementation Subcommittee on November 8, 2014; by the Practice Committee on February 6, 2015; and by the AANI Board of Directors on August 12, 2015.

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.

STUDY FUNDING

This systematic review was developed with financial support from the American Academy of Neurology. Authors who serve as AAN subcommittee members (A.R.-G., G.G., M.J.A., P.N.) were reimbursed by the AAN for expenses related to travel to subcommittee meetings where drafts of manuscripts were reviewed.

DISCLOSURE

Dr. Jodie K. 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 and the Consortium of Multiple Sclerosis Centers (CMSC).
Dr. Christina Hughes reports no relevant disclosures.
Dr. Alex 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.
Dr. Lily Jung Henson reports to relevant disclosures.
Dr. Christopher T. 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.
Dr. Albert C. Lo has reported no relevant disclosures..
Dr. Theodore R. 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.
Dr. George H. Kraft serves on the advisory board for Acorda Therapeutics; has received funding for travel to Acorda Axon Council meetings, is a consulting editor for Physical Medicine and Rehabilitation Clinics of North America, has received royalties from publishing from Demos, has received honoraria from multiple academic and professional organizations for lecturing, has served on a speakers bureau for Acorda, and has received research support from the National Institute on Disability and Rehabilitation Research.
Mr. Thomas Getchius is a full-time employee of the AAN.
Dr. Gary Gronseth serves as an associate editor for *Neurology* and as an editorial advisory board member of *Neurology Now*, and receives compensation from the AAN for work as the chief evidence-based medicine methodologist.
Dr. Melissa J. Armstrong serves on the Level of Evidence Review Team for *Neurology* (not compensated financially) and as an evidence-based methodologist for the AAN.
Dr. Pushpa Narayanaswami reports no relevant disclosures.

ABBREVIATIONS

6MW: 6-meter walk
9-HPT: 9-hole peg test
AAN: American Academy of Neurology
ABC: Activities-specific Balance Confidence scale
ACSM: American College of Sports Medicine
ADL: activities of daily living
BBS: Berg Balance Scale
BBTW: balance-based torso weighting
BDI: Beck Depression Inventory
BI: Barthel Index
CI: confidence interval
CWT: conventional walking training
DGI: Dynamic Gait Index
EDSS: Expanded Disability Status Scale
ES: effect size
ET: exercise therapy
FEV_1: forced expiratory volume in 1 second
FIM: Functional Independence Measure
FIS: Fatigue Impact Scale
FSS: Fatigue Severity Scale
FVC: forced vital capacity
GHQ-28: General Health Questionnaire-28
HADS: Hospital Anxiety and Depression Scale
HAQUAMS: Hamburg Quality of Life Questionnaire in Multiple Sclerosis
HRQL: health-related quality of life
iTBS: intermittent transcranial magnetic theta burst stimulation
MFIS: Modified Fatigue Impact Scale
MFMP: multidisciplinary fatigue management program
MS: multiple sclerosis
MSES: Multiple Sclerosis Self-efficacy Scale
MSIS-29: Multiple Sclerosis Impact Scale
MSQOL-54: Multiple Sclerosis Quality of Life
MVC: Maximal voluntary contraction
MWT: meter walk test
PDI: Pulmonary Dysfunction Index
PE_{max}: maximal expiratory pressure
PI_{max}: maximal inspiratory pressure
POMS: Profile of Mood States
PPMS: primary progressive multiple sclerosis
PT: physical therapy
QOL: quality of life
RAGT: robot-assisted gait training
RCT: randomized, controlled trial
RD: risk difference

RMI: Rivermead Mobility Index
RPE: Borg Rate of Perceived Exertion
RRMS: relapsing–remitting multiple sclerosis
SD: standard deviation
SET: Social Experience Checklist of Tempelaar
SF-36: Short-Form [36] Health Survey
SPMS: secondary progressive multiple sclerosis
SRAHP: Self-Rated Abilities for Health Practices Scale
SWP: standard weight placement
T25W/7.62 MWT: Timed 25-Foot Walk
TMW: Two-Minute Walk Test
TUG: Timed Up and Go test
VAS: visual analog scale
VO_2max: maximal oxygen consumption

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 or outpatient physical therapy for 8 weeks** probably is effective for improving balance, disability, and gait (MS type unspecified, participants able to walk ≥5 m) 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 reducing disability/improving 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).

Multiple sclerosis (MS) affects approximately 400,000 individuals in the United States and is a leading cause of disability in young adults.[e1–e5] Rehabilitation interventions are frequently used clinical strategies for improving or maintaining functional status.[e6]

This systematic review addresses the following questions:

1. In patients with MS, does outpatient or inpatient comprehensive multidisciplinary rehabilitation minimize impairment, reduce disability, or improve health-related quality of life (HRQL)?
2. In patients with MS, do supervised outpatient or inpatient physical therapy (PT), physical training, or physical exercise programs minimize impairments, reduce disability, or improve HRQL?
3. In patients with MS, do other specific therapy techniques minimize impairment, reduce disability, or improve HRQL?
4. In patients with MS, 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) Guideline Development, Dissemination, and Implementation (GDDI) Subcommittee assembled an oversight committee to select a panel of neurologists, physiatrists, and scientists to develop this systematic review (see appendices e-1 and e-2). The oversight committee obtained and reviewed conflict of interest (COI) forms from all authors before project initiation. The GDDI leadership and the project methodologist then finalized author panel selection, resulting in a panel in which less than half the participants had a relevant COI.

The panel searched MEDLINE, EMBASE, CINAHL, and Science Citation Index from MEDLINE onset to February week 3, 2013 (see appendix e-3 for complete search strategy). The search employed standard techniques and was limited to adults with clinically definite or laboratory-supported MS.[e7] We excluded studies that involved fewer than 20 participants, evaluated pharmaceutical efficacy, assessed electrical simulation, evaluated pain as the sole outcome, or assessed an instrument's psychometrics. The studies utilized several scales as outcome measures. We classified each of these 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. In these cases we have clarified the study class in parenthesis for each outcome. In cases where multiple studies used the same data, the studies were analyzed together. All outcomes except for the specified primary outcome in the first publication were considered secondary, unless the authors specified multiple primary outcomes in successive publications; in this latter case, the studies were analyzed as not having a specified primary outcome. When studies using multiple scales to evaluate the same outcome yielded inconsistent results, we evaluated both the appropriateness of the scales used to measure the outcome and the psychometrics to measure the outcome of interest, and interpreted the results accordingly. For instance, in studies using both the Expanded Disability Status Scale (EDSS)[e8] and the Functional Independence Measure (FIM)[e9] to evaluate disability, results for both measures were evaluated because the measures likely assess different aspects of disability and may be affected differentially by study duration. Studies also varied in their assessment of

what a single outcome measure was evaluating. For example, some studies used timed walk tests as tests of walking speed, others as tests of endurance, and still others as measures of function overall. We have mentioned the outcomes being studied and parenthetically indicated the measure used. Table e-1 describes the scales mentioned in this systematic review. Most studies included patients with different MS subtypes, without subgroup analyses. Conclusions therefore were not made with reference to specific MS subtypes. When needed, we applied Bonferroni corrections for multiple outcomes.

Pairs of panelists reviewed 5,464 abstracts, and 491 articles were selected for full-text review. These were further reviewed and abstracted in pairs. Ultimately, 142 articles were rated according to the 2004 AAN classification of evidence scheme for therapeutic articles (see appendix e-4).[e10] In accordance with the 2004 AAN development process, we use the term *probably* in relation to moderate levels of evidence (statements supported by 1 Class I study or ≥2 Class II studies) and the term *possibly* in relation to weak levels of evidence (statements supported by 1 Class II study or ≥2 Class III studies). Additionally, we excluded studies lacking a control group because of a resulting high risk of bias. Disagreements were resolved by consensus. Class I, II, and III studies are discussed. Tables e-2 and e-3 summarize the evidence.

ANALYSIS OF EVIDENCE

In patients with MS, does outpatient or inpatient comprehensive multidisciplinary rehabilitation minimize impairment, reduce disability, or improve HRQL?

One study, reported in 2 articles,[e11,e12] evaluated the effects of comprehensive outpatient rehabilitation (n = 111, 12 weeks, primary progressive MS [PPMS], secondary progressive MS [SPMS], EDSS 4.0–8.0). The authors reported different primary outcomes in the 2 publications, using the same data set. Both studies therefore were treated in this review as lacking a primary outcome (Class II for objective measures of disability, FIM and EDSS; Class III for self-reported outcomes of fatigue,[e13] depression,[e14] quality of life [QOL]).[e15] Participants were randomized to comprehensive multidisciplinary outpatient therapy 6 days/week for 6 weeks, followed by 6 weeks of home self-exercise (n = 58) or 12 weeks of home self-exercise (n = 53). No change was seen in EDSS (treatment mean change -0.1, control mean change +0.1, other data not provided). HRQL (HRQL, Short Form [36] Health Survey [SF-36]) results improved at 6 and 12 weeks on the following subscales: physical functioning (treatment mean ± standard deviation [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 (FIS) scores (RD 19.4, 95% CI 15.5–23.3, effect size [ES] Kazis -0.77), social function (Social Experience Checklist of Tempelaar [SET],[e16] RD 2.3, 95% CI 0.65–3.95, ES -0.46), and Beck Depression Inventory (BDI) (RD 2.3, 95% CI 1.34–3.26, ES -0.50). The second analysis, using the same data (Class II),[e12] found that 55% of the treatment group improved by ≥2 steps on the FIM[e9] relative to 4% of the controls at 12 weeks (RD 10.2, 95% CI 6.98–13.42). The authors calculated Kazis's ES as mean change/SD of the

initial score distribution.[e17] By Cohen's criteria, ES values were interpreted as small (0.2), moderate (0.5), or large (≥0.8).[e18] Change in FIM subscale scores were as follows: locomotion (RD 1.6, 95% CI 0.94–2.26, ES Kazis 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, ES Kazis 0.40); 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 (EDSS may be more sensitive to changes over longer periods of time, whereas FIM may detect short-term change).

A Class III single-blind, crossover study (n = 51, 4 weeks, relapsing–remitting MS [RRMS], PPMS, chronic progressive MS, and MS type unknown, ambulant 100 m without aid, 21% dropouts, participants nonblinded, self-reported outcomes, independent assessment by patients) evaluated an outpatient multidisciplinary fatigue management program (MFMP).[e19] The MFMP consisted of a weekly 2-hour information session that provided strategies for managing fatigue. The comparison group discussed topics that were not related to fatigue management. In the first phase, the first group received MFMP, and the second group, comparison treatment, and each group was assessed at 3 weeks and 6 months post-intervention. In the second phase, the comparison group crossed over to the intervention, and the original intervention group did not receive any treatment. Treatment did not change the proportion of participants with clinically meaningful improvement in fatigue, defined as a 10-point improvement in the Modified Fatigue Impact Scale (MFIS)[e20] at 3 weeks or 6 months after the intervention (3 weeks: treatment 4/24, 17%, controls 7/16, 44%, RD 0.27, 95% CI -0.011 to 0.522; 6 months: treatment 9/24, 38%, controls 5/16, 31%, RD -0.062, 95% CI -0.32 to 0.23). Likewise, no change was noted at 3 weeks or 6 months in the second phase, where the comparison group received the intervention, and the prior active group, no intervention (MFIS mean change 4.12 [$p = 0.078$] and 2.87 [$p = 0.34$], respectively). Moreover, no change was seen in the secondary outcome measures of Fatigue Severity Scale (FSS),[e21] mental health, and self-efficacy (data not provided). At 6 months, the proportion of participants with clinically relevant improvement in MFIS was higher, although not significant, in the MFMP group as compared with no MFMP (control 6/16, 38%, treatment 7/24, 29%, RD 0.08, 95% CI -0.2 to 0.3).The study lacked precision to detect a benefit.

One study[e22] evaluated comprehensive, multidisciplinary inpatient rehabilitation (N = 70, SPMS, PPMS, EDSS 5.0–9.5) (Class III). Participants were randomized to approximately 20 days of multidisciplinary, comprehensive inpatient rehabilitation or wait-list controls. At 6 weeks the intervention (n = 32) and control (n = 34) groups did not differ significantly in EDSS scores (numbers not provided, 95% CI for change scores clustering around zero per authors, ESSS small [$p = 0.42$]), Kurtzke's Functional Systems Scores (data not provided), or London Handicap Scale[e23] (mean change 5.3, 95% CI 1.0 to -9.6). ES calculations did not show significant improvement in the treated group (treatment group ES +0.23, mean +2.76, 95% CI -0.44 to 5.96; control group ES -0.27, mean -2.71, 95% CI -5.73 to 0.29). There was improvement in disability after Bonferroni adjustment in the FIM overall motor domain score ($p < 0.022$) and in scores on 3 of 4 FIM subscales (self-care [$p < 0.0022$], transfers [$p < 0.022$], and sphincter control [$p < 0.022$]; data provided were insufficient for calculation of 95% CIs).[e16] The ES for the overall FIM motor domain indicated a small improvement in the intervention group (+0.21) and slight decline in the control group (-0.16).

A randomized, controlled trial[e24] (RCT), rated Class III for subjective, patient-reported outcomes, evaluated the impact of inpatient or outpatient multidisciplinary rehabilitation (n = 49, RRMS, SPMS, PPMS; EDSS 0–6.5+; mean 34 days) and included a wait-list control group (n = 52). Improvement was seen in the primary outcome, as measured by subscale scores (all at 12 months) on the FIM: Motor subscale (mean difference 4.78, 95% CI 3.04–6.52), FIM transfers subscale (mean difference 1.25, 95% CI 0.76–1.74), locomotion subscale (mean difference 0.25, 95% CI 0.34–1.34), and self-care subscale (mean difference 2.21, 95% CI 1.27–3.15). Scores did not improve on the Multiple Sclerosis Impact Scale[e25] (MSIS-29) and General Health Questionnaire-28[e26] (GHQ-28): MSIS-29 psychological scale (mean difference -1.2, 95% CI -4.16 to 1.77), MSIS-29 physical scale (mean difference 3.44, 95% CI -2.76 to 9.63), and GHQ subscales of anxiety, depression, somatic, and social (mean differences and 95% CI: -0.055, -1.85 to 1.74; 0.212, -1.32 to 1.74; -1.25, -3.30 to 0.79; and -0.68, -2.91 to 0.83). The inpatient and outpatient groups were not analyzed separately, making interpretation difficult.

A Class III nonrandomized trial[e27] that included a non-intervention control group evaluated the effect of inpatient rehabilitation on fatigue (n = 86, 3 weeks, MS = 64, RRMS, SPMS, and PPMS, controls = 22). Data for the control group were not provided, and differences between treatment and control groups could not be calculated.

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).[e12]
2. Data are inadequate to support or 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,[e19] 1 Class III study[e11])
    b. Comprehensive multidisciplinary **inpatient** rehabilitation for reducing disability (2 Class III studies examining different populations and time frames[e22,e24])
    c. Three weeks of **inpatient** rehabilitation for reducing fatigue (RRMS, SPMS, and PPMS, EDSS 1–6) (1 Class III study, data for control group not provided)[e27]

In patients with MS, 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 MS participants (type unspecified, EDSS 4–6.5) able to walk ≥5 meters with or without aid in a crossover study.[e28] 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 (RMI), improved[e29,e30] 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 to 8.07, home PT to none 5.49, 2.19 to 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 seconds, -23 to -6). Dexterity (9-hole peg test [9-HPT][e31]) 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 to 25.7, home PT to none 22.4, 16.6 to 28.3; home to hospital none), participant visual analog scale (VAS) for mobility (ES, 95% CI: hospital to none 25.2, 18.3 to 32, home PT to none 24.2, 17.3 to 31), and VAS for caregiver assessment of mobility (ES, 95% CI: hospital to none 16, 6.7 to 25.3, home to none 17.6, 8.1 to 27.1). Finally, improvements also occurred in VAS for falls (ES, 95% CI: hospital to none 18.3, 9 to 27.6, home to none 20.7, 11.2 to 30.2) and Hospital Anxiety and Depression Scale (HADS[e32]) 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[e33] (Class II for objective outcomes, Class III for patient-reported outcomes, n = 50, 3 weeks, RRMS, SPMS, PPMS, EDSS 3–6.5) randomized participants either to twice-daily individualized inpatient physical exercise followed by home exercises or to home exercises only. 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 ≥2 steps in the intervention group as compared with the control group by 48% vs 9%, respectively (p = 0.004), at 3 weeks, and by 44% vs 4.5%, respectively, at 9 weeks (controls retained the 3-week gains, p = 0.001); at 15 weeks no difference was seen. 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).

A Class III study[e34] (n = 30, RRMS, SPMS, independently mobile participants, 12 weeks) assessed the long-term impacts on QOL and fatigue of an exercise program at an outpatient physiotherapy gym combined with home exercises, as compared with no treatment. After Bonferroni correction, the exercise group showed improved exercise capacity (Borg Rate of Perceived Exertion [RPE][e35]; median [lower quartile, upper quartile] at 3 months: control 1, 95% CI -0.5 to 2, exercise -3, 95% CI -5 to -0.5, corrected p = 0.02). Improvement also was seen in one QOL measure at 6 months (Functional Assessment of Multiple Sclerosis[e36]; control -4.5, 95% CI -25 to 8, exercise 19, 95% CI 14 to 31, corrected p = 0.03) but not in another measure, the MSIS-29.[e25] Heart rate and fatigue did not improve.

One RCT,[e37] rated Class III due to baseline differences between control and treatment groups (n = 30, 8 weeks, PPMS, SPMS, EDSS 6.5–8), did not reveal improvement in the primary outcome measure, MSIS-29, a measure of QOL, and the physical and psychological impact of MS, after a

home-based program of physiotherapy. However, there was insufficient precision to exclude a meaningful improvement in the treatment group (mean MSIS-29 change, 95% CI: at 8 weeks treatment 2.1, -9.4 to 13.64, vs controls 7.3, -5.33 to 20.13).

Resistance training

A Class III nonrandomized study[e38] (n = 38, 20 weeks, RRMS, SPMS, PPMS, EDSS 2–6.5) evaluated the American College of Sports Medicine (ACSM)–based resistance training with simultaneous electrostimulation and without electrostimulation, as compared with no treatment (control = 14, resistance only = 11, resistance with electrical stimulation = 11). Changes were not seen in functional mobility (dynamic balance [Timed Up and Go {TUG}],[e39] walking speed [Timed 25-Foot Walk {T25W}[e40] and Two-Minute Walk Test {TMW}],[e41] functional reach)[e42] and disability (RMI) (data not provided). Maximal isometric knee extensor and flexor strength also did not change after Bonferroni correction. The study had insufficient precision to exclude an important effect on the basis of a calculation of precision for isometric knee extensor strength: resistance only vs control, mean difference 30.4 (95% CI -1.8 to 62.6).

In another Class III study[e43] (n = 38, 12 weeks, RRMS, EDSS 3–5.5), participants were randomized to lower-extremity progressive resistance training or control. The primary outcomes were muscle strength of knee extensors and functional capacity score (composite of several lower-extremity timed tests). Muscle strength improved in the knee extensor maximal voluntary contraction (MVC) (percent change, 95% CI: exercise group 15.7, 4.3 to 27.0, vs control 1.3, -7.3 to 10.0, $p = 0.05$). The number needed to treat, defined as a strength improvement of ≥10% knee extensor MVC, was 3.8. Functional score percentage, the coprimary outcome, also improved (percent change from baseline, 95% CI: 21.5, 17 to 26.1, vs controls -3.3, -8.1 to 1.5, $p < 0.05$). In a secondary analysis of the same data set,[e44] the authors evaluated mean change and 95% CI for thigh volume (0.3, – 0.86 to 1.46), body fat composition (0.2, -5.06 to 5.46), muscle fiber and cross-sectional area (mean change 215 μm^2, -833 to 1,263), and muscle fiber–type distribution, none of which was significantly different when adjusted for multiple comparisons. The study did not have sufficient precision for these outcomes. In a third analysis of the same data set,[e45] fatigue, QOL, and mood did not significantly improve when corrected for multiple outcomes, but the study probably lacked sufficient precision for these outcomes.

In another RCT,[e46] rated Class III for lack of concealed allocation and a 26% dropout rate (n = 45, 8 weeks, RRMS, SPMS, EDSS <6), the impact of progressive bicycling ergometry resistance training combined with balance exercise was compared (1) with home-based lower-limb strengthening and balance or (2) with control. The primary outcome, walking speed (10-meter walk test [MWT]) improved (change scores ±SD ergometry -1.9 +/- 1.2, home exercise -0.08 +/- 0.7, p not significant for difference between ergometry and home exercise, control 0.1 +/- 0.8, $p < 0.05$ for difference between ergometry and control). After Bonferroni adjustment, no change was seen in other measures of gait, functional reach, falls, fatigue, and depression.

Aerobic exercise programs

Three RCTs,[e47–e49] rated Class III for lack of concealed allocation and a 21% dropout rate, used a single data set with outcomes[e50–e52] and compared a 3-week inpatient strength and aerobic

training program, followed by a 23-week home program, with a home program (n = 114, RRMS, SPMS, PPMS, EDSS 1.0–5.5). At 6 months, improvement occurred in walking speed (T25W/7.62 MWT, mean score change, 95% CI: intervention -0.44, -0.62 to -0.27, ES 0.5, vs controls -0.25, -0.43 to -0.08, ES 0.19, p <0.04). The clinical significance of this minor change is uncertain. Walking endurance (500 MWT) also improved (mean time change, 95% CI: intervention -0.33, -0.53 to -0.12, ES 0.26, controls -0.02, -0.23–0.19, ES 0.02, p = 0.008). Lower-extremity strength, upper-extremity endurance, dexterity, peak oxygen uptake, and static balance did not change. One measure of disability/function/impairment, the Multiple Sclerosis Functional Composite Measure (MSFC),[e50] improved at 6 months (intervention group mean score change, 95% CI: 0.114, 0.010 to 0.218, control -0.128, -0.232 to -0.025, corrected p = 0.039). No changes were seen in HRQL (Multiple Sclerosis Quality of Life [MSQOL-54]),[e53] other measures of disability (FIM, EDSS), depression (Center for Epidemiologic Studies Depression Scale),[e54] Fatigue Index of the knee flexors and extensors,[e55] Fatigue Severity Scale (FSS), or Ambulatory Fatigue Index[e52]; however, there was insufficient precision to exclude an important effect for some of these outcomes.

Another Class III study[e56] (n = 54, 15 weeks, MS type unspecified, EDSS <6) randomized participants to aerobic exercise or no exercise. After Bonferroni adjustment, improvements were seen at 15 weeks in maximal oxygen consumption (VO_2max)[e57] and Physical Work Capacity (PWC) (exercise VO_2max increased 22%, controls 1%, p <0.01; exercise PWC increased 48%, controls 12%, p <0.01 at 15 weeks; mean change exercise group 5.2, 95% CI 1.34 to 9.06, p <0.01; controls mean change 0.4, 95% CI -3.44 to 4.24, p = nonsignificant). At 15 weeks, the upper-extremity strength mean change in the exercise group was 223 (95% CI -8.2 to 454.2) and controls was -29 (95% CI -285 to 227). Lower-extremity strength mean change in the exercise group was 237 (95% CI -157.5 to 631.5) and controls was 52 (95% CI -422.9 to 526). The study reported significant group-by-time interactions for bowel and bladder symptoms, VO_2max, and measurements of shoulder flexion, shoulder extension, elbow flexion, knee extension, and change in upper-extremity and lower-extremity strength; however, the data provided were insufficient for calculating measures of precision, and 95% CIs calculated for within-group changes were wide. Health status (Sickness Impact Profile [SIP])[e58] physical dimension did not improve, but the study lacked sufficient precision to exclude a benefit (mean change, 95% CI: exercise -3.2, -8.35 to 1.95, vs controls 1.5, -2.34 to 5.34). No changes were seen in the EDSS (disability), mood (Profile of Mood States [POMS]),[e59] or fatigue (FSS), but the study likely lacked statistical precision for these outcomes as well.

Another Class III study[e60] (n = 37, 3–4 weeks RRMS, chronic progressive MS, and chronic relapsing MS, EDSS 1–6.5) evaluated short-term aerobic bicycle exercise training as compared with no training. After adjustment for multiple comparisons, no differences were seen in gas exchange and lung function, fatigue (FSS), and HRQL (SF-36), but the study had insufficient precision for detecting benefits (mean change in FSS in the exercise group post-intervention 0.7, 95% CI -0.8 to 2.2).

The impact of aerobic bicycle training was compared with that of nontraining in wait-list controls in another Class III study[e61] (n = 39, 8 weeks, RRMS, SPMS, PPMS, EDSS 2.3 +/- 0.3). After Bonferroni adjustment, the Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS)[e62] mood subscale score improved slightly in the training group (mean change -0.3,

95% CI -0.64 to 0.04) but worsened in the control group (mean change +0.3, 95% CI -0.27 to 0.87, p <0.024; for group-time interaction, post hoc p not provided). However, these results were inconsistent, as 2 other scales of mood, evaluating anxiety and depression (HADS, POMS), did not improve. Likewise, no improvements were seen in fitness, coordination, posture, fatigue (MFIS), QOL, or self-efficacy (Multiple Sclerosis Self-efficacy Scale [MSES]).[e63]

Gait and balance training

A Class I study[e64] (n = 35, 3 weeks, RRMS, SPMS, PPMS, EDSS 6–7.5) examined the effect of robot-assisted gait training (RAGT). 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. No difference was seen in the primary outcome (20-m timed walking velocity, mean change, 95% CI: RAGT group 0.11, 0.02 to 0.28, and CWT group 0.07, 0.0 to 0.14; ES difference between groups 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, as evident from the wide CIs for the ES change in the primary outcome, the 20-minute timed walk.

A Class II study[e65] evaluated balance training (n = 44, RRMS, SPMS, PPMS, 3 weeks). 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, 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),[e66] improved in both balance training groups post-treatment (mean change, 95% CI: group 1 6.65, 3.59 to 9.71, group 2 4.6, 0.81 to 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])[e67] improved in group 1 but not in group 2 or group 3 (mean change, 95% CI: group 1 3.85, 2.1 to 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)[e68] and self-confidence (Activities-specific Balance Confidence scale [ABC])[e69] did not change, but the study lacked precision for detecting a benefit for these outcomes, as evidenced by the wide CIs.

Community/group programs

A study,[e70] rated Class III for a 22% dropout rate, lack of concealed allocation, and use of self-reported outcomes (n = 32, 12 weeks, MS type unspecified, EDSS 5–6.5), evaluated the effect of a community-based group exercise intervention targeting mobility, balance, and resistance vs usual care. The primary outcome, walking speed (T25W), did not improve. The treatment mean difference was -5.4 (95% CI -16.62 to 5.82) at 8 weeks and -7.2 (95% CI -18.83 to 4.43) at 12 weeks. The control group mean change was -0.7 (95% CI -10.56 to 9.16) at 8 weeks and -3 (95% CI -12.33 to 6.33) at 12 weeks (p = nonsignificant). The study lacked precision to detect a benefit for this outcome. There were improvements in activity (Phone-FITT questionnaire treatment

mean difference, 95% CI: 8 weeks 61.6, 2.4 to 30.4, 12 weeks 78.2, 6.5 to 43.3; control at 8 weeks -16, -37.3 to 4.79, at 12 weeks 0, -18.8 to 18.8). After Bonferroni adjustment, there was improvement at 8 weeks (p <0.024 for group effect) but not at 12 weeks (p = 0.12, nonsignificant). There were improvements in self-perceived balance confidence, ABC (mean difference, 95% CI: at 8 weeks 13.5, 0.44 to 26.6, at 12 weeks 23.6, 8.75 to 38.45; control at 8 weeks 6.9, -18.6 to 32.4, at 12 weeks 9.1, -16.4 to 34.6) (corrected p for group effect 0.024). Changes did not occur in multiple other outcomes of walking endurance/speed (6MW), balance (BBS), physical function/dynamic balance (TUG), dynamometer assessment of quadriceps strength, body mass index, fatigue, anxiety and depression (HADS), QOL (MSQOL-54 scale),[e71] and goal attainment (Goal Attainment Scale)[e72]; however, the study likely lacked precision for these outcomes.

In a Class III study[e73] (n = 46, 6 weeks, RRMS, SPMS, PPMS, EDSS 3–8), the efficacy of group exercise training was compared with that of usual care on the basis of participant preference. After the intervention, no change was seen in disability (EDSS) (group mean change training 0, 95% CI -0.72 to 0.72, control 0.1, 95% CI -0.77 to 0.97, p = nonsignificant), fatigue (FSS) (mean change training -0.45, 95% CI -1.12 to 0.22, control 0.07, 95% CI -0.63 to 0.77, p = nonsignificant), or RPE (group mean change treatment 1, 95% CI -0.02 to 2.02, corrected p = 0.1). Muscle strength, walking speed (timed walk tests), and QOL (MSQOL-54) also did not change when corrected for multiple outcomes, but the study likely lacked precision to detect these benefits.

The effect of 2 interventions to promote physical activity was assessed in a study[e74] rated Class III for lack of concealed allocation and a 23% dropout rate (n = 50, 8 weeks, MS type unspecified, patients who were ambulatory). Participants were randomized to either individualized physical rehabilitation or group wellness intervention. There were no ES summary differences between groups for the following outcome measures: fatigue (MFIS 0.52 [p = nonsignificant], mean change in scores and CI not provided), QOL (SF-36 mental 0.6, SF-36 physical summary 0.59 [p = nonsignificant], mean change in scores and CI not provided), and depression (Mental Health Inventory[e75] 0.32 [p = nonsignificant], mean change in scores and CI not provided).

Conclusions

Outpatient and home PT

1. Weekly **home PT** 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).[e28] These programs probably are ineffective for improving upper-extremity dexterity (1 Class I study).[e28] Data are inadequate to support or refute the use of these programs for improving self-reported falls/mobility, depression, or anxiety (1 study rated Class III for subjective outcomes).[e28]

2. Three weeks of individualized **inpatient exercise followed by home exercises** for 15 weeks possibly are effective for reducing disability (RRMS, PPMS, SPMS, EDSS 3.0–6.5) (1 Class II

study).[e33] Data are inadequate to support or refute the use of this regimen for improving HRQL (1 study rated Class III for subjective outcomes).[e33]

3. Three weeks' worth of **motor and sensory balance training or motor balance training** possibly is effective for improving static and dynamic balance, and 3 weeks' worth of **motor balance training** possibly is effective for improving static balance (RRMS, SPMS, PPMS) (1 Class II study[e65]). Data are inadequate to support or 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 of findings difficult; insufficient precision for subjective outcomes).[e65]

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

a. **Home PT** for improving QOL (1 Class III study with insufficient precision)[e37]
b. Long-term benefit (6 months) of an **outpatient exercise program combined with home exercises** for improving fatigue or QOL[e34]
c. **ACSM-based resistance training with or without electrostimulation** for improving lower-extremity muscle strength, functional mobility, or disability[e38]
d. **Lower-extremity progressive resistance training** on lower-extremity strength, function,[e43] fatigue, mood, or QOL[e45]
e. **Progressive bicycle ergometry resistance training combined with balance exercises** for improving gait, walking speed, functional reach, falls, fatigue, or depression[e46]
f. Three weeks of **inpatient strength and aerobic training followed by a 23-week home exercise program** for improving upper-extremity endurance, dexterity, lower-extremity strength, balance, walking speed, aerobic capacity, fatigue, or HRQL[e47–e49]
g. **Short-term (3–15 weeks) aerobic exercise programs** for improving the following: (1) muscle strength, aerobic capacity, disability, health status, fatigue, mood (1 Class III study lacking statistical precision)[e56]; (2) lung function, fatigue, HRQL[e60]; (3) coordination, posture, self-efficacy, anxiety, or depression[e61] (3 Class III studies, different durations and study populations)
h. **RAGT** for improving walking speed and knee extensor strength (1 imprecise Class I study)[e64]
i. **Group exercise therapy** for improving the following: (1) activity, balance confidence, walking endurance, physical function, leg strength, fatigue, mood, goal attainment[e70]; (2) disability, walking speed, muscle strength, fatigue[e73]; (3) HRQL[e70,e73] (2 Class III studies, different durations and interventions)
j. **An individualized physical rehabilitation program or a group wellness intervention** for improving fatigue, QOL, or depression[e74]

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.

In patients with MS, do other specific therapy techniques minimize impairment, reduce disability, or improve HRQL?

A Class II randomized trial[e76] 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 for function or gait) 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, and MS type unknown, EDSS 2–5) completed phase 1, and 18 patients completed phase 2. 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: T25FW (mean change -0.6, 95% CI -1.83 to 0.63, in BBTW group, vs 0, 95% CI -1.49 to 1.49, in the control group, corrected p <0.02). It is uncertain whether this difference is clinically meaningful. In phase 2, 3 patients had TUG scores 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 -1.2, 95% CI -5.32 to 2.92, in the BBTW group, vs -0.2, 95% CI -4.1 to 3.7, in the SWP group, 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[e77] assessed the effect of a home program of breathing-enhanced upper-extremity exercises (as compared with no intervention)[e74] 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],[e78] a subjective clinical assessment of respiratory function, and Borg RPE). The following outcomes improved (differences in means, 95% CI): forced expiratory volume in 1 second (FEV_1) 10.3, 3.48 to 17.11, PDI -0.43, -0.66 to -0.19, 6MW 8, 4.2 to 11.8. No changes were seen (differences in means, 95% CI) in EDSS (-0.31, -0.56 to -0.05), FEV_1/forced vital capacity (FVC) (7.2, -0.47 to 13.93, estimate imprecise), 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 (PE_{max}) (4.6, -0.99 to 10.19, estimate imprecise).

Another study[e79] evaluated the effect of an inspiratory muscle training program as compared with no intervention (n = 46, 10 weeks, RRMS, SPMS, and PPMS, EDSS 2–6.5). The outcomes were multiple pulmonary function variables (Class II, objective) and fatigue (FSS) (Class III, patient-reported). PI_{max} improved (mean change, 95% CI 23.5, 8.92 to 38.08, in treatment group, vs -0.7, -17.08 to 15.68, in the control group, corrected p <0.008), but precision for the other outcomes was insufficient to exclude a possible benefit.

A Class III study[e80] evaluated the impact of expiratory muscle strength training on respiratory and speech measures (N = 31, 8 weeks, 17 patients with MS type unspecified, EDSS 1.5–6.5; 14 healthy controls). Both groups showed significant improvement in PE_{max} (mean +/- SD pretraining 85.73±36.45, 8 weeks post-training 114.73±42.36, and 4 weeks detraining

109.09±37.60, F = 53.28, corrected p <0.0005). Voice production and voice-related QOL did not improve in the MS group.

The Grimaldi method consists of applying a series of fast accelerations to a muscle group while the limb is being moved by forces applied in the opposite direction. In a Class III study,[e81] the Grimaldi method, involving a sudden passive stretch applied to improve active muscle recruitment of hip abductors, was compared with a routine stretching maneuver for hip adductors resembling the Grimaldi method (n = 40, 3 sessions, MS type unspecified). Outcomes were measured before and immediately after each session. Improvements were seen in hip abductor range of motion (intervention 68% improved vs control 19% improved), endurance (intervention 29% improved vs control 4% improved), and work output (intervention 43% improved vs control 12% improved). None of the differences was significant after correction for multiple comparisons.

A Class III study[e82] (n = 26, 4 weeks, PPMS, SPMS, EDSS 3–5.5) randomized participants with "prominent ataxia" to exercise alone or exercise with Johnstone pressure splints. Neither disability (EDSS, mean difference -0.3, 95% CI -0.66 to 0.06) nor multiple measures of coordination and equilibrium improved after Bonferroni correction.

A Class III crossover study[e83] (n = 20, 16 weeks, RRMS, SPMS, PPMS, EDSS 2–6) randomized participants to 8 weeks of Feldenkrais therapy, a specific bodywork method, followed by 8 weeks of sham therapy or vice versa. The largest effects were seen in the MS Perceived Stress Scale[e84] (percentage improved in intervention group 20 ± 4.6 vs in control group 17± 6.1, corrected p = nonsignificant). After Bonferroni correction, there were no differences in dexterity (9-HPT), function (symptom inventory, performance scales), mood (HADS), or self-efficacy (MSES).

Three cycling exercise intensities (continuous, intermittent, or a combination of these 2) were compared in a Class III study[e85] (n = 55, 6 weeks, RRMS, SPMS, PPMS, and MS type unknown). In general, higher exercise intensities produced more improvement but were less well tolerated. No between-group differences were found in the primary outcome, gait speed (TMW, mean change +/- 2 SD and 95% CI: intermittent 12.94 ±4.71, 3.97 to 21.92; continuous 4.77±4.24, -3.8 to 13.22, imprecise; combined -0.9±1.9, -4.7 to 2.9), or in multiple secondary outcomes, including leg extensor strength, endurance, speed of leg extension, dynamic balance (TUG), activities of daily living (ADL) (Barthel Index [BI]),[e86] fatigue (FSS), and QOL (SF-36); however, the study lacked precision to detect these differences.

A Class III study[e87] (n = 25, 20 weeks, MS type unspecified, EDSS 2–6.5) found that a whole-body vibration exercise protocol as compared with no treatment did not improve leg muscle performance or functional capacity (multiple tests, including TMW, TUG, T25W, BBS).

An RCT, Class III[e88] for a 35% dropout rate, nonblinding of patients, and use of patient-reported outcomes (n = 32, 8 weeks, RRMS, EDSS <3.5), evaluated the effect of aquatic exercise training (n = 12) as compared with no treatment (n = 11) on fatigue (MFIS) and HRQL (MSQOL-54 subsets) at 4 and 8 weeks. The MSQOL-54 physical component improved at 4 weeks (mean changes, 95% CI: aquatic group 10.4, 4.67 to 16.3, vs control group 0.5, -4.79 to 5.79) and at 8

weeks (mean changes, 95% CI: aquatic group 21.5, 15.2 to 27.8, vs control group 0.7, -3.88 to -5.28, all p <0.001). MSQOL-54 mental component also improved at 4 weeks (aquatic group 12.5, 5.61 to 19.39, vs control group 0, -9.52 to 9.52) and at 8 weeks (aquatic group 25.8, 18.55 to 33.05, vs control group 1.1, -7.56 to 9.76, all p <0.001). MFIS did not improve after correction for multiple outcomes.

In an RCT, rated Class III[e89] for lack of concealed allocation (n = 35, 8 weeks, MS type unspecified), a home telerehabilitation program as compared with usual care did not improve manual dexterity (9HPT, mean change, 95% CI: intervention 5.5 secs, -25.9 to 36.9, vs controls 0.4 secs, -77.5 to 78.2), or arm grasp (Action Research Arm Test,[e90] mean change intervention -3, -12.4 to 6.4, vs controls -3.7, -49 to 41), but the study lacked precision to detect a benefit.

The effect of low-level cardiovascular endurance as compared with noncardiovascular activity was assessed in a Class III RCT[e91] (nonblinded and patient-reported outcomes, and baseline differences between groups, n = 30, 3 weeks, RRMS, SPMS, PPMS, EDSS 0–5). The primary outcomes were self-determined distance and time walked on a treadmill. Improvements were seen in both walking distance (mean increase in meters, 95% CI, in the intervention group as compared with controls: 553, 299.6 to 806) and walking time (mean increase in minutes, 95% CI, in the intervention group as compared with controls: 10, 6.8 to 13.2). Secondary outcomes of fatigue (MFIS), depression (BDI), and QOL (HAQUAMS) did not change.

An RCT, rated Class III for lack of concealed allocation (n = 38, 2 weeks, RRMS),[e92] evaluated intermittent transcranial magnetic theta burst stimulation (iTBS) plus exercise therapy (ET), sham iTBS (15% of stimulator output) plus ET, and iTBS alone. When compared with baseline, the following outcomes improved in the iTBS-plus-ET group (mean change, 95% CI): spasticity (modified Ashworth scale)[e93] 0.8, 0.42 to 1.18; subjective spasticity (Multiple Sclerosis Spasticity Scale-88[e94]) 21.1, 10.6 to 31.6; fatigue (FSS) 7.9, 3.8 to 12; ADL (BI) 2.5, 0.5 to 2.5; and HRQL (MSQOL-54 physical health composite) 5.5, 3 to 8. Only the objective measure of spasticity (modified Ashworth) improved with iTBS alone at 2 weeks (mean decrease 1.7, 95% CI 0.95 to 2.45). There was no change after sham iTBS plus ET or ET alone.

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 study, Class II for objective outcomes).[e77] This regimen possibly is ineffective for improving disability (1 study, Class II for objective outcome).[e77] Data are inadequate to support or refute the use of this regimen for improving other pulmonary function parameters (I Class II study lacking precision[e77]) or subjective feeling of exhaustion or respiratory dysfunction (1 study, Class III for subjective outcomes[e77]). 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).[e79]

3. Data are inadequate to support or refute the use of the following (1 Class III study each unless otherwise stated):
    a. BBTW for improving mobility (1 Class II study with inconsistent results between sham-weight and no-weight groups)[e76]
    b. Inspiratory muscle training for improving multiple pulmonary function test parameters or fatigue[e79]
    c. Expiratory muscle training for improving expiratory muscle strength or voice/speech production[e80]
    d. Grimaldi's PT method for improving hip abductor function or strength[e81]
    e. Johnstone pressure splints for improving disability, coordination, or equilibrium[e82]
    f. Feldenkrais bodywork therapy for improving dexterity, function, mood, self-efficacy, or perceived stress[e83]
    g. The relative efficacy of 3 cycling-intensity protocols for improving gait, fatigue, ADL, or QOL[e85]
    h. A whole-body vibration exercise protocol for improving leg muscle performance or functional capacity[e87]
    i. Aquatic exercise training for reducing fatigue or improving HRQL[e88]
    j. Low-level cardiovascular endurance exercise for reducing fatigue or improving endurance and walking speed, mood, or QOL[e91]
    k. ITBS with or without ET for reducing spasticity, disability, or fatigue, or for improving HRQL or ADL[e92]
    l. A home telerehabilitation program for improving manual dexterity or arm grasp[e89]

In patients with MS, do energy efficiency/conservation techniques, specialty devices, or educational programs affect function or HRQL?

In a single-blind, crossover study (n = 20, MS type unspecified, EDSS 1.5–6.5), the efficacy of lightweight cooling garment technology was assessed as compared with sham cooling (inoperable cooling system) (Class III).[e95] Participants were assessed while wearing the cooling garments. Function/disability (MSFC),[e96] shown as *z* score (SD), was 0.952 (0.88) in the active group and 0.723 (1.11) in the sham group (corrected $p = 0.238$, 95% CI cannot be calculated with data provided, ES 2.6, large). Improvement in isometric strength of the knee extensors approached, but did not reach, significance (active cooling mean 24.6 kg, median 17.3, interquartile range 32.6; sham mean 22.7 kg, median 14.5, and interquartile range 33.4; corrected $p = 0.06$, 95% CI cannot be calculated with data provided). No improvements were seen in spasticity, foot dorsiflexion and grip strength, postural sway, or patient reports of pain, bladder voiding control, sweating, or generalized well-being; however, the study lacked sufficient precision to detect differences.

A 2-phase RCT[e97] (rated Class III for lack of concealed allocation or specified primary outcome, n = 84 relapsing or progressive MS, EDSS <6) evaluated the effects of acute and chronic (1-month) cooling. Acute-phase participants were randomized and assessed before and after a single 1-hour session of low-dose cooling (70°F, sham) or high-dose cooling (55°F). In the chronic, nonblinded phase, half the participants were assigned to home cooling (1 hour/day) for 4 weeks and half to observation; then everyone returned for a high-dose cooling session. After a 1-week washout, participants crossed over to the alternate treatment. After correction for multiple

outcomes, no differences were seen in the acute phase on the MSFC total (mean difference between high-dose and low-dose groups -0.03, 95% CI -0.11 to 0.05) or subscales (9-HPT, T25W, Paced Auditory Serial Addition Test),[e98] or in visual acuity at various contrast levels (visual acuity at 100% contrast, number correct, mean difference between groups -1.15, 95% CI -2.63 to 0.33).[e99] In the chronic phase, the MSFC or subscale scores did not change, and visual acuity at 3 of 4 levels of contrast improved in both the observation group and the cooling group, but visual acuity did not change between the cooling group and observation group (visual acuity at 5% contrast, number correct, mean difference between groups 0.1, 95% CI -1.03 to 1.23). Patients reported subjective improvements in fatigue, strength, and cognition during the cooling month. The study probably lacked precision to detect a difference.

An RCT[e100] rated Class III for patient-reported outcomes (n = 41, 6 weeks, MS type unspecified, EDSS <6) randomized patients to participation in the "Fatigue: Take Control Program" for 2-hour sessions or to a spot on a wait-list. Total MFIS scores (primary outcome) improved (mean difference between groups 4.07, 95% CI 2.63 to 5.51). The MFIS physical subscale scores also improved (mean change between groups 2.48, 95% CI 0.93 to 4.03). A secondary outcome measure of fatigue, FSS scores, did not improve, but the study lacked statistical precision for this outcome (mean change between groups -1.5, 95% CI -5.73 to 2.73).

Two studies evaluated an energy conservation program described by Packer et al.[e101] The first study,[e102] Class III (22% dropout rate and lack of concealed allocation) (n = 169, 6 weeks, RRMS, SPMS, PPMS, and MS type unknown), evaluated the effect of this energy conservation program, as compared with no treatment, on fatigue (FIS), QOL (SF-36) (primary outcomes), and self-efficacy. After correction for multiple outcomes, there were improvements in FIS physical (mean difference -2.89, 95% CI -4.94 to -0.84) and social (mean difference -4.74, 95% CI -8.32 to -1.16) subscales. Scores on the SF-36 subscales Role Physical (mean difference 12.68, 95% CI 0.09 to 25.28) and Vitality (mean difference 8.97, 95% CI 3.55 to 14.39) were significant in the intent-to-treat population. The combined changes in SF-36 and FIS scores also improved ($p < 0.0015$).

A Class III 1-year follow-up to the previous study[e103] revealed that, when compared with the baseline scores, scores at 1 year were significantly improved in the intent-to-treat population for the FIS subscales cognitive (mean difference -3.97, 95% CI -5.38 to -2.55), physical (mean difference -4.45, 95% CI -5.73 to -3.17), and social (mean difference -7.54, 95% CI -9.98 to -5.09); and for the SF-36 subscales role physical (mean difference 12.45, 95% CI 4.68 to 20.23), vitality (mean difference 6.42, 95% CI 2.67 to 10.18), and social function (mean difference 6.88, 95% CI 2.26 to 11.50).

A single-blind RCT rated Class III for reliance on patient-reported outcomes[e104] (n = 62, 8 weeks, RRMS, SPMS, PPMS, EDSS 0–7) randomized participants to a multidisciplinary health promotion intervention (the OPTIMISE program, to increase knowledge, skills, and confidence in undertaking health promotion activities) or usual care. Immediately after completion of the program, at 8 weeks, improvement was seen in the primary outcome measure (frequency of engagement in health-promoting activities, Health-Promoting Lifestyle Profile)[e105] (mean difference between groups -16.8, 95% CI -8.8 to -24.8). This improvement was maintained at 3 months. Improvements also occurred on the health responsibility, physical activity, growth, and

stress management subscales. The secondary outcome measure of self-efficacy (Self-Rated Abilities for Health Practices Scale [SRAHP])[e106] also improved (SRAHP mean difference -11.93, 95% CI -1.88 to -21.98).

Conclusion

1. Data are inadequate to support or refute use of the following (1 Class III study each unless otherwise stated):
   a. The short-term use of cooling garments for reducing disability, fatigue, spasticity, pain, or sweating, and improving function, muscle strength, postural sway, or bladder voiding control (2 imprecise Class III studies)[e95,e97]
   b. One-month use (1 hour/day) of cooling garments for improving function, cognition, visual acuity, or strength, or for reducing fatigue[e97]
   c. Group fatigue program (Fatigue: Take Control Program) for reducing fatigue[e100]
   d. Packer[e101] energy conservation program for reducing fatigue or improving QOL or self-efficacy over 6 weeks (1 Class III study[102]) or 1 year (1 Class III study[e103]) in all MS types
   e. An outpatient health promotion education program (OPTIMISE) for improving engagement in health-promoting activities, self-efficacy, or HRQL[e104]

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. The therapies and techniques used in the studies should be described in detail to permit comparison between studies and meta-analyses, if needed. Many studies were ineligible for inclusion in this review 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 a 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 post-intervention, 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. Also, the benefit of rehabilitation interventions 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 for 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.

DISCLAIMER

Clinical practice guidelines, practice advisories, systematic reviews and other guidance published by the American Academy of Neurology and its affiliates are assessments of current scientific and clinical information provided as an educational service. The information: 1) should not be considered inclusive of all proper treatments, methods of care, or as a statement of the standard of care; 2) is not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time information is developed and when it is published or read); 3) addresses only the question(s) specifically identified; 4) does not mandate any particular course of medical care; and 5) is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. AAN provides this information on an "as is" basis, and makes no warranty, expressed or implied, regarding the information. AAN specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. AAN assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

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 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.[e10]

ACKNOWLEDGMENTS

We acknowledge the assistance of Maureen L. Carney, MD, for review of abstracts and appreciate the input from Jay Rosenberg, MD, with regard to conceptualization.

Appendix e-1: 2014–2015 GDDI Subcommittee members

Cynthia Harden, MD (Chair); Steven R. Messé, MD (Co-Vice-chair); Sonja Potrebic, MD, PhD (Co-Vice-Chair); Eric J. Ashman, MD; Richard L. Barbano, MD, PhD; Brian Callaghan, MD; Jane Chan, MD Diane Donley, MD; Richard M. Dubinsky, MD, MPH; Terry Fife, MD; Jeffrey Fletcher, MD; Michael Haboubi, MD; John J. Halperin, MD; Yolanda Holler, MD; Andres M. Kanner, MD; Annette M. Langer-Gould, MD, PhD; Jason Lazarou, MD; Nicole Licking, DO; David Michelson, MD; Pushpa Narayanaswami, MBBS, DM; Maryam Oskoui, MD; Richard Popwell, Jr., MD; Tamara Pringsheim, MD; Alejandro A. Rabinstein, MD; Alexander Rae-Grant, MD; Anant Shenoy, MD; Kevin Sheth, MD; Kelly Sullivan, PhD; Jonathan P. Hosey, MD (Ex-Officio); Stephen Ashwal, MD (Ex-Officio); Deborah Hirtz, MD (Ex-Officio); Jacqueline French, MD (AAN Guideline Historian, Ex-Officio, Voting)

Appendix e-2: Mission Statement of GDDI

The mission of the GDDI is to develop, disseminate, and implement evidence-based systematic reviews and clinical practice guidelines related to the causation, diagnosis, treatment, and prognosis of neurologic disorders.

The GDDI is committed to using the most rigorous methods available within its budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

Appendix e-3: Complete search strategy

For complete search strategy, access the PDF "Appendix e-3: Complete search strategy," available as an online data supplement to the complete article on the *Neurology* journal website at Neurology.org.

Appendix e-4: Classification of evidence for therapeutic studies

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).

E-REFERENCES

e1. Anderson DW, Ellenberg JH, Leventhal CM, Reingold SC, Rodriguez M, Silberberg DH. Revised estimate of the prevalence of multiple sclerosis in the United States. Ann Neurol 1992;31:333–336.

e2. Noonan CW, Kathman SJ, White MC. Prevalence estimates for MS in the United States and evidence for an increasing trend for women. Neurology 2002;58:136–138.

e3. Nelson LM, Hamman RF, Thompson DS, et al. Higher than expected prevalence of multiple sclerosis in northern Colorado: dependence on methodologic issues. Neuroepidemiology 1986;5:17–28.

e4. Benito-León J. Multiple sclerosis: is prevalence rising and if so why? Neuroepidemiology 2011;37:236–237.

e5. Alonso A, Hernán MA. Temporal trends in the incidence of multiple sclerosis: a systematic review. Neurology 2008;71:129–135.

e6. Kraft GH. Rehabilitation still the only way to improve function in multiple sclerosis. Lancet 1999;354:2016–2017.

e7. Poser CM, Paty DW, Scheinber L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983;13:227–231.

e8. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444–1452.

e9. Granger CV, Cotter AC, Hamilton BB, Fiedler RC, Hens MM. Functional assessment scales: a study of persons with multiple sclerosis. Arch Phys Med Rehabil 1990;71:870–875**.**

e10. American Academy of Neurology. Clinical Practice Guidelines Process Manual, 2004 ed. St. Paul, MN: The American Academy of Neurology; 2004. https://www.aan.com/Guidelines/Home/UnderDevelopment. Published 2004. Accessed February 12, 2012.

e11. Patti F, Ciancio MR, Reggio E, et al. The impact of outpatient rehabilitation on quality of life in multiple sclerosis. J Neurol 2002;249:1027–1033.

e12. Patti F, Ciancio MR, Cacopardo M, et al. Effects of a short outpatient rehabilitation treatment on disability of multiple sclerosis patients—a randomised controlled trial. J Neurol 2003;250:861–866.

e13. Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray TJ. The impact of fatigue on patients with multiple sclerosis. Can J Neurol Sci 1994;21:9–14.

e14. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:567–571.

e15. Apolone G, Mosconi P. The Italian SF-36 Health Survey: translation, validation and norming. J Clin Epidemiol 1998;51:1025–1036.

e16. Tempelaar R, De Haes JC, De Ruiter JH, Bakker D, Van Den Heuvel WJ, Van Nieuwenhuijzen MG. The social experiences of cancer patients under treatment: a comparative study. Soc Sci Med 1989;29:635–642.

e17. Kazis LE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. Med Care 1989;27:S178–S189.

e18. Cohen J. The concepts of power analysis. In: Statistical power analysis for the behavioural sciences. London: Academic Press, 1977:1–20.

e19. Kos D, Duportail M, D'hooghe M, Nagels G, Kerckhofs E. Multidisciplinary fatigue management programme in multiple sclerosis: a randomized clinical trial. Mult Scler 2007;13:996–1003.

e20. Multiple Sclerosis Council for Clinical Practice Guidelines. Fatigue and multiple sclerosis: evidence-based management strategies for fatigue in multiple sclerosis. Paralyzed Veterans of America, 1998.

e21. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46:1121–1123.

e22. Freeman JA, Langdon DW, Hobart JC, Thompson AJ. The impact of inpatient rehabilitation on progressive multiple sclerosis. Ann Neurol 1997;42:236–244.

e23. Harwood RH, Ebrahim S. Manual of the London Handicap Scale. Nottingham: University of Nottingham, Department of Health Care of the Elderly, 1995.

e24. Khan F, Pallant JF, Brand C, Kilpatrick TJ. Effectiveness of rehabilitation intervention in persons with multiple sclerosis: a randomised controlled trial. J Neurol Neurosurg Psychiatry 2008;79:1230–1235.

e25. Hobert, J, Lamping D, Fitzpatrick R, Riazi A, Thompson A. The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. Brain 2001;124:962–973.

e26. Goldberg DP. Manual of the General Health Questionnaire. Windsor: National Foundation for Educational Research, 1978.

e27. Judica E, Martinelli Boneschi F, Ungaro D, et al. Impact of fatigue on the efficacy of rehabilitation in multiple sclerosis. J Neurol 2011;258:835–839.

e28. Wiles CM, Newcombe RG, Fuller KJ, et al. Controlled randomised crossover trial of the effects of physiotherapy on mobility in chronic multiple sclerosis. J Neurol Neurosurg Psychiatry 2001;70:174–179.

e29. Collen FM, Wade DT, Robb GF, Bradshaw CM. The Rivermead Mobility Index: a further development of the Rivermead Motor Assessment. Int Disabil Stud 1991;13:50–54.

e30. Vaney C, Blaurock H, Gattlen B, et al. Assessing mobility in multiple sclerosis using the Rivermead Mobility Index and gait speed. Clin Rehabil 1996;10:216–226.

e31. Goodkin DE, Hertsgaard D, Seminary J. Upper extremity function in multiple sclerosis: improving assessment sensitivity with box-and-block and nine-hole peg tests. Arch Phys Med Rehabil 1988;69:850–854.

e32. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–370.

e33. Solari A, Filippini G, Gasco P, et al. Physical rehabilitation has a positive effect on disability in multiple sclerosis patients. Neurology 1999;52:57–62.

e34. McCullagh R, Fitzgerald AP, Murphy RP, Cooke G. Long-term benefits of exercising on quality of life and fatigue in multiple sclerosis patients with mild disability: a pilot study. Clin Rehabil 2008;22:206–214.

e35. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14:377–381.

e36. Cella DF, Dineen K, Arnason B, et al. Validation of the functional assessment of multiple sclerosis quality of life instrument. Neurology 1996;47:129–139.

e37. Miller L, Paul L, Mattison P, McFayden A. Evaluation of a home-based physiotherapy programme for those with moderate to severe multiple sclerosis: a randomized controlled pilot study. Clin Rehabil 2011;25:720–730.

e38. Broekmans T, Roelants M, Feys P, et al. Effects of long-term resistance training and simultaneous electro-stimulation on muscle strength and functional mobility in multiple sclerosis. Mult Scler 2011;17:468–477.

e39. Podsiadlo D, Richardson S. The timed ‘‘Up & Go’’: a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc 1991;39:142–148.

e40. Nilsagard Y, Lundholm C, Gunnarsson LG, Dcnison E. Clinical relevance using timed walk tests and ‘timed up and go’ testing in persons with multiple sclerosis. Physiother Res Int 2007;12:105–114.

e41. Butland RJ, Pang J, Gross ER, Woodcock AA, Geddes DM. Two-, six-, and 12-minute walking tests in respiratory disease. Br Med J (Clin Res Ed) 1982;284:1607–1608.

e42. Duncan PW, Weiner DK, Chandler J, Studenski S. Functional reach: a new clinical measure of balance. J Gerontol 1990;45:192–197.

e43. Dalgas U, Stenager E, Jakobsen J, et al. Resistance training improves muscle strength and functional capacity in multiple sclerosis. Neurology 2009;73:1478–1484.

e44. Dalgas U, Stenager E, Jakobsen J, Petersen T, Overgaard K, Ingemann-Hansen T. Muscle fiber size increases following resistance training in multiple sclerosis. Mult Scler 2010;16:1367–1376.

e45. Dalgas U, Stenager E, Jakobsen J, et al. Fatigue, mood and quality of life improve in MS patients after progressive resistance training. Mult Scler 2010;16:480–490.

e46. Cakt BD, Nacir B, Saracoglu GH, et al. Cycling progressive resistance training for people with multiple sclerosis. Am J Phys Med Rehabil 2010;89:446–457.

e47. Romberg A, Virtanen A, Ruutiainen J, et al. Effects of a 6-month exercise program on patients with multiple sclerosis: a randomized study. Neurology 2004;63:2034–2038.

e48. Romberg A, Virtanen A, Ruutiainen J. Long-term exercise improves functional impairment but not quality of life in multiple sclerosis. J Neurol 2005;252:839–845.

e49. Surakka J, Romberg A, Ruutiainen J, et al. Effects of aerobic and strength exercise on motor fatigue in men and women with multiple sclerosis: a randomized controlled trial. Clin Rehabil 2004;18:737–746.

e50. Fischer JS, Rudick RA, Cutter GR, Reingold SC; National MS Society Clinical Outcomes Assessment Task Force. The Multiple Sclerosis Functional Composite Measure (MSFC): an integrated approach to MS clinical outcome assessment. Mult Scler 1999;5:244–250.

e51. Schwid SR, Goodman AD, Mattson DH, et al. The measurement of ambulatory impairment in multiple sclerosis. Neurology 1997;49:1419–1424.

e52. Schwid SR, Thornton CA, Pandya S, et al. Quantitative assessment of motor fatigue and strength in MS. Neurology 1999;53:743–750.

e53. Vickrey BG, Hays RD, Harooni R, Myers LW, Ellison GW. A health-related quality of life measure for multiple sclerosis. Qual Life Res 1995;4:187–206.

e54. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385–401.

e55. Surakka J, Romberg A, Ruutiainen J, Virtanen A, Aunola S, Mäentaka K. Assessment of muscle strength and motor fatigue with a knee dynamometer in subjects with multiple sclerosis: a new fatigue index. Clin Rehabil 2004;18:652–659.

e56. Petajan JH, Gappmaier E, White AT, Spencer MK, Mino L, Hicks RW. Impact of aerobic training on fitness and quality of life in multiple sclerosis. Ann Neurol 1996;39:432–441.

e57. Schapiro RT, Petajan JH, Kosich D, et al. Role of cardiovascular fitness in multiple sclerosis: a pilot study. J Neurolo Rehabil 1988;2:43–49.

e58. Gibson BS, Bergner M, Bobbit RA, et al. The sickness impact profile: final development and testing, 1975-1978. Seattle: Department of Health Services, School of Public Health and Community Medicine, University of Washington, 1979.

e59. McNair DM, Lorr M, Droppleman LF. Profile of Mood States (POMS). San Diego, CA: Educational and Industrial Testing Service, 1992.

e60. Mostert S, Kesselring J. Effects of a short-term exercise training program on aerobic fitness, fatigue, health perception and activity level of subjects with multiple sclerosis. Mult Scler 2002;8:161–168.

e61. Schulz KH, Gold SM, Witte J, et al. Impact of aerobic training on immune endocrine parameters, neurotropic factors, quality of life and coordinative function in multiple sclerosis. J Neurol Sci 2004;225:11–18.

e62. Gold SM, Heesen C, Schulz H, et al. Disease specific quality of life instruments in multiple sclerosis: validation of the Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS). Mult Scler 2001;7:119–130.

e63. Rigby SA, Domenech C, Thornton EW, Tedman S, Young CA. Development and validation of a self-efficacy measure for people with multiple sclerosis: the multiple sclerosis self-efficacy scale. Mult Scler 2003;9:73–81.

e64. Beer S, Aschbacher B, Manoglou D, Gamper E, Kool J, Kesselring J. Robot-assisted gait training in multiple sclerosis: a pilot randomized trial. Mult Scler 2008;14:231–236.

e65. Cattaneo D, Jonsdottir J, Zocchi M, Regola A. Effects of balance exercises on people with multiple sclerosis: a pilot study. Clin Rehabil 2007;21:771–781.

e66. Berg KO, Wood-Dauphinee SL, Williams JI, et al. Measuring balance in the elderly: preliminary development of an instrument. Physiother Can 1989;41:304–311.

e67. McConvey J, Bennett SE. Reliability of the Dynamic Gait Index in individuals with multiple sclerosis. Arch Phys Med Rehabil 2005;86:130–133.

e68. Jacobson GP, Newman CW. The development of the Dizziness Handicap Inventory. Arch Otolaryngol Head Neck Surg 1990;116:424–427.

e69. Powell LE, Myers AM. The Activities-specific Balance Confidence (ABC) Scale. J Gerontol A Biol Sci Med Sci 1995;50A:M28–M34.

e70. Learmonth YC, Paul L, Miller L, Mattison P, McFadyen AK. The effects of a 12-week leisure centre-based, group exercise intervention for people moderately affected with multiple sclerosis. Clin Rehabil 2011;26:579–593.

e71. Ford HL, Gerry E, Tennant A, Whalley D, Haigh R, Johnson MH. Developing a disease-specific quality of life measure for people with multiple sclerosis. Clin Rehabil 2001;15:247–258.

e72. Stoke LT. Goal attainment scaling in rehabilitation: a practical guide. King's College London, 2009.

e73. Mutluay FK, Tekeoglu A, Sebahattin S, et al. Group exercise training approach to multiple sclerosis. Nobel Med 2008;4:20–26.

e74. Plow MA, Mathiowetz V, Lowe DA. Comparing individualized rehabilitation to a group wellness intervention for persons with multiple sclerosis. Am J Health Promot 2009;24:23–26.

e75. Ritvo P, Fischer JS, Miller DM, et al. Multiple Sclerosis Quality of Life Inventory; A User's Manual. New York, NY: National Multiple Sclerosis Society; 1997.

e76. Widener GL, Allen DD, Gibson-Horn C. Randomized clinical trial of balance-based torso weighting for improving upright mobility in people with multiple sclerosis. Neurorehabil Neural Repair 2009;23:784–791.

e77. Mutluay FK, Demir R, Ozyilmaz S, Caglar AT, Altintas A, Gurses HN. Breathing-enhanced upper extremity exercises for patients with multiple sclerosis. Clin Rehabil 2007;21:595–602.

e78. Smeltzer SC, Lavietes MH, Troiano R, Cook SD. Testing of an index of pulmonary dysfunction in multiple sclerosis. Nurs Res 1989;38:370–374.

e79. Fry DK, Pfalzer LA, Chokshi AR, Wagner MT, Jackson ES. Randomized control trial of effects of a 10-week inspiratory muscle training program on measures of pulmonary function in persons with multiple sclerosis. J Neurol Phys Ther 2007;31:162–172.

e80. Chiara T, Martin D, Sapienza C. Expiratory muscle strength training: speech production outcomes in patients with multiple sclerosis. Neurorehabil Neural Repair 2007;21:239–249.

e81. Crippa A, Cardini R, Pellegatta D, Manzoni S, Cattaneo D, Marazzini F. Effects of sudden, passive muscle shortening according to Grimaldi's method on patients suffering from multiple sclerosis: a randomized controlled trial. Neurorehabil Neural Repair 2004;18:47–52.

e82. Armutlu K, Karabudak R, Nurlu, G. Physiotherapy approaches in the treatment of ataxic multiple sclerosis: a pilot study. Neurorehabil Neural Repair 2001;15:203–211.

e83. Johnson SK, Frederick J, Kaufman M, Mountjoy B. A controlled investigation of bodywork in multiple sclerosis. J Altern Complement Med 1999;5:237–243.

e84. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983;24:385–396.

e85. Collett J, Dawes H, Meaney A, et al. Exercise for multiple sclerosis: a single-blind randomized trial comparing three exercise intensities. Mult Scler 2011;17:594–603.

e86. Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: a reliability study. Int Disabil Stud 1988;10:61–63.

e87. Broekmans T, Roelants M, Alders G, Feys P, Thijs H, Eijnde BO. Exploring the effects of a 20-week whole-body vibration training programme on leg muscle performance and function in

persons with multiple sclerosis. J Rehabil Med 2010;42:866–872.

e88. Kargarfard M, Etemadifar M, Baker P, Mehrabi M, Hayatbakhsh R. Effect of aquatic exercise training on fatigue and health-related quality of life in patients with multiple sclerosis. Arch Phys Med Rehabil 2012;93:1701–1708.

e89. Huijgen BC, Vollenbroek-Hutten MM, Zampolini M, et al. Feasibility of a home-based telerehabilitation system compared to usual care: arm/hand function in patients with stroke, traumatic brain injury and multiple sclerosis. J Telemed Telecare 2008;14:249–256.

e90. McDonnell M. Action research arm test. Aust J Physiother 2008;54:220.

e91. Dettmers C, Sulzmann M, Ruchay-Plössl A, Gütler R, Vieten M. Endurance exercise improves walking distance in MS patients with fatigue. Acta Neurol Scand 2009;120:251–257.

e92. Mori F, Ljoka C, Magni E, et al. Transcranial magnetic stimulation primes the effects of exercise therapy in multiple sclerosis. J Neurol 2011;258:1281–1287.

e93. Ghotbi N, Ansari NN, Naghdi S, Hasson S, Jamshidpour B, Amiri S. Interrater reliability of the Modified Ashworth Scale in assessing lower limb muscle spasticity. Brain Inj 2009;23:815–819.

e94. Hobart JC, Riazi A, Thompson AJ, et al. Getting the measure of spasticity in multiple sclerosis: the Multiple Sclerosis Spasticity Scale (MSSS-88). Brain 2006;129:224–234.

e95. Meyer-Heim A, Rothmaier M, Weder M, Kool J, Schenk P, Kesselring J. Advanced lightweight cooling-garment technology: functional improvements in thermosensitive patients with multiple sclerosis. Mult Scler 2007;13:232–237.

e96. Cutter GR, Baier ML, Rudick RA, et al. Development of a multiple sclerosis functional composite as a clinical trial outcome measure. Brain 1999;122:871–882.

e97. Schwid SR, Petrie MD, Murray R, et al.; NASA/MS Cooling Study Group. A randomized controlled study of the acute and chronic effects of cooling therapy for MS. Neurology 2003;60:1955–1960.

e98. Rao SM, Leo GJ, Bernadin L, Universzagt F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. Neurology 1991;41:685–691.

e99. Balcer LJ, Baier ML, Cohen JA, et al. Contrast letter acuity as a candidate visual outcome measure for the Multiple Sclerosis Functional Composite. Neurology 2003;61:1367–1373.

e100. Hugos CL, Copperman LF, Fuller BE, Yadav V, Lovera J, Bourdette DN. Clinical trial of a formal group fatigue program in multiple sclerosis. Mult Scler 2010;16:724–732.

e101. Packer TL, Brink N, Sauriol A. Managing fatigue: a six-week course for energy conservation. Tucson, AZ: Therapy Skill Builders, 1995.

e102. Mathiowetz V, Finlayson ML, Matuska KM, Chen HY, Luo P. Randomized controlled trial of an energy conservation course for persons with multiple sclerosis. Mult Scler 2005;11:592–601.

e103. Mathiowetz VG, Matuska KM, Finlayson ML, Luo P, Chen HY. One-year follow-up to a randomized trial of an energy conservation course for persons with multiple sclerosis. Int J Rehabil Res 2007;30:305–313.

e104. Ennis M, Thain J, Boggild M, Baker GA, Young CA. A randomized controlled trial of a health promotion education programme for people with multiple sclerosis. Clin Rehabil 2006;20:783–792.

e105. Walker SN, Sechrist KR, Pender NJ. The Health-Promoting Lifestyle Profile: development and psychometric characteristics. Nurs Res 1987;36:76–81.

e106. Becker H, Stuifbergen AK, Oh HS, Hall S. Self-rated abilities for health practices: a health self-efficacy measure. Health Values 1993;17:42–50.