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Criteria to Determine Disability Related to Multiple Sclerosis

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. This report on *Criteria to Determine Disability Related to Multiple Sclerosis* was requested and funded by the Social Security Administration. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Outcomes and Evidence, Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850.

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Structured Abstract

Context: The Social Security Administration (SSA) processes more than 3.5 million claims for disability benefits each year. Multiple sclerosis (MS) is the third most common neurological diagnosis cited as the cause for disability. SSA requested evidence on whether current medical knowledge supports its MS disability policies.

Objectives: Our first major objective was to identify, review, and evaluate the medical literature on five major topics: reliability of MS diagnostic criteria; predictors of physical and mental impairments; effect of treatment and symptom management therapies; association of clinical findings with work ability; and impact of environmental factors on work capacity. Our second objective was to describe information needed to address any data insufficiencies, if any, in these five areas.

Data Sources: Nearly 1500 English-language articles were identified, principally from searches of MEDLINE®, CINAHL®, and Web of Science. The term *multiple sclerosis* was merged with concepts specific to the topic areas.

Study Selection: Nearly 50 percent, or 739 articles, initially met the selection criteria; of these, 168 (23 percent) passed three levels of screening (titles and abstracts; full-text articles; data abstraction). Inclusion requirements included a population with MS, relevance to specific question(s) based on appropriate thresholds, and satisfactory level of evidence.

Data Extraction: Descriptive data were partially abstracted into standardized evidence tables by a non-clinician abstractor and then completed by two clinicians (primary abstractor and over-reader). Methodological quality of each article was assessed for internal and external validity and reported in the evidence tables.

Data Synthesis: In two recent high-quality studies, the McDonald criteria identified a high proportion of patients presenting with clinically isolated syndrome who will go on to develop clinically definite MS over 1-4 years of follow up, with a specificity of 83 to 87 percent. We found few prospective studies describing prediction of changes in physical and mental impairments over a 9- to 24-month time frame. In clinical trials, few patients improved with disease-modifying treatments and then only in the range of 1.0 point on the Extended Disability Status Scale (EDSS); rehabilitation and symptomatic treatment of spasticity, fatigue, depression, voiding dysfunction, and cognitive impairments resulted in symptom and functional status improvement. Work ability has been little studied, and few data link it to symptoms or objective physical and cognitive measures. We found no studies linking thermal sensitivity and work ability.

Conclusions: McDonald criteria appear to have substantial evidence for validity and inter-rater reliability in diagnosing MS; clinical data are poor at predicting 1-year clinical outcomes. Treatments do not result in improvements in impairments, but symptomatic treatments can result in improvements in functional status. Further research is required to understand the associations between clinical data and work status or work ability.

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Appendixes and Evidence Tables are provided electronically at http://www.ahrq.gov/clinic/epcindex.htm

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Summary

Introduction

The Social Security Administration (SSA) operates the world's largest and most stringent disability program, processing more than 3.5 million claims each year, with multiple sclerosis (MS) representing the third most common neurological diagnosis cited as the cause for disability.[1] The purpose of this project, nominated by SSA and contracted through the Agency for Healthcare Research and Quality (AHRQ), is to determine whether current medical knowledge supports the SSA's stated policies regarding MS. In January 2003, the Duke Evidence-based Practice Center began work on this 13-month task to review evidence from the medical literature for use in updating SSA's listing of impairments for multiple sclerosis (MS) and for revising its disability policy (if indicated).

Research Questions

The seven major research questions addressed during this review are as follows:

Question 1a: What is the reliability of new McDonald criteria (incorporating supplementary information from radiologic and laboratory studies including magnetic resonance imaging [MRI], visual evoked potential [VEP], and cerebrospinal fluid [CSF] analyses) compared with long-term follow-up diagnosis of clinically definite MS according to the Poser criteria?

Question 1b: What is the inter-rater reliability of diagnosis of MS according to Poser or McDonald criteria among neurologists or between neurologists and non-neurologist physicians?

Question 2: What clinical indicators, including particularly time-course of impairments, predict physical or mental impairment at 12 months?

Question 3a: Among patients with MS, do current disease-modifying treatments result in long-term improvements in physical or mental outcomes compared to placebo or usual care?

Question 3b: Among patients with MS, do treatments aimed at symptom management result in improvements in physical or mental outcomes compared to usual care?

Question 4: Among individuals with MS, what physical, mental, laboratory, or radiographic findings have been associated with inability to work?

Question 5: Among individuals with MS, how does elevated temperature or other environmental factors impair the capacity to work?

Key Terms and Definitions

Knowledge of the terms used in the SSA disability evaluation process, components of that process, and Medical Listing criteria related to MS is critical to the reader's understanding of this report. To assist in the preparation of the report, SSA provided explanations of terms and processes as currently defined by SSA regulations and rulings. The terms cited below, as well as other terms and processes used by SSA for disability determination, are defined and described in the SSA publication, *Disability Evaluation Under Social Security 2003*.[2]

The statutory definition of "Disability" is "the inability to engage in any substantial gainful activity by reason of a medically determinable physical or mental impairment(s) which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months." This definition differs from the clinically used definition of the World Health Organization's *International Classification of Impairments, Disabilities and Handicaps*,[3] which defines disability as "any restriction or lack of

ability to perform an activity in a manner or within the range considered normal for a human being." While much of the medical literature uses the latter, broader definition, the reader must be aware that the goals of this report relate to the statutory definition.

The following terms are defined by current (2003) SSA regulations:

- "Claimant" is anyone who has filed a disability claim.
- "Substantial Gainful Activity" is the ability to earn an average of $800 per month.
- "Medically Determinable Impairment" is a physical or mental impairment that results from anatomical, physiological, or psychological abnormalities which can be shown by medically acceptable clinical and laboratory diagnostic techniques.
- "Evidentiary Requirements" for disability determination are described by SSA regulation. An acceptable medical source must report signs, symptoms, and laboratory findings diagnostic of an impairment. Although a claimant's reported signs and symptoms are not sufficient to meet the evidentiary requirements for establishing the presence of a medically determinable impairment, all available evidence including the claimant's report of symptoms is used to evaluate the impact of any documented impairment(s) on the claimant's ability to carry out work tasks.
- "Severe Impairment" is defined by the agency as any "impairment that more than minimally limits the claimant's ability to do basic work activities."

The regulations include a Listing of Impairments for each body system that define disability. Often referred to as the "medical listings," this list allows quick disability determinations to be made on the basis of medical criteria alone. The SSA publication, *Disability Evaluation Under Social Security 2003*,[2] under the neurological category of impairments, includes Listing 11.09.

11.09 Multiple Sclerosis with:

A. Disorganization of motor function as described in 11.04; or

B. Visual or mental impairment as described under the criteria in 2.02, 2.03, 2.04, or 12.02: or

C. Significant, reproducible fatigue of motor function with substantial muscle weakness on repetitive activity, demonstrated on physical examination, resulting from neurological dysfunction in areas of the central nervous system known to be pathologically involved by the multiple sclerosis process.

Full details on the Medical Listing for multiple sclerosis, including the imbedded references to sections 2, 11, and 12, are available in the above-cited SSA publication.[2]

"Residual Functional Capacity" is assessed when a claimant is determined to have a "severe" impairment that does not meet or equal the intent of the medical listings. Physical capacity (lifting, carrying, walking, standing, sitting, pedaling, and so on) and mental capacity (cognitive and behavioral, thought processing, concentration, pace, behavior) are assessed in determining residual functional capacity.

To adjudicate claims by individuals with MS for disability benefits, SSA must determine whether the claims file includes information from an acceptable medical source that documents the signs, symptoms, and laboratory findings that are diagnostic of a physical or mental impairment. SSA adjudicators also determine whether the impairment would be expected to more than minimally interfere with the claimant's capacity to carry out basic work activities for at least 12 consecutive months or end in death. If a severe impairment is identified, the adjudicator determines whether the medical findings meet or equal an impairment in the medical listings. If the documented impairment does not meet or equal a listed impairment, the adjudicator must determine the claimant's residual functional capacity and consider vocational factors prior to making a final disability determination.

Methods

A systematic and comprehensive search of the medical literature was conducted and was followed by a thorough review and evaluation of the literature determined to be relevant to the major research questions.

Literature Sources

The primary sources of literature were MEDLINE® (1966-April 2003), CINAHL® (1983-April 2003), Cochrane Database of Systematic Reviews, and Web of Science. Searches of these databases were supplemented by reviews of reference lists contained in all included articles and in relevant review articles and meta-analyses.

Search Strategies

Searches were limited to the English language and to human subjects. For efficacy-of-treatment topics, the searches were also limited to studies with randomized controlled trial designs. In all, there were five major searches:

1. Search 1 was a general search targeting MS and employment issues that merged search terms for *multiple sclerosis*, *transverse myelitis*, and *optic neuritis* with employment terms such as *disability evaluation*, *work capacity evaluation*, *employment*, and *activities of daily living*. No study designs were excluded.
2. Search 2 was targeted to studies on the reliability of diagnostic criteria for MS. Major search terms employed were *multiple sclerosis* (exploded), *multiple sclerosis*/di (limited to diagnostic articles), text word options for *poser* and *mcdonald*, and exploded terms *reproducibility of results*/

or observer variation/ or psychometrics, along with the text word reliability. No study designs were excluded.

3. Search 3 focused on treatment of fatigue for MS and specified several drugs used in the treatment of MS-related fatigue. No study designs were excluded.
4. Search 4 looked for a wide range of symptomatic therapies (other than fatigue) and disease-modifying therapies. A wide selection of treatments was specified, and the search was limited to randomized controlled trial designs.
5. Search 5 was focused on the predictive value of the McDonald diagnostic criteria, specifically on their use of additional paraclinical diagnostic methods (MRI, VEP, and CSF) and on studies reporting sensitivity, specificity, and reproducibility.

All searches, including narrowly focused sub-searches, yielded 1,487 potentially relevant citations.

Abstract and Full-text Screening Criteria

For each question, we developed fairly detailed instructions and decision rules for the screeners' reference. There were very broad inclusion requirements for abstracts: MS study subjects and potential relevance to any of the five questions. For the full-text screening, screeners were asked to record their include/exclude decision, research question assignment, and, if appropriate, exclusion criteria that detailed insufficiencies in study design and clinical substance requirements.

The titles and abstracts of the 1,487 articles were reviewed against the inclusion/exclusion criteria by at least two of five clinical investigators. The full text of each article passing the title-and-abstract screening was retrieved from the library for further review.

At the full-text review stage, each article was independently evaluated by two investigators, who forwarded their decisions to the task order manager for recording and comparison. If indicated, reviewers were asked to reconcile differences of opinion and return a reconciled final decision. If reviewers had difficulty reaching agreement, or submitted indecisive codes, the principal investigator was the arbiter.

Approximately 50 percent of the articles were included after the abstract screening and full-text article review stages.

Data Abstraction and Development of Evidence Tables

Data from articles included after full-text screening were abstracted directly into an evidence table template, which served as a data abstraction form. The study's writer/editor began the process with a partial abstraction of each included article. The partial abstraction included descriptions of the study design, interventions, number of subjects at the start of the study, and types of outcomes data to be collected. The partial abstraction form was forwarded to a clinician for completion and then returned to the writer/editor, who checked it for completeness and consistency of information and forwarded it to a second clinician for over-reading. The over-reader returned the table to the writer/editor for a final check of the completeness of the content, editing, and formatting.

At the end of the data abstraction stage and the very close scrutiny of each article, 168 articles were included.

Results and Discussion

The primary goal of this review was to examine the evidence in the medical literature for data that can guide policy in determining disability in MS patients. Although the literature in general (and certain studies in particular) suffers from limitations, reasonably strong conclusions can still be drawn for most of the seven research questions.

Reliability of Criteria for Diagnosing MS

This topic encompassed two questions:

Question 1a: What is the reliability of new McDonald criteria (incorporating supplementary information from radiologic and laboratory studies including MRI, VEP, and CSF analyses) compared with long-term follow-up diagnosis of clinically definite MS according to the Poser criteria?

Question 1b: What is the inter-rater reliability of diagnosis of MS according to Poser or McDonald criteria among neurologists or between neurologists and non-neurologist physicians.

Analytic approach. Regarding Question 1a, the most important difference between the Poser criteria[4] and the new McDonald criteria[5] is the addition of MRI findings to the diagnosis of MS, in lieu of the presence of a second attack. Our approach to this question was to identify studies in two categories: (1) those that specifically compared the new McDonald criteria to long-term diagnosis of clinically definite MS according to the Poser criteria; and (2) those that provided data on the accuracy of various MRI techniques, VEP analyses, and CSF analyses as supplements to clinical diagnosis of MS.

For Question 1b, the relevant diagnostic criteria were the Poser and McDonald criteria plus any other clinical, laboratory, neurological exam, MRI, VEP, CSF, or other data supporting the MS diagnosis. Results had to describe data on agreement or disagreement on the MS diagnosis between evaluating physicians. Agreement statistics could include kappa scores, sensitivity and specificity rates, or other data of the type that could be used to complete a two-by-two table.

Results. The validity of the McDonald criteria is well-supported by two types of evidence: (1) follow-up studies of patients with clinically isolated syndrome (CIS) diagnosed according to the McDonald criteria and (2) studies that correlate specific MRI findings (components of the McDonald criteria) with clinical diagnosis. First, two studies[6,7] show that between 73 and 94 percent of patients presenting with CIS who go on to develop clinically definite MS over 1 to 4 years of follow up could be diagnosed with MS according to the McDonald criteria (but would have been undiagnosed under

previous Poser criteria). Furthermore, the specificity of the McDonald criteria is reasonably high, ranging from 83 to 87 percent. Second, many studies[8-16] support the MRI component of the McDonald criteria by showing a strong and consistent association between the number of T2 lesions on MRI and the subsequent development of clinically definite MS among patients with CIS or optic neuritis.

Two studies[17,18] examined the inter-rater reliability of neurologist-physicians in diagnosing MS according to the Poser criteria; one of these[18] also examined inter-rater reliability in diagnosing MS according to the McDonald criteria. We found no data examining inter-rater reliability among non-neurologist clinicians. Overall, there was substantial agreement between observers in classifying MS. Poorer agreement was observed in determining whether a patient had one or more "attacks" of MS and in interpretation of MRI.

Discussion. From the studies identified in the review, the McDonald criteria appear to have substantial evidence for validity and offer the obvious potential advantage of resulting in an earlier diagnosis of MS than the Poser criteria permit. The McDonald criteria have been criticized for their complexity in comparison with previous criteria; however, we found data that demonstrate that these criteria yield a good overall diagnostic reliability, at least as good as the previous Poser criteria. However, data about reliability are available only for neurologists specializing in MS; adoption of the new criteria by clinicians with less expertise could result in deterioration of reliability. Further research on the inter-rater reliability of these criteria in broader clinical settings would be helpful to determine the quality of MS diagnosis.

Prediction of Physical or Mental Impairment at 12 Months

The research question for this topic was What clinical indicators, including particularly time-course of impairments, predict physical or mental impairment at 12 months?

Analytic approach. There were four main categories of clinical predictors of particular interest to the analysis: (1) clinical characteristics such as exacerbation rates, disease type, age at disease onset, sex, degree of remission after relapse, and type and number of neurological symptoms; (2) imaging studies, particularly MRI; (3) laboratory test results such as apolipoprotein E (APOE) $\varepsilon 4$ allele and intrathecal immunoglobulin-G (IgM) synthesis; and (4) self-reported health status using validated scales.

Our evaluation was limited to those studies with a time course of 12 months (SSA's statutory limit), a timeframe which treating physicians would not ordinarily consider an important decision point. The course of MS has typically been studied over time horizons of many years.

Results. We found relatively little data describing changes in neurological or other impairments over 9 to 24 months; however, we used the data that were available to approximate the 12-month time horizon dictated by statutory requirements. Clinical characteristics have been the best studied, with four reports providing evidence for this review.[19-22] Brain[23,24] and spinal cord[25] MRI have not been shown to be promising. Suggestive evidence is available for laboratory markers[26-29] and self-reported quality of life,[30] but these indicators will need further study to establish their reliability and utility. While clinical features do not individually provide reliable guidance on prognosis, multivariate predictive models based on relatively easy-to-obtain features may have better performance; such models have not, however, been validated.

Discussion. The ability to predict the future course of MS has been an active area of research; however, most studies examining disease course do so over relatively long time periods (5 to 20 years). The limited predictive ability of some multivariate models has not been validated in populations other than those in which the models were developed; thus, their value for predicting disability has yet to be determined.

Disease-modifying Therapies and Long-term Improvement

Research Question 1a was targeted to current disease-modifying therapies: A*mong patients with MS, do current disease-modifying treatments result in long-term improvements in physical or mental outcomes compared to placebo or usual care?*

Analytic approach. Interventions of interest were all current (2003) disease-modifying immunomodulatory and immunosuppressive treatments. Outcomes of interest were absolute improvements that might result in an individual who is unable to work becoming able to work. The following domains were considered: physical functioning (primarily Expanded Disability Status Score [EDSS]), relapse frequency, cognitive functioning, quality of life, and adverse events.

Results. Most of the data suggest that few patients improve on disease-modifying therapy. Those few who do improve generally do so only in the range of 1.0 point on the EDSS. We found no data regarding improvement in work ability and no data that would correlate a 1.0-point improvement in EDSS with improvement in work ability. The significance of a 1.0-point EDSS improvement varies depending on baseline EDSS score (because the scale is non-linear), but the improvement data available are not generally stratified according to baseline EDSS score. With regard to work ability, the significance of the available data on clinical improvement is unclear. We found no data that quantified individual patient improvement with regard to cognitive function or quality-of-life measures.

Discussion. Our review does not support a conclusion that the current therapies are likely to result in substantial improvement in a significant proportion of patients with MS. This finding is consistent with expert opinion and demonstrated by the design inherent in current clinical trials, that is, the use of *lack of decline* in EDSS scores as the primary

outcome measure. Current therapies are generally regarded as allowing for a modest reduction in progression of MS – particularly in the relapsing-remitting patient population – but are not generally expected to result in significant long-term improvement. Recently, however, combination therapies have begun to be used in the treatment of MS; such combinations of current therapies or new therapies may have greater potential to result in improvements in neurological status.

Symptom Management and Improvement

Symptom management was the focus of Question 3b: *Among patients with MS, do treatments aimed at symptom management result in improvements in physical or mental outcomes compared to usual care.*

Analytic approach. The effectiveness of symptomatic therapies for spasticity, rehabilitation, urinary management, fatigue, depression, and cognitive impairment was examined. Relevant outcomes were analyzed within six categories: (1) symptom-specific functional status or quality-of-life outcomes; (2) physical functioning (primarily EDSS); (3) cognitive functioning; (4) work or employment outcomes; (5) generic quality-of-life outcomes; and (6) adverse events.

Results and discussion. Treatment aimed at alleviation of symptomatic manifestations of MS, rather than at the underlying disease, could have an important role in maximizing functioning among people with MS. Among the six areas we investigated, the degree of impairments and the effectiveness of the treatments varied. We found:

- *Although drugs such as baclofen, diazepam, dantrolene and tizanidine are often used to reduce spasticity in MS, the research evidence for a beneficial therapeutic effect is inconsistent.* Uncertain findings here, as with other symptoms (cognitive impairment, fatigue), may be due, in part, to measurement issues. Better measurement tools may be required in order to confirm the clinical impression that widely used anti-spasticity drugs such as baclofen, tizanidine, and dantrolene are more effective than placebo. Given current measurement techniques, it is not surprising that active-treatment comparison studies fail to show clinically important differences among these drugs.
- *Physiotherapy interventions failed to influence impairments as measured by EDSS.* These interventions were, however, associated with measurable changes in functional status. Improvements in health (handicap) were observed in the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) and several other measures. The interventions employed in rehabilitation studies were multifaceted, and it is difficult to attribute beneficial effects to particular components of the interventions.
- *Depression treatments, including psychotherapy, behavioral therapy, and certain drug therapies, can lead to measurable improvements in mood, but the link to improved functional status and, further, to ability to work was not demonstrated in these studies per se.* There are few data linking treatment of depression to improvements in other symptoms (such as fatigue or cognitive impairments) or other outcomes (such as functional status or quality of life).
- *Measurement of fatigue is limited by a definition that spans several domains, leading to difficulty with validation.* Amantadine appears to have some ability to alleviate fatigue in MS, as demonstrated by statistically significant differences in some outcomes in several trials;[31-34] however, the clinical significance of these effects is likely small. Pemoline has been less often studied and shows results suggesting some effect.[33-35] There is little support for the efficacy of 4-aminopyridine.[36] Modafinil has shown promising results in phase-II trials,[37] but has not yet been evaluated in a double-blind randomized controlled trial. Further research on new pharmacological therapies (such as modafinil) and development of additional data on the validity of instruments for fatigue measurement and their sensitivity to change would be helpful directions for future research.
- *Studies of treatments for voiding dysfunction show clear improvements in symptoms, but provide less clear data on how improvements in urinary symptoms impact other areas of health, and no data on how these symptomatic improvements impact work ability.* Desmopressin was highly effective at reducing urine volume and also consistently effective at reducing urinary frequency.[38-42] This was shown to translate into improvements in uninterrupted sleep hours and in fewer episodes of incontinence. Physical treatments, including both pelvic floor rehabilitation[43] and use of a handheld vibrator during micturition,[44] were also shown to reduce urinary symptoms compared with control. Many interventions commonly used for urinary disorders in MS have not been studied in randomized controlled trials of MS patients. Commonly used interventions for which no randomized controlled trials have been performed among MS patients include anticholinergic and antimuscarinic drugs, behavior modification, and intermittent or indwelling urinary catheterization.
- *None of the studied treatments for cognitive impairments has had a consistent measurable effect on cognitive performance in MS.* Treatment of cognitive impairments has been little studied and indirectly studied, in the sense that most data on cognitive effects are inferred from studies aimed at treatment of fatigue or depression. One study suggested that fatigue symptoms do not correlate with cognitive impairment, though they do correlate with symptoms of depression.[34] Future studies would benefit from more precise delineation of study population based on screening for cognitive performance deficits within a relatively narrow and defined range; this would likely improve the chances of finding a treatment effect and would also make

clearer the population for whom the results would be applicable.

Association of Clinical Findings and Work Ability

In contrast to the previous questions, Question 4 directly linked clinical results with ability to work: *Among individuals with MS, what physical, mental, laboratory, or radiographic findings have been associated with inability to work?*

Analytic approach. The phrasing of this question predetermined the outcome of interest as ability to work. Findings reported as absolute and relative measures of physical and mental/cognitive function and laboratory and radiographic testing related to work activity were assessed.

Results and discussion. There is a significant gap between what is included in the literature and the type of research evidence required to link objective clinical measures (physical, mental, laboratory, and radiographic findings) with ability to work. Although objective physical and cognitive measures have been developed, their application in the occupational literature is sparse. Furthermore, assessment of how symptoms such as pain and fatigue impact work ability is essentially absent. The reported findings on work ability displayed some consistency across studies. For example, individuals who had higher EDSS levels[45,46] or low cognitive function[47] were more likely to report not working. However, the strength of association across these studies was not clearly demonstrated, as most reported frequencies or crude estimates of association. Several studies had small sample sizes, which hindered researchers from calculating risk estimates that were adjusted for potential biases such as age, education, level of employer assistance, job type, and desire to work. In addition, most studies considered only physical function or cognitive function, when both can hinder employment.

Environmental Factors and Work Ability

Similar to the previous question, the focus of Question 5 was the ability to work: *Among individuals with MS, how does elevated temperature or other environmental factors impair the capacity to work?*

Analytic approach. The evidence sought for this question was on the association of workplace environmental conditions and demands (ambient temperature, individual's body temperature, heat or cold exposure) on the ability of an individual with MS to work. Relative and absolute measures of association were assessed.

Results. With regard to work impairment, limitation, or disability related to temperature conditions, we found remarkably little research that met our inclusion criteria; thus, this question remains mostly unanswered. The one included report confirmed that some MS patients perceive that excessive heat impedes their work capacity.[48]

Discussion. The evidence provides no basis for generalizations such as maximum appropriate working temperature levels unique to MS patient populations. It is unlikely that medical data in Social Security Disability Insurance (SSDI) application files in the current era will include objective diagnostic test results identifying MS patients who respond adversely to heat challenges. However, subjective patient reports may describe such associations with or without clinician comment or correlation with objective clinical status measures. Although not necessarily founded on randomized controlled trial data, current clinical impression seems to hold that ambient and/or exercise-induced body temperature effects may bear a relationship to MS symptom status in some patients, perhaps more so than is thought to be the case for chronic disease states in general.

Future Research

Future research about work ability among individuals with MS can shed a great deal of light on factors that foster or hinder employment. Our full report,[49] particularly the evidence reported on association of clinical findings and work ability, highlights significant evidence and information gaps concerning

- Patterns of MS patient reports regarding functional limitations.
- Information commonly collected in medical encounters with MS patients (and therefore available to SSA).
- Knowledge about the impact on performance of specific work tasks of commonly objectified parameters such as coordination, strength, and vision, and especially of factors such as fatigue or cognitive dysfunction, which are either difficult to measure or are less commonly assessed in detail.
- Effective research methods for categorizing job or task demands in such a way as to isolate those demands that are likely to be "critical" for an SSDI applicant with MS.

In the context of these gaps, it may be productive to pursue research approaches that simultaneously address four domains:

1. Subjective reports (this domain is not sufficient alone for SSDI determination purposes).
2. Objective clinical data (ideally of the sort commonly encountered in medical records).
3. In-depth objective measures (which may be available and not widely applied clinically. but which may be used with subsets of subjects to explore correlation with other domains).
4. Work status measures (ideally longitudinal, with stratifications based on work demands).

Such an approach may apply to thermal sensitivity as well, with some additional specification and focus. Parallel assessment of concomitant ambient temperature, physical

exertion, and core body temperature would address key relevant physiological exposure factors.

Outcome measures could include the domains outlined above, for example:

- Self-perceived well-being and level of symptoms such as fatigue.
- Clinical parameters such as walking speed or muscle strength.
- In-depth measures such as potentially associated biomarkers or physiological parameters.
- Work status measures, including absenteeism and disability benefits use.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Duke Evidence-based Practice Center, under Contract No. 290-02-0025. It is expected to be available in May 2004. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 100, *Criteria to Determine Disability Related to Multiple Sclerosis*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

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Evidence Report

Chapter 1. Introduction

Purpose

The purpose of this project, nominated by the Social Security Administration (SSA) and contracted through the Agency for Healthcare Research and Quality (AHRQ), was to determine whether current medical knowledge supports the SSA's stated policies regarding MS. In January 2003, the Duke Evidence-based Practice Center began work on this 13-month task to review evidence from the medical literature for use in updating SSA's listing of impairments for multiple sclerosis (MS) and for revising its disability policy (if indicated).

Background

The Social Security Administration runs the world's largest disability program and processes more than 3.5 million claims each year. Multiple sclerosis is the third most common neurological diagnosis cited as the cause for disability. SSA uses the most stringent criteria of any disability program in the world to define disability.[1]

Knowledge of the terms used in the SSA disability evaluation process, components of that process, and Medical Listing criteria related to MS is critical to the reader's understanding of this report. To assist in the preparation of the report, SSA provided explanations of terms and processes as currently defined by SSA regulations and rulings. The terms cited below, as well as other terms and processes used by SSA for disability determination, are defined and described in the SSA publication, *Disability Evaluation Under Social Security 2003*.[2]

The statutory definition of "Disability" is: The inability to engage in any substantial gainful activity by reason of a medically determinable physical or mental impairment(s) which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months. This definition differs from the clinically used definition of the World Health Organization's *International Classification of Impairments, Disabilities and Handicaps* (1980),[3] which defines disability as "any restriction or lack of ability to perform an activity in a manner or within the range considered normal for a human being." While much of the medical literature uses the latter, broader definition, the reader must be aware that the goals of this report relate to the statutory definition.

The following terms are defined by current (2003) SSA regulations:

"Claimant" is anyone who has filed a disability claim.

"Substantial Gainful Activity" is the ability to earn an average of $800 per month.

"Medically Determinable Impairment" is a physical or mental impairment that results from anatomical, physiological, or psychological abnormalities which can be shown by medically acceptable clinical and laboratory diagnostic techniques.

"Evidentiary Requirements" for disability determination are described by SSA regulation. An acceptable medical source must report signs, symptoms, and laboratory findings diagnostic of an impairment. Although a claimant's reported signs and symptoms are not sufficient to meet the evidentiary requirements for establishing the presence of a medically determinable impairment, all available evidence including the claimant's report of symptoms is used to

Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/epcindex.htm.

evaluate the impact of any documented impairment(s) on the claimant's ability to carry out work tasks.

"Severe Impairment" is defined by the agency as any "impairment that more than minimally limits the claimant's ability to do basic work activities."

The regulations include a Listing of Impairments for each body system that define disability. Often referred to as the "medical listings," this list allows quick disability determinations to be made on the basis of medical criteria alone. The SSA publication, *Disability Evaluation Under Social Security 2003*,[2] under the neurological category of impairments, includes Listing 11.09.

11.09 Multiple Sclerosis with:

A. Disorganization of motor function as described in 11.04; or

B. Visual or mental impairment as described under the criteria in 2.02, 2.03, 2.04, or 12.02: or

C. Significant, reproducible fatigue of motor function with substantial muscle weakness on repetitive activity, demonstrated on physical examination, resulting from neurological dysfunction in areas of the central nervous system known to be pathologically involved by the multiple sclerosis process.

All pages pertinent to the Medical Listing for multiple sclerosis, including the imbedded references to sections 2, 11, and 12, are found in Appendix A.

"Residual Functional Capacity" is assessed when a claimant is determined to have a "severe" impairment that does not meet or equal the intent of the medical listings. Physical capacity (lifting, carrying, walking, standing, sitting, pedaling, etc.) and mental capacity (cognitive and behavioral, thought processing, concentration, pace, behavior) are assessed in determining residual functional capacity.

In order to adjudicate claims by individuals with MS for disability benefits, SSA must determine whether the claims file includes information from an acceptable medical source that documents the signs, symptoms, and laboratory findings that are diagnostic of a physical or mental impairment. SSA adjudicators also determine whether the impairment would be expected to more than minimally interfere with the claimant's capacity to carry out basic work activities for at least 12 consecutive months or end in death. If a severe impairment is identified, the adjudicator determines whether the medical findings meet or equal an impairment in the medical listings. If the documented impairment does not meet or equal a listed impairment, the adjudicator must determine the claimant's residual functional capacity and consider vocational factors prior to making a final disability determination.

Research Questions

This evidence report covers five major topic areas framed within seven research questions, all of which are targeted to the adult population with MS. Our primary goal was to identify, review, and evaluate the published literature to answer the research questions; our secondary goal was to identify areas where no evidence exists or where the evidence has important limitations and then describe the type of data that would be needed to more fully address the question.

The questions are listed below by topic area, along with a brief description of our analytical approach, including interventions and outcomes of interest.

Reliability of MS Diagnostic Criteria

Question 1a. *What is the reliability of new McDonald criteria (incorporating supplementary information from radiologic and laboratory studies including magnetic resonance imaging [MRI], visual evoked potential [VEP], and cerebrospinal fluid [CSF] analyses) compared with long-term follow-up diagnosis of clinically definite MS according to the Poser criteria?*

The major difference between the Poser criteria[4] and the new McDonald criteria[5] is the addition of MRI findings. Our approach to this question was to identify studies in two categories: (1) those that specifically compared the new McDonald criteria with the reference standard of long-term diagnosis of clinically definite MS according to Poser criteria; and (2) those that provided data on the accuracy of various MRI techniques, CSF, and VEP (paraclinical diagnostic techniques incorporated into the criteria) with regard to the diagnosis of MS and thus supported their use as a supplement to clinical diagnosis.

In reporting results, the focus was on both relative measures (e.g., Hazard ratios) and absolute rates (e.g., percentages of patients with or without positive CSF who met Poser criteria at long-term follow up), with a primary focus on the latter.

Question 1b. *What is the inter-rater reliability of diagnosis of MS according to Poser or McDonald criteria among neurologists or between neurologists and non-neurologist physicians?*

The relevant diagnostic criteria were the Poser and new McDonald criteria plus any other clinical, laboratory, neurological exam, MRI, CSF, VEP, or other data supporting the MS diagnosis. Results had to describe data on agreement or disagreement on the MS diagnosis between evaluating physicians. Agreement statistics could include kappa scores, sensitivity and specificity rates, or other data of the type that could be used in completing a two-by-two table.

Predictors of Physical and Mental Impairments at 12 Months

Question 2. *What clinical indicators, including particularly time-course of impairments, predict physical or mental impairment at 12 months?*

There were four main categories of clinical predictors of particular interest to the analysis: (1) clinical characteristics such as exacerbation rates, disease type, age at disease onset, sex, degree of remission after relapse, and type and number of neurological symptoms; (2) imaging studies, particularly MRI; (3) laboratory test results such as apolipoprotein E (APOE) ε4 allele and intrathecal immunoglobulin-M (IgM) synthesis; and (4) self-reported health status using validated scales.

The evaluation of studies for this question was limited to those with a time course of 12 months (SSA's statutory limit), a timeframe which treating physicians would not ordinarily consider an important decision point. For this disease, the course has typically been studied over time horizons of many years.

Effect of Treatment and Symptom Management on Disease Course

Question 3a. *Among patients with MS, do current disease-modifying treatments result in long-term improvements in physical or mental outcomes compared to placebo or usual care?*

Interventions of interest for this question were all current (2003) disease-modifying immunomodulatory treatments (interferons and glatiramer acetate) and immunosuppressive

treatments (e.g., azathioprine, mitoxantrone, cyclophosphamide, intravenous [IV] immunoglobulin-G [IgG]).

Outcomes of interest were physical functioning (primarily Expanded Disability Status Scale [EDSS] scores), proportion of patients with "improvement," relapse frequency, cognitive functioning, quality of life, and adverse events.

Question 3b. *Among patients with MS, do treatments aimed at symptom management result in improvements in physical or mental outcomes compared to usual care?*

The effectiveness of symptomatic therapies for spasticity, rehabilitation, urinary management, fatigue, depression, and cognitive impairment was evaluated. Relevant outcomes were analyzed within six categories: (1) symptom-specific functional status or quality-of-life outcomes; (2) physical functioning (primarily EDSS); (3) cognitive functioning; (4) work or employment outcomes; (5) generic quality-of-life outcomes; and (6) adverse events.

The analysis of studies relevant to Questions 3a and 3b was complicated by issues of definition, particularly for outcomes reporting "improvement," "long-term improvement," and "relapse rates." Our reporting of the results and subsequent analysis are presented within SSA's regulatory definition of "disability," which considers physical or mental impairments that can be expected to result in death or which have lasted or can be expected to last for a continuous period of not less than 12 months.

Association of Clinical Findings with Work Ability

Question 4. *Among individuals with MS, what physical, mental, laboratory, or radiographic findings have been associated with inability to work?*

The phrasing of this question predetermined the outcome of interest as ability to work. Findings reported as absolute and relative measures of physical and mental/cognition function and laboratory and radiographic testing related to work activity were assessed.

Environmental Factors and Work Ability

Question 5. *Among individuals with MS, how does elevated temperature or other environmental factors impair the capacity to work?*

This question was interpreted as the association of workplace environmental conditions and demands (specifically, ambient temperature, individual's body temperature, or exposure to heat or cold) on the ability of an individual with MS to work. Relative and absolute measures of association were assessed.

Limitations of Report

In requesting this evidence report, SSA sought evidence from the medical and scientific literature to determine whether current medical knowledge supports SSA's stated policies regarding MS. Seven specific questions were framed within five topic areas. The information compiled in this report may enable SSA, for example: (1) to improve consistency of disability claims by applying more objective criteria, but only if the criteria are valid; (2) to change the population eligible for disability through a change in the diagnostic criteria for MS; (3) to influence changes in treatment that might reduce the number of people permanently disabled by

MS; and (4) beyond motor and cognitive impairments, to consider how other significant symptoms, such as fatigue and urinary urgency, may be incorporated into considerations of disability status.

We believe the evidence presented in this report could also be used as the basis for a consensus conference of multidisciplinary experts on Listing of Impairments for MS that would employ formal consensus methods to update the current listing, as well as possibly expanding the disability process to include sociocultural factors that impinge upon desiring, seeking, finding, acquiring, and sustaining a job.

Chapter 2. Methods

The basis of this evidence report is a systematic comprehensive review and evaluation of the literature relevant to five topic areas proposed by the Social Security Administration.

Literature Search and Review

Sources

The primary sources of literature were MEDLINE® (1966-April 2003), CINAHL® (1983-April 2003), Cochrane Database of Systematic Reviews, and Web of Science. Searches of these databases were supplemented by reviews of reference lists contained in all included articles and in relevant review articles and meta-analyses.

Search Strategies

The basic search strategy used the National Library of Medicine's Medical Subject Headings (MeSH) key word nomenclature developed for MEDLINE® and was adapted for use in the other databases. The searches were limited to the English language and to human subjects. For efficacy of treatment topics, the searches were also limited to studies with randomized controlled trial designs. The texts of the five major search strategies are given in Appendix B. In addition, we used Web of Science (Thompson ISI, Philadelphia, PA) to identify articles that cited the recent McDonald criteria from the International Panel on the Diagnosis of Multiple Sclerosis.[5]

The searches yielded a total of 1487 citations, whose records are maintained in a ProCite (Thompson ISI ResearchSoft, Berkeley, CA) database.

Abstract and Full-text Screening Criteria

The seven specified questions spanned several topic areas and produced a considerably large and varied literature, which complicated the screening process. For each question, we developed fairly detailed inclusion/exclusion criteria. The titles and abstracts of the 1487 articles were reviewed against these criteria by at least two of five clinical investigators ("title-and-abstract screening" stage). Where no abstract was available, the title, source, and keywords were screened. At this stage, articles were included if requested by one investigator. The full text of each article passing the title-and-abstract screening was obtained for further review.

At the "full-text review" stage, each article was independently evaluated by two investigators, who forwarded their decisions to the task order manager for recording and comparison. If indicated, reviewers were asked to reconcile differences of opinion and return a reconciled final decision. If reviewers had difficulty reaching agreement, or submitted indecisive codes, the principal investigator was the arbiter.

We developed detailed screening instructions for the title-and-abstract screening (Appendix C) and additional decision rules for the full-text screening (Appendix D). For the full-text screening, we also produced a summary decision sheet, on which screeners recorded their include/exclude decision, research question assignment, and specific exclusion criterion (if appropriate) for each article.

Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/epcindex.htm.

Summaries of the results of the title-and-abstract screening and full-text review are provided in Tables 1 and 2.

Data Abstraction and Development of Evidence Tables

We determined that the data from the included articles could be abstracted directly into an evidence table template, which would serve as a "data abstraction form." To facilitate the development of the evidence tables and to use everyone's particular skills and time to their best advantage, the writer/editor began the data abstraction process with a partial abstraction of each article that was included at the full-text review stage. The partial abstraction/evidence table included descriptions of the study design, interventions, number of subjects at the start of the study, and the *types* of outcomes data to be collected; this partial abstraction was forwarded to the primary abstractor. The completed evidence table was returned to the writer/editor, who checked for completeness and consistency of information and then forwarded the table to a second investigator for over-reading. The over-reader returned the table to the writer/editor for final check of the completeness of the content, editing, and formatting. The data abstraction/evidence table templates for each research question are provided in Appendix E.

Quality Assessment Criteria

At the data abstraction stage, we evaluated each included article for factors affecting internal and external validity. The quality assessment criteria were incorporated into the last column of the data abstraction/evidence table templates (Appendix E) and varied by question. The questions and their associated criteria and range of responses follow.

Question 1a: *What is the reliability of new McDonald criteria (incorporating supplementary information form radiologic and laboratory studies including magnetic resonance imaging [MRI], visual evoked potential [VEP], and cerebrospinal fluid [CSF] analyses) compared with long-term follow-up diagnosis of clinically definite multiple sclerosis (MS) according to the Poser criteria?* The quality assessment criteria were:

1) Patients evaluated using Poser criteria regardless of results on initial tests? Yes/No/Unclear
2) Follow-up > 80%? Yes/No/Not reported (NR)/Not applicable (NA; relevant to retrospective cohort studies or case-control studies)

Question 1b: *What is the inter-rater reliability of diagnosis of MS according to Poser or McDonald criteria among neurologists or between neurologists and non-neurologist physicians?* There were two criteria:

1) Evaluating physicians blinded to one another's diagnosis? Yes/No/Unclear
2) Did study sample include an appropriate spectrum of patients (not just "difficult" cases)? Yes/No/Unclear

Question 2: *What clinical indicators, including particularly time-course of impairments, predict physical or mental impairment at 12 months?* The criteria were:

1) Study described as "population-based"? Yes/No
2) Sample of patients assembled at a *common* point in the course of their disease? Yes/No/Unclear
3) Sample of patients assembled at an *early* point in the course of their disease? Yes/No/Unclear

4) Follow up > 80%? Yes/No/NR/NA (retrospective or case-control study)
5) Outcomes assessed using a widely used scale? Yes/No
6) Outcomes assessed in a blind fashion? Yes/No/Unclear
7) If subgroups with different prognoses are identified: (a) was there adjustment for important prognostic factors? Yes/No/Unclear/NA; (b) was there independent validation? Yes/No/Unclear/NA

Question 3a: *Among patients with MS, do current disease-modifying treatments result in long-term improvements in physical or mental outcomes compared to placebo or usual care?* AND Question 3b: *Among patients with MS, do treatments aimed at symptom management result in improvements in physical or mental outcomes compared to usual care?* The criteria used for each of these questions were:

1) Described as "randomized"? Yes/No
2) Method of randomization clearly described? Yes/No
3) Concealment of allocation? Yes/No/Unclear
4) Described as "double-blind"? Yes/No
5) Patients blinded? Yes/No/Unclear
6) Investigators blinded? Yes/No/Unclear
7) Outcome assessors blinded? Yes/No/Unclear
8) Number of withdrawals in each group stated? Yes/No

For crossover trials only:

9) Period or carry-over effects? Yes/No/Not discussed
10) Washout period? Yes (give duration)/No
11) Number of patients in each sequence clearly described? Yes/No
12) Were patients who did not complete all of the period excluded from the analysis? Yes/No/Unclear

Question 4: *Among individuals with MS, what physical, mental, laboratory, or radiographic findings have been associated with inability to work?* AND Question 5: *Among individuals with MS, how does elevated temperature or other environmental factors impair the capacity to work?* The quality assessment criteria for these two questions were:

1) Study described as "population-based"? Yes/No
2) Follow up > 80%? Yes/No/NR/NA
3) Work outcomes assessed using a widely used scale? Yes/No
4) Work outcomes assessed in a blind fashion? Yes/No/Unclear
5) If subgroups with different work ability are identified: (a) was there adjustment for important prognostic factors? Yes/No/Unclear/NA; (b) was there independent validation? Yes/No/Unclear/NA

We did not sum the criteria into an overall quality assessment score, but rather we considered and reported each criterion individually. We favored this approach for several reasons:

- Previous work has shown that numeric grading systems may not discriminate well between "high-quality" and "low-quality" studies, even for randomized trials.[6,7]
- Development and use of a new quality score would require additional work for validation, for which there was no time or budget allocation in the task order.
- Identification of specific weaknesses in each study was helpful in identifying trends, which in turn assisted with our recommendations for future research.

- Describing key design components, rather than assigning a single aggregate score, is also consistent with recent recommendations from an expert panel on meta-analysis of observational studies.[8]

Peer Review Process

We employed internal and external quality-monitoring checks through every phase of the study to reduce bias, enhance consistency, and verify accuracy. Examples of internal monitoring procedures include: three progressively stricter screening opportunities for each article (title-and abstract screening, full-text article review, data abstraction review); hands-on involvement of three individuals (two clinicians) in each data abstraction; agreement of at least two clinicians on all included studies.

Our principle external quality-monitoring device was the peer-review process. Nominations for peer reviewers were solicited from several sources, including a technical advisory panel and interested federal agencies. The list of nominees was forwarded to the Agency for Healthcare Research and Quality (AHRQ) for vetting and approval.

Chapter 3. Results

Diagnostic Reliability of McDonald Criteria

Introduction

This section addresses results for Question 1a: *What is the reliability of new McDonald criteria (incorporating supplementary information from radiologic and laboratory studies including magnetic resonance imaging [MRI], visual evoked potential [VEP], and cerebrospinal fluid [CSF] analyses) compared with long-term follow-up diagnosis of clinically definite multiple sclerosis (MS) according to the Poser criteria?*

The diagnosis of MS has traditionally been based on clinical history and examination, and on the absence of an alternative diagnosis. Paraclinical tests such as imaging techniques,[9] evoked potentials,[10] and CSF analyses have been used to aid diagnosis, but their precise role in formal diagnostic criteria for MS has been a source of debate. With the advent of MRI, which provides much more detailed images of the brain and spinal cord than were possible with computed tomography (CT), debate over the role of paraclinical tests in the diagnosis of MS has been renewed.

Of the various diagnostic criteria proposed for MS, the most widely used have been those by Poser et al. (1983).[4] The Poser criteria focus on objective examination evidence of abnormalities in at least two separate areas of the central nervous system, with historical information to suggest at least two periods of MS involvement over time. The criteria may be summarized as follows:[4]

- Clinically definite MS:
  - 2 attacks and clinical evidence of 2 separate lesions; *or*
  - 2 attacks; clinical evidence of 1 lesion and paraclinical evidence of another, separate lesion.
- Laboratory-supported definite MS:
  - 2 attacks; clinical or paraclinical evidence of 1 lesion; and CSF immunologic abnormalities; *or*
  - 1 attack; clinical evidence of 2 separate lesions; and CSF immunologic abnormalities; *or*
  - 1 attack; clinical evidence of 1 lesion and paraclinical evidence of another, separate lesion; and CSF immunologic abnormalities.
- Clinically probable MS:
  - 2 attacks and clinical evidence of 1 lesion; *or*
  - 1 attack and clinical evidence of 2 separate lesions; *or*
  - 1 attack; clinical evidence of 1 lesion and paraclinical evidence of another, separate lesion.
- Laboratory-supported probable MS:
  - 2 attacks and CSF immunologic abnormalities.

In light of the growing potential of paraclinical tests – particularly MRI – to contribute to the diagnosis of MS, the International Panel on the Diagnosis of Multiple Sclerosis met in July 2000 to reassess existing diagnostic criteria. The panel recommended changes to the criteria that (1) integrated MRI into the overall diagnostic scheme and (2) provided for the diagnosis of primary progressive disease.[5] The new criteria (here referred to as the McDonald criteria)[5] were

Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/epcindex.htm.

designed to be used by practicing physicians and adapted, as necessary, for clinical trials. They dropped the Poser categories of "clinically definite," "laboratory-supported definite," "clinically probable," and "laboratory-supported probable" MS and proposed that the disease be diagnosed using the following criteria:[5]

- 2 or more attacks; objective clinical evidence of 2 or more lesions
  - No additional data needed
- 2 or more attacks; objective clinical evidence of 1 lesion; *plus*
  - Dissemination in space, demonstrated by:
    - MRI, *or*
    - 2 or more MRI-detected lesions consistent with MS plus positive CSF, *or*
    - Further clinical attack implicating a different site.
- 1 attack; objective clinical evidence of 2 or more lesions; *plus*
  - Dissemination in time (demonstrated by MRI).
- 1 attack; objective clinical evidence of 1 lesion (monosymptomatic presentation, clinically isolated syndrome); *plus*
  - Dissemination in space, demonstrated by:
    - MRI, *or*
    - 2 or more MRI-detected lesions consistent with MS plus positive CSF, *and*
  - Dissemination in time, demonstrated by:
    - MRI *or*
    - Second clinical attack.
- Insidious neurological progression suggestive of MS; *plus*
  - Positive CSF, *and*
  - Dissemination in space, demonstrated by:
    - 9 or more T2 lesions in brain, *or*
    - 2 or more lesions in spinal cord, *or*
    - 4-8 brain lesions plus 1 spinal cord lesion, *or*
    - abnormal VEP associated with 4-8 brain lesions, *or*
    - abnormal VEP with fewer than 4 brain lesions plus 1 spinal cord lesion; *and*
  - Dissemination in time, demonstrated by:
    - MRI, *or*
    - Continued progression for 1 year.

The publication of the McDonald criteria has renewed the discussion of the value of incorporating paraclinical testing, particularly MRI, in the diagnosis of MS. The Social Security Administration (SSA), aware of the difficulties brought on by improper or inadequate diagnosis, has sought evidence from the literature regarding the value of the various diagnostic criteria. Question 1a seeks specific information regarding the reliability of the McDonald criteria.

In this review, we sought to identify specifically those studies that evaluated whether patients diagnosed with MS according to the McDonald criteria would later meet the Poser criteria for clinically definite MS. We also sought articles that, although not specifically using the McDonald criteria, may have evaluated components of the McDonald criteria against later diagnosis of MS according to the Poser criteria.

There exists a significant literature regarding the diagnostic utility of newer MRI techniques, such as magnetization transfer or various measures of atrophy,[11-21] but we did not include such articles as they are not a part of currently used diagnostic criteria in general or the McDonald criteria specifically.

Results

Thirteen articles[22-34] describing 11 different study populations met the inclusion criteria for this question (see Evidence Table 1a in Appendix F). Of the included articles, two[27,34] specifically addressed the comparative performance of the Poser and McDonald criteria, nine[22-25,28,30-33] examined the performance of various standard MRI techniques in addition to clinical diagnosis, one[29] evaluated the performance of other paraclinical testing in addition to Poser criteria, and one[26] contained data regarding the performance of the McDonald criteria, although it was not specifically designed to answer this question.

Those studies that did not specifically address the relative performance of the Poser and McDonald criteria nevertheless provided background information regarding the improved diagnostic yield achieved by adding MRI and paraclinical testing to the clinical diagnosis. These studies generally did not utilize MRI in the same manner as the McDonald criteria, and therefore it is difficult to apply these results directly. For example, several studies examined the performance of MRI abnormalities at baseline with subsequent diagnosis of MS. As the data summarized in Table 3 indicate, the results of these studies document the significant predictive value of baseline MRI findings for the subsequent development of MS. The McDonald criteria utilize serial MRI studies to add to the diagnostic performance. Therefore, although these studies provide background information documenting the utility of MRI, they do not specifically address the McDonald criteria use of MRI.

The two studies that did specifically address the performance of the McDonald criteria in comparison with the Poser criteria[27,34] reported remarkably similar results (Table 4). The first study[27] evaluated 119 patients with clinically isolated syndromes at baseline and reevaluated 50 of these patients at 3 years. MRI studies from 3 months, 1 year, and 3 years were retrospectively analyzed in a blinded fashion using the McDonald criteria. In this study, the diagnosis of MS had been made clinically (using the Poser criteria) prior to the retrospective application of the McDonald criteria. The second study[34] followed 139 patients with clinically isolated syndromes prospectively for a mean of 39 months, with 86 patients followed for at least 3 years. In this study, the diagnosis of MS was made prospectively according to the Poser criteria and compared with the prospective application of the McDonald criteria. The two studies showed sensitivity of the McDonald criteria ranging from 0.73 to 0.94, with specificity ranging from 0.83 to 0.87, when compared to diagnosis using the Poser criteria.

Using the Poser criteria as the diagnostic gold standard in this way is problematic, mainly because the limited duration of any clinical study means that some patients may be classified as non-diseased at the conclusion of a study who later go on to meet the Poser criteria for MS. Once the Poser criteria are defined as the gold standard, other tested criteria can at best correlate highly with Poser diagnosis. It is possible that the McDonald criteria might perform better than the Poser criteria (in terms of sensitivity, ability to diagnose MS early, and/or association with prognosis) if both could be compared to a (hypothetical) true gold standard. The high level of agreement of McDonald criteria with later Poser criteria diagnosis observed in the studies reviewed here is not inconsistent with this possibility.

Inter-rater Reliability of Diagnosis with McDonald and Poser Criteria

Introduction

The preceding discussion of Question 1a was concerned with the validity of new diagnostic criteria for MS; this section examines the inter-rater reliability of the application of these criteria as posed by Question 1b: *What is the inter-rater reliability of diagnosis of MS according to Poser or McDonald criteria among neurologists or between neurologists and non-neurologist physicians?* High inter-rater reliability of the McDonald criteria would suggest that their use in clinical practice should achieve similar validity to the findings of the literature as reviewed in Question 1a.

Our primary goal was to evaluate studies that provide direct analysis of inter-rater reliability of the McDonald or Poser criteria. We also sought studies that evaluated the inter-rater reliability of components of the McDonald criteria, such as MRI studies of T2 lesions or gadolinium-enhancing lesions. We excluded studies of inter-rater reliability of MRI techniques that are not utilized in the McDonald criteria, such as measurements of cerebral atrophy, magnetic resonance spectroscopy, and measurements of T2 lesion volume.

Results

Two studies met our inclusion criteria (see Evidence Table 1b in Appendix F).[37,38] Both examined inter-rater reliability of neurologist-physicians in diagnosing MS according to the Poser criteria. One of the studies[38] also examined inter-rater reliability for diagnosing MS according to the McDonald criteria. We found no data examining the inter-rater reliability among other clinicians.

Ford et al. (1996)[37] examined the inter-rater reliability of the Poser criteria. Overall, there was substantial agreement between the two observers in classifying MS (kappa = 0.65; 95 percent confidence interval [CI], 0.52 to 0.78). There was disagreement as to whether a patient had one or more "attacks" of MS. Agreement was substantial for clinical evidence of separate lesions and was almost perfect for both paraclinical evidence and laboratory support (all kappa values > 0.90). The primary disagreement was in defining "attacks" of MS, and the authors appropriately noted that this might be due to the retrospective nature of the evaluation.

The primary shortcomings of this study were that only two evaluators were compared, and diagnoses were based on retrospective analysis of data from clinical records. This process is significantly different from prospective diagnosis. Prospective diagnosis allows the clinician access to detailed information that may be inadequately recorded in the medical record, such as lesion location, intensity of enhancement, and overall appearance of MRI changes. Likewise the details of clinical exacerbations may be communicated to an examining physician making prospective diagnoses, but may be inadequately or incompletely recorded in the medical record. In general, retrospective diagnosis is frequently based on relatively less complete information as recorded in the medical record.

Zipoli et al. (2003)[38] specifically addressed Question 1b by examining the inter-rater reliability of both the Poser and McDonald criteria (see Table 5). In this study, four neurologists assessed all patients consecutively admitted for diagnosis to a university department of

neurology from September 2001 through June 2002 who had been followed for at least 6 months. The mean follow up was 12.7 months. The study evaluated 41 MS patients, of whom 15 had relapsing-remitting MS, two had secondary progressive MS, five had primary progressive MS, and 19 had clinically isolated syndromes. Three additional patients who were not diagnosed with MS were included in the evaluation. Data were abstracted from medical records onto standardized forms by a non-evaluating neurologist. No diagnoses were recorded. The four evaluating neurologists were stated to have similar clinical experience in MS diagnosis and management. The study does not report any specific training of these neurologists with regard to the McDonald criteria or MRI analysis. The four evaluating neurologists reviewed the standardized forms and all MRI scans independently without discussing their findings. Eighteen patients had follow-up MRI scans in addition to baseline scans.

In this study, the primary difficulty in the McDonald criteria appeared to be decreased agreement in MRI interpretation, specifically in those patients with high lesion loads. The authors commented that this study utilized neurologist evaluators rather than neuroradiologists. Previous studies have correlated level of radiographic training with agreement in interpretation.[39,40] Judging dissemination in time was of particular difficulty in those patients with clinically isolated symptoms. The authors suggested that neuroradiologists be encouraged to interpret scans in MS patients with the McDonald MRI criteria in mind, providing specific information regarding lesion location and timing.

Predictors of Physical and Mental Impairments at 12 Months

Introduction

This section examines the evidence pertaining to Question 2: *What clinical indicators, including particularly time-course of impairments, predict physical or mental impairment at 12 months?* The notion here is that an individual diagnosed with MS but not yet work disabled could, within the follow-up period of disability evaluation, become work disabled. In formulating a response to this question, we considered three crucial study features: the assessment of possible prognostic features, the period of follow up, and the assessment of a valid measure of physical or mental impairment. The assessment of possible prognostic features had to occur between the time of diagnosis of MS and the occurrence of work disability; in most studies this assessment occurred at or near study entry, but this was not necessary. The 12-month timeframe specified in this question was the major limiting criterion in the number of studies that could be included for evaluation; to expand the pool of studies, we included any evaluations in which follow up occurred within a window of 9 to 24 months from study entry (or measurement of the purported prognostic feature). Thus, a study that related prognostic data available at one time with outcome data at another time 9 to 24 months later would be eligible; furthermore, a study might provide such data over multiple different time frames (see Figure 1). In all cases, the available outcome measure was the Disability Status Scale (DSS) or the Expanded Disability Status Scale (EDSS). For purposes of judging a level approximately associated with work disability, we focused on the transition from an EDSS score of less than 6 to greater than 6. Since deficits associated with MS unrelated to acute exacerbations are not expected to regress, we did not include studies in which patients were already severely disabled.

Results

Twelve publications[41-52] describing 11 separate studies met the inclusion criteria (see Evidence Table 2 in Appendix F). Four main categories of predictors were analyzed in the included articles: (1) clinical characteristics; (2) imaging study results; (3) laboratory test results; and (4) self-reported status. The following discussion is organized by these categories.

Clinical characteristics. Clinical characteristics were described in four reports[42,43,45,49] describing three studies. In a 1989 study by Goodkin et al.,[45] exacerbation rates and adherence to disease types were analyzed. A non-population-based cohort of 425 patients was followed; 254 patients with definite MS completed the evaluations, including the following patterns of disease: stable (n = 80), relapsing-remitting stable (n = 155), relapsing-remitting progressive (n = 48), and chronic progressive (n = 142). After a follow up of 1 to 5 years (mean, 2.6 years), disease pattern was not found to be a stable characteristic of patients, with 44 percent of patients changing from stable or relapsing-remitting to progressive disease, while 40 percent of patients with progressive disease stabilized. Further, disease pattern did not predict change in EDSS scores at 2 years.

Runmarker et al. (1994)[49] followed patients with relapsing-remitting course at onset for up to 25 years. Of 308 patients identified at the onset, 200 had sufficient data for analysis. Multivariate survival models were developed to predict time from onset to start of progressive disease and time from onset to a DSS score of 6; similar models were developed for predicting events from the end of the fifth year of disease onward. Several factors appeared to be predictive in one or more of the models, including age at onset, sex, degree of remission after relapse, mono- or poly-regional symptoms, type of affected nerve fibers, and number of affected neurological systems. Patients with early onset had a low initial risk of progression, rising to a maximum over about 15 years; patients with a late onset had a higher initial risk, which rose for several years, then fell. The predictions were not validated internally or externally.

The most recent included study, by Cottrell et al. (1999a[42] and 1999b[43]), evaluated a prospective, population-based cohort of patients with primary progressive MS. The original cohort was followed for a mean of 23 years; this was supplemented by an additional cohort, with a follow-up time not reported. The probability of progressing from one DSS level to the next was highest initially (87 percent probability of progressing from level 1 to 2 in 1 year), relatively constant for patients in DSS levels 2 to 5 (probability of progression of 1 level ranging from 26 percent to 40 percent), and lower for patients in DSS levels 6 to 9 (ranging from 2 percent to 10 percent). Using a multivariate analysis of potential predictors of progression to DSS of 8, several factors were significant, including sex, age at onset, years from onset to reaching a DSS of 3, and number of systems involved. The model was not validated, nor was its discriminative ability examined. However, in univariate survival curves, the discrimination of these individual factors appears modest at best.

Imaging study results. Three studies of MRI satisfied inclusion criteria, with the majority of exclusions attributable to lack of comparison of MRI with subsequent course. Two studies[46,48] evaluated monthly MRIs on patients with relapsing-remitting disease. Koziol et al. (2001)[46] studied 50 patients in the context of a trial of cladribine in an effort to identify predictors of exacerbation. Three potential predictors were considered: enhancing lesions in three consecutive monthly MRIs, new enhancing lesions in three consecutive months, and new hypointense lesions in three consecutive monthly images. In all cases, the sequential MRIs had poor sensitivity (36 percent, 31 percent, and 31 percent, respectively), but higher specificity (85

percent, 89 percent, and 89 percent, respectively). As a result, the positive predictive value was low (approximately 25 percent for an exacerbation in the next month), but the negative predictive value was fairly high (89 percent for each predictor).

In a substudy of patients in a trial of glatiramer acetate, Rovaris et al. (2003)[48] examined the univariate correlations of baseline T1 and T2 lesion volume versus change in EDSS score. Without adjusting for baseline EDSS (which was correlated with baseline lesion volume), modest Spearman rank correlation coefficients were seen in the comparison of baseline lesion volume to EDSS at 9 months. Absolute changes in EDSS were not reported, and the investigators acknowledged that the associations were not clinically strong.

In one imaging study,[50] 28 patients with various disease patterns and 13 healthy control subjects had spinal cord images performed at the second cervical level. While changes in spinal cord size were noted, there was no statistically significant association noted between cord area and change in EDSS.

Laboratory test results. Laboratory tests were evaluated in four included studies: one of apolipoprotein E (APOE) $\in$4 allele,[41] two of immunological markers (one in blood,[51] one in cerebrospinal fluid[52]), and one of evoked potentials.[44]

APOE $\in$4 allele, associated with impaired neuronal repair, was assessed by Chapman and colleagues for its ability to predict clinical progression of MS.[41] Forty-seven patients with relapsing-remitting MS were evaluated for the presence of APOE $\in$4 allele. Results indicated that the presence of this genotype was associated with more rapid disease progression, with mean increase in EDSS of 4.0 during a 2-year follow up in patients with the allele compared to a mean increase of 2.7 for individuals without the genotype. Notably, the APOE $\in$4 allele was not found to be associated with other factors possibly associated with relapse, including baseline EDSS, prior rate of relapse, or exacerbation rate in the prior 2 years.

Villar et al. (2002)[52] examined intrathecal immunoglobulin-M (IgM) synthesis in 22 patients with relapsing-remitting disease to determine if its presence during early stages of the disease correlated with a worse prognosis. Patients were evaluated as to their time to conversion to clinically definite MS, number of relapses, and changes in EDSS. While half of the patients with intrathecal IgM synthesis progressed at least one EDSS unit after 1 year, none of the patients without this marker progressed in that period. Notably, relapse rate was similar in patients with and those without intrathecal IgM synthesis.

Trotter et al. (1989)[51] measured interleukin-2 (IL-2) levels in serum of 10 patients with chronic progressive MS and 12 normal controls, as well as concavalin A suppressor, mitogen stimulation, and phenotyping of peripheral blood mononuclear cells. Only IL-2 levels at baseline correlated with disability over 18 months. Though no cutoff value for elevation was selected a priori, a value of 40 U/mL corresponded to a sensitivity of 67 percent and specificity of 100 percent for the outcome of worsening one or more units in EDSS. Notably, these results were not examined after adjusting for other predictive features, particularly those diagnostic of MS.

One study was identified that compared results from motor and visual evoked potentials at baseline with subsequent EDSS. Fuhr et al. (2001)[44] studied 30 patients with relapsing-remitting (n = 25) or secondary progressive (n = 5) patterns using measures of motor and visual evoked potentials, such as the sum of Z scores of central motor conduction time. Results of these tests at baseline were moderately correlated with EDSS score at 24 months (0.43, p = 0.03). No cutoff was defined a priori for a positive evoked potential study. However, from the data provided, a Z score at baseline exceeding 0 was associated with a sensitivity of 53 percent and specificity of 70

percent for any worsening of EDSS at 24 months. For the population studied, the overall likelihood of progressing was 17/27 (63 percent); of 11 patients with a positive study, nine (82 percent) progressed, and of 15 with a negative study, eight (53 percent) progressed.

Self-reported status. Self-reported health status was compared to subsequent course in one study.[47] Of 97 patients with relapsing-remitting MS, six were lost to follow up before 12 months. Quality of life (QOL) was assessed using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), with results dichotomized into poor/fair versus good/very good/excellent. The relative risk for any worsening in EDSS at one year was 1.9 (95 percent CI, 1.0 to 3.5). In absolute terms, having a poor or fair QOL assessment at baseline was associated with a 42 percent likelihood of progression to any degree, while a better QOL response was associated with a 23 percent chance of worsening. This association persisted with multivariate adjustment for baseline clinical characteristics. The association did not extend to other dimensions of the SF-36. Moreover, no assessment was made regarding the presence of a disability claim.

Disease-modifying Therapies and Long-term Improvement

Introduction

In this section we report results for Question 3a: *Among patients with MS, do current disease-modifying treatments result in long-term improvements in physical or mental outcomes compared to placebo or usual care?* In attempting to answer this question, we were looking for data indicating whether individual patients *improve* on current disease-modifying therapy. Specifically, we were looking for data suggesting that disease-modifying treatments might result in enough clinical improvement to decrease an individual's level of impairment to the point where he or she might not be disabled at some future time.

As readers familiar with the relevant literature will recognize, most studies of the efficacy of disease-modifying agents assume that individual patient improvement is unlikely and do not consider data on improvement as part of the outcome assessment. In general, the literature assumes that while disease-modifying agents may be expected to reduce progression, they are not likely to result in improvement. This "disconnect" between the question we were asking and the assumptions of the clinical trial literature led us to conduct a broad search of the literature to examine indicators of efficacy, with a more specific examination of any available data delineating individual patient improvement.

Our search strategy focused on reports that described data from randomized controlled trials of disease-modifying agents in patients with any degree of impairment. For the data to be meaningful with regard to improvement, we selected studies that included the outcome measures of change in physical function, cognitive function, work/employment status, and reduction in relapse rates where outcomes were reported over at least 12 months. We excluded studies evaluating therapies not currently in use. Ultimately, our focus was on those studies that reported data on individual patient outcomes – particularly the *improvement* of individual patients. We excluded studies that did not contain placebo controls because the demonstration of individual patient improvement without a comparison to control patients might only reflect

improvement that is part of the natural history of MS rather than a treatment-specific improvement.

Results

Fifty-one publications[53-103] describing 34 separate trials, met our inclusion criteria (see Evidence Table 3a in Appendix F). The treatments evaluated included interferon beta, glatiramer acetate, mitoxantrone, glucocorticoids, intravenous (IV) immunoglobulin-G (IgG), azathioprine, cyclophosphamide, plasma exchange, methotrexate, cladribine, cyclosporine, and combinations of these therapies. Outcome measures were primarily group or mean changes in rates of relapses, changes in rates of progression on the EDSS, and occasionally changes in some measures of cognition or quality of life. These studies are adequate to answer issues regarding the efficacy of therapy, but do not provide information regarding individual patient improvement.

Relapse rates. Data on relapse rate outcome measures are summarized in Table 6.[53,54,59,62-65,68,72-78,82-84,86,89,92,93,95-97,100,103] In most of these studies the baseline mean annual relapse rate was approximately one relapse per year. The effect of most of the therapies studied was a mean reduction in the range of 0.3 relapses per year; higher reductions (up to one relapse per year) were reported after treatment with IV IgG when baseline relapse rates were in the range of 1.5 to 2 relapses per year. We found only one study that reported reductions in individual patient relapse rates. Kappos et al. (2001)[79] reported that treatment with interferon beta increased the proportion of patients who were relapse-free or had decreased relapse rates from 45 percent (placebo) to 53.1 percent (treatment). In summary, the effect of treatment with any of the currently used therapies is a mean reduction in relapses of less than one relapse per year. The benefit may be higher in patients with higher baseline relapse rates, but we did not find data stratified in this manner.

Physical function (EDSS). Studies reporting data on individual patient improvement in EDSS scores are summarized in Table 7.[53,55,58,59,63-65,67,68,75-78,80,83,90,96,97,102,103] Most of these studies provided a definition (and in some cases more than one definition) of improvement, usually corresponding to at least a one-point decrease in EDSS score. Changes of half a point (0.5) in EDSS may not be reliable due to uncertainty regarding this degree of change and uncertain clinical significance. The proportion of patients meeting varied definitions of improvement in placebo groups ranged from 0 to 22 percent; the differences in proportions of patients improving ranged from -1 to 49 percent, although most fell into the range of 0 to 12 percent. Higher EDSS change thresholds (-2 points or -3 points) resulted in lower proportions of patients meeting improvement definitions in one study.[55]

Improvement in cognitive function. Two included studies evaluated the efficacy of therapy with regard to cognitive function.[76,78] Both studies demonstrated benefit of therapy over placebo but did not present data with regard to the quantitative improvement seen in individual patients.

Improvement in quality-of-life measures. Two included studies (described in three publications) evaluated the efficacy of therapy with regard to quality-of-life measures.[59,66,79] Both studies demonstrated benefit of therapy over placebo in the groups studied, but did not present data with regard to the quantitative improvement seen in individual patients.

Symptom Management and Improvement

Introduction

This section of the report considers Question 3b: *Among patients with MS, do treatments aimed at symptom management result in improvements in physical or mental outcomes compared to usual care?* Several symptomatic complaints are common among patients with MS. Among the most common are fatigue and voiding dysfunction. Less well recognized are cognitive dysfunction and pain. We assessed the effectiveness of therapies aimed at particular symptoms including spasticity, voiding dysfunction, fatigue, depression, and cognitive impairment, as well as more comprehensive treatment aimed at multiple symptoms or multiple areas of functional status, i.e., rehabilitation. We excluded trials of drugs that are not currently commercially available in the US.

We sought randomized controlled trials reporting physical and mental health outcomes. We excluded studies that reported data on patient preferences for treatments as the only outcome. We examined outcomes within six categories: (1) symptom-specific functional status or quality-of-life outcomes; (2) physical functioning (primarily EDSS); (3) cognitive functioning; (4) work or employment outcomes; (5) generic quality-of-life outcomes; and (6) adverse events. In contrast to our treatment of the previous question (Question 3a), we did not require data to be reported as the proportion of patients meeting a definition of symptom "improvement." We report all data comparing treatment and control groups on the above outcomes regardless of the format in which they were presented or analyzed.

Results

We included a total of 68 articles describing 65 separate studies (see Evidence Table 3b in Appendix F). By topic, these included: for spasticity, 35 articles[104-138] describing 32 separate studies; for rehabilitation, 10 articles/studies;[139-148] for depression, eight articles/studies;[149-156] for fatigue seven articles/studies;[157-163] for voiding dysfunction, seven articles/studies;[164-170] and for cognitive problems, one article/study.[171]

Spasticity. Among the 32 studies of specific treatments aimed at management of spasticity were randomized controlled trials (RCTs) of oral medications, intramuscular medications, and intrathecal medications, as well as physical treatments (magnetic stimulation and electrical neuromuscular stimulation). Trials of drug treatments were most common and considered the following agents: tizanidine, baclofen, diazepam, gabapentin, dantrolene, threonine, botulinum toxin, cannabinoids/delta-9-tetrahydrocannabinol (delta-9-THC), progabide, and amantadine. Baclofen was the subject of six comparisons with placebo,[105,109,117,124,129,130] six comparisons with tizanidine,[104,108,113,122,126,134,136] two comparisons with diazepam,[106,110] and one with stretching exercises.[105] In addition, one trial compared intrathecal baclofen with placebo.[125]

Tizanidine was studied in two placebo comparisons,[133,137] six comparisons with baclofen (see above), and one with diazepam.[127]

Dantrolene was studied in one placebo comparison[111] and one comparison with diazepam.[131,132] We found two studies each of gabapentin,[107,121] progabide,[119,120,128] botulinum toxin,[114,135] and threonine[112,116] versus placebo. Delta-9-THC was tested in two trials[115,138]

against both placebo and cannabis sativa plant extract. Electrical[118] and magnetic[123] neuromuscular stimulation were each compared to sham stimulation.

Study quality. All 32 trials randomly allocated patients to treatment groups, but the methods of randomization were clearly described for only 5/32 (16 percent). Most failed to provide enough information to determine whether there had been adequate concealment of the allocation schedule (25/32; 78 percent). In the seven studies that reported enough information for evaluation, there was adequate concealment in four, and inadequate concealment in three.

Thirty of 32 trials (94 percent) were described as double-blind; patients were described as blinded in 29 trials, and in one trial[118] it was unclear whether patients were blinded. Treating investigators were blinded in 28 trials; outcome assessors were blinded in 30 trials, but it was unclear whether they were blinded in another study.[105] Most studies (27/32; 84 percent) reported the number of withdrawals in each treatment group.

Twenty of the 32 studies were of crossover design; the remaining trials were of parallel-group design. Among the crossover trials, we assessed several dimensions of quality unique to the crossover design. The presence of period effects or carry-over effects was not discussed in over half the studies (11/20; 55 percent). One trial reported having a period or carry-over effect and appropriately analyzed first-period data only.[121] Most crossover trials (17/20; 85 percent) included a washout period. Thirteen (65 percent) failed to report clearly the number of patients assigned to each treatment sequence. In six studies it was unclear whether patients who did not complete both treatment periods were excluded; two studies appeared to use an inappropriate unpaired analysis retaining patients who did not complete the crossover in the final analysis.

Study populations. Only 11 of the studies describe the study population in terms of EDSS score at baseline; mean baseline EDSS ranged from 4.7 to 7.4 in studies reporting means. The two studies of botulinum toxin[114,135] appeared to include the most severely impaired patients, with median EDSS scores above 7.5. Other study populations included mostly subjects with EDSS scores in the range of 5.0 to 7.0.

Studies used a variety of outcome measures, many of which were not validated. Of the placebo-controlled trials, 12 of 20 (60 percent) used the Ashworth Scale or Modified Ashworth Scale. However, this scale was often combined with other measures[135] or summed across sides and muscle groups to create outcome variables and statistical testing that have not been validated.

Findings. Trial design and results are summarized in Table 8. Assessments of muscle tone were not consistently positive for most of the drug treatments, with the exception of two studies each of gabapentin[107,121] and progabide.[119,120,128] Results of functional assessments were largely inconclusive; the only positive findings on functional assessments were associated with delta-9-THC; deterioration in 9-Hole Peg Test (9-HPT) and Multiple Sclerosis Functional Composite (MSFC) was associated with delta-9-THC in one small study[115] while a much larger study found improvements in 10-meter walk time[138] with delta-9-THC compared to placebo. Both studies reported these changes in the absence of a significant effect on objective measures of muscle tone. However, beneficial effects in the latter study for mobility are not easily ascribable to the drug's psychoactive properties alone.

In contrast to oral treatments, which were of uncertain effectiveness, intrathecal baclofen treatment showed a profound effect on muscle tone and spasms in one trial;[125] however, the patients in this study were selected based on response to a pre-trial intrathecal dose of baclofen.

None of the trials comparing active drug treatments showed statistically significant differences in efficacy between agents, although there were some differences in tolerability.

Rehabilitation. Among the 10 studies we classified as rehabilitation were RCTs of a variety of interventions delivered in a variety of settings. Probably the most comprehensive was a study of home-based management, which included not only traditional rehabilitation services but also nursing, education, psychological support, and social services.[144] Several studies examined more typical rehabilitation interventions delivered in inpatient or outpatient settings.[139,140,142,145] One study examined supervised exercise,[143] and one physiotherapy.[148] Three studies used interventions that were probably less intense than traditional rehabilitations described as professionally guided self-care,[141] wellness intervention (education in health behaviors and lifestyle change),[146] and symptom management and adjustment (education and behavioral therapy).[147]

Only one study used an active treatment comparison group, comparing inpatient rehabilitation to outpatient rehabilitation.[139] Two other studies used control interventions presumed to be ineffective: a home exercise program[145] and self-exercise treatment.[142]

Study quality. All 10 trials randomly allocated patients to treatment groups, but the methods of randomization were clearly described for only five (50 percent). Most failed to provide enough information to determine whether there had been adequate concealment of the allocation schedule (six; 60 percent). In the four studies that reported enough information for evaluation, there was adequate concealment in three and inadequate concealment in one.

Because of the nature of the interventions, none of these studies was able to blind patients or therapists; however, four (40 percent) masked outcome assessors. Most studies (seven; 70 percent) reported the number of withdrawals in each treatment group. All but one of the studies was parallel-group in design; one study of home physiotherapy used a crossover design.[148]

Study populations. Most of the studies (seven; 70 percent) described the study population in terms of EDSS score at baseline. Two studies had populations with notably lower mean EDSS scores of 3.4: the single study of supervised exercise[143] and one of the more educational/behavioral intervention studies,[147] which notably had a broad range of EDSS scores, from 0 to 9. In other studies, the populations were more impaired on average, with mean EDSS scores of 5.9 to 6.2 and medians of 5.5 to 6.5.

Outcome measures used in these studies included measures of impairment (e.g., EDSS), disability (e.g., Functional Independence Measure [FIM]), and handicap (e.g., SF-36), and not only related to individual functions, but often used comprehensive measures of overall disability and handicap.

Findings. Physiotherapy interventions failed to influence impairments as measured by EDSS (see Table 9). These interventions were, however, associated with measurable changes in functional status. Improvements in health (handicap) were observed in the SF-36 and several other measures.

Depression. Among the eight studies of treatments aimed at depression were RCTs of a variety of interventions delivered in a variety of settings. Two placebo-controlled studies used drug treatments either alone[155] or with a psychotherapy co-intervention.[156] One study tested psychotherapy,[149] and five trials used behavioral therapy, described as cognitive-behavioral therapy[150,151,153,154] or cognitive remediation.[152]

The two drug studies were placebo-controlled and were the only studies to employ blinding of patients and investigators. The remaining studies used control groups that were passive (wait-list[150,151] or no treatment[152,154]) or active (current events discussion group,[149] support group[153]); one study used both an active and passive control group.[149]

Study quality. All eight trials randomly allocated patients to treatment groups, but the methods of randomization were clearly described for only two (25 percent). Six trials (75 percent) failed to provide enough information to determine whether there had been adequate concealment of the allocation schedule; the other two trials did not have adequate concealment of allocation. Because of the nature of the interventions, none of the behavioral therapy studies was able to blind patients or therapists; however, neither did any of these studies mask outcome assessors. Both studies of drug treatments were double-blind. Half of the studies failed to report the number of withdrawals in each treatment group. All but one of the studies were parallel-group in design; one study of amitriptyline used a crossover design.[155] Although this study did not report the number of patients in each sequence, it did employ a 1-week washout period and stated that there was no period or carry-over effect.

Study populations. Among the eight trials, the populations studied were quite variable with regard to the presence of depression or depressive symptoms. Some studies selected patients with MS without regard to the presence of a diagnosis of depression or depressive symptoms;[149,150,152] however, most studies either required a formal diagnosis of a depressive disorder[153,156] or required a certain score on a depression scale.[151,154] One study specifically included patients based on the particular complaint of episodes of involuntary laughing or weeping.[155]

Findings. The included trials are summarized in Table 10. All but one of the studies reported statistically significant improvement in mood outcomes; Mendoza et al. (2001)[152] failed to achieve statistical significance for changes in the Beck Depression Inventory (BDI), but the results did show a strong trend in favor of cognitive remediation. Treatment effects were similarly significant for studies of patients with depression diagnoses or those meeting minimum depression scale scores.

The studies were consistent in finding that untreated control groups[149-152,154] showed no improvement over time. In contrast, a control group of patients receiving psychotherapy as a co-intervention did show improvement.[156] Two studies that used active controls (current events discussion group[149] or support group[152]) found marginal improvements in some outcomes, but still allowed detection of treatment effects.

Fatigue. Among the seven studies of specific treatments aimed at management of fatigue associated with MS were RCTs of oral and topical medications. Amantadine was the subject of four placebo comparisons.[157-159,161] Pemoline was evaluated in three placebo comparisons,[159,161,163] two of which were three-arm studies including both amantadine and pemoline.[159,161] Two more placebo comparisons evaluated 4-aminopyridine[162] and transdermal histamine/caffeine.[160]

Study quality. All seven trials randomly allocated patients to treatment groups, but the methods of randomization were clearly described for only one.[157] None provided enough information to determine whether there had been adequate concealment of the allocation schedule. All of the studies were described as double-blind, and all described the number of dropouts or withdrawals from each treatment group.

Four of the trials used a crossover design.[157,158,162,163] One reported a period effect and appropriately analyzed first-period data;[157] the other three crossover studies tested for and reported no period or carry-over effects. One of the trials did not use a washout period.[162] Two reported the number of patients in each sequence.

Study populations. All studies selected patients based on complaints of persistent fatigue; some studies required either a threshold score on a fatigue measurement scale or a run-in period

during which fatigue symptoms were demonstrated to be stable. Mean EDSS scores at baseline were reported for six of the seven studies (86 percent). Two studies had populations with higher EDSS scores than the others: Rossini et al. (2001),[162] with a mean EDSS score of 6.2; and Gillson et al. (2002),[160] with entry criteria requiring EDSS between 5.0 and 6.5. The other studies had less impaired populations on average, with mean EDSS scores ranging from 2.6 to 4.3.

Findings. Included trials are summarized in Table 11. Four studies comparing amantadine with placebo found statistically significant results on a few outcome measures, and statistical trends on others, consistent with a treatment effect. The two largest studies[157,161] found statistically significant treatment effects on the MS-Specific Fatigue Scale (MS-FS) or visual analog fatigue scores. Two of three studies comparing pemoline to placebo also reported statistically significant treatment effects.[161,163] One small study reported a treatment effect on the Modified Fatigue Impact Scale (MFIS) associated with transdermal histamine/caffeine, but no effects on functional measures (25-foot timed walk, 9-HPT) or cognitive performance.[160] The single trial of 4-aminopyridine included in our review failed to show a treatment effect.[162]

Voiding dysfunction. Among the seven studies of treatments for voiding dysfunction were five placebo-controlled trials of desmopressin nasal spray,[164-167,170] one trial of pelvic floor rehabilitation,[169] and one trial of abdominal vibration or pressure.[168]

Study quality. All seven trials randomly allocated patients to treatment groups, but none clearly described the methods of randomization. None provided enough information to determine whether there had been adequate concealment of the allocation schedule. All of the desmopressin studies were described as double-blind. Blinding was not possible for the vibration and rehabilitation studies. All but one[167] of the studies described the number of dropouts or withdrawals from each treatment group.

Six of the seven studies were of crossover design; one study of amitriptyline used a parallel-group design.[169] Only one of the crossover trials incorporated a washout period,[168] and only one tested for carry-over or period effect.[170]

Study populations. Only two studies characterized populations in terms of EDSS, with means of 4.4 and 6.7. All studies recruited patients with MS and some kind of voiding dysfunction such as nocturia, urinary frequency, or incontinence.

Findings. Included studies are summarized in Table 12. The five studies of desmopressin nasal spray all demonstrated statistically significant reductions in short term urinary frequency (number of voidings) during 6-hour periods after dosing. Most studies dosed at bedtime to control nocturia, but one study used daytime dosing to control daytime urinary frequency.[166] At longer time intervals (24 hours) the treatments failed to show significant effects. The number of episodes of incontinence showed a statistical trend in one study,[170] but this outcome was not reported in the other studies of desmopressin.

Among the two nonpharmacological treatments, a program of pelvic floor rehabilitation (biofeedback and exercise) was effective in reducing incontinence episodes and nocturia;[169] this study also showed a measurable reduction in urinary symptom-related handicap ($p < 0.05$). A small study of the use of a handheld abdominal vibrator at time of voiding succeeded in reducing post-void residual urine volumes and also appeared to reduce incontinence, but not urinary frequency.[168] Interpretation of the results of this study was limited by poor reporting of the data and statistical analysis (no statistical tests were reported for several outcomes).

Cognition. Studies aimed at treatment of cognitive deficits in MS are challenging to characterize. We did not identify a single study that (1) selected a study population with

demonstrable cognitive deficits, (2) delivered a treatment (drug, behavioral, or psychological) aimed at improving cognitive performance, and (3) measured effects of treatment using tests of cognitive performance. However, one trial met at least two of these criteria and merits discussion here.[171] In addition, some of the studies aimed at treatment of depression assessed cognitive performance at baseline or as secondary outcomes.[152] Some of the rehabilitation trials evaluated mood-related outcomes in addition to functional outcomes, but none evaluated cognitive performance as an outcome measure. Finally, two of the studies aimed at treatment of fatigue also evaluated effects on cognitive function.[159,160]

Study quality. Lincoln et al. (2002)[171] describe both the method of randomization and adequate concealment of allocation. Because of the nature of the intervention, blinding of patients and therapists was not possible; however, outcome assessors were masked. The study reported the number of withdrawals and dropouts in each treatment group.

Study populations. No studies selected patients based on screening for cognitive deficits at study entry. Lincoln et al. (2002)[171] enrolled MS patients without regard to cognitive performance for their study of a cognitive intervention; however, 78 percent of the study population enrolled scored greater than 1 (the recommended cut off) on the mental disability question from Guy's Neurological Disability Scale (GNDS), and 95 percent either reported cognitive problems or showed significant impairment (score below cut off) on the Brief Repeatable Battery (BRB-N). Thus, while the proportion of patients with cognitive deficits may be elevated in this study due to selection biases, the prevalence of measurable cognitive deficits in other MS trials is likely also elevated.

Findings. Lincoln et al. (2002)[171] found no differences between the cognitive rehabilitation, assessment, and screening groups in any of the outcomes measured at 4 months (shortly after the end of the 6-week intervention) or at 8 months. Although the prevalence of cognitive deficits at baseline was relatively high, a large number of patients had self-reported cognitive deficits that were not detectible on GNDS or BRB-N, which may have hampered the ability to detect treatment effects. Furthermore, the population was heterogeneous with regard to their cognitive performance, which at best results in increased variance, making it more difficult to show statistical significance to differences between groups.

Geisler et al.(1996)[159] evaluated the effect of amantadine and pemoline on fatigue and cognition. Although the Symbol Digit Modalities Test (SDMT), a measure of attention and visuomotor search, showed a drug treatment effect (with the amantadine-treated group showing the greatest improvement), all other neurobehavioral outcomes failed to demonstrate a treatment effect. The authors acknowledge that the study did not have sufficient statistical power to detect small- to medium-sized treatment effects. But also, the study found no statistically significant correlation between fatigue symptoms and cognitive deficits either at baseline or post-treatment.

Gillson et al. (2002)[160] reported results from the Paced Auditory Serial Additions Test (PASAT) in a trial of transdermal histamine and caffeine in a population of MS patients with fatigue. No significant treatment effect was detected.

Association of Clinical Findings with Work Ability

Introduction

This section summarizes findings related to Question 4: *Among individuals with MS, what physical, mental, laboratory, or radiographic findings have been associated with inability to work?*

Aspects surrounding ability to work are multifactorial in nature involving individual skill level, education level, interest in working, financial needs, domestic responsibilities, transportation needs, and other factors such as social norms and expectations. Functional limitations (physical and/or mental) associated with MS are presumably the primary determinants of work capacity. Adverse, intermittent, and poorly measurable symptoms such as fatigue and pain compound the task of determining if an individual with MS is able to work. Employers' willingness or ability to provide workplace accommodations for workers who have limitations also impacts whether or not an individual with MS can work.

Several different types of physical and cognitive function measures (e.g., EDSS, disease subtype, mobility aids) were employed within and across studies to determine work ability among individuals with MS. For the purpose of this review we have grouped the summary of study findings according to these types of measures, which are listed in Table 13. Some studies used various types of measures and therefore are listed and discussed in more than one section. Categorizing studies or specific tests into physical function versus mental/cognitive function for this review was somewhat challenging since some tools measure both types of function. For example, the EDSS focuses on the functioning of numerous systems, including mental functioning, but is weighted more heavily towards testing ambulation. For the purpose of this review, tools like this are categorized according to the dominant area of function tested, resulting in the categorization of EDSS under "physical function." Tools testing multiple types of function are discussed in greater detail below.

Results

A total of 22 articles[172-193] representing 20 research studies were included in this review (see Evidence Table 4 in Appendix F). The majority of studies (n = 15) employed tests to measure physical function, while fewer studies (n = 5) measured cognitive or mental function (Table 13). To date, no studies have been ascertained that used laboratory or radiographic measures to determine work ability among individuals with MS.

Most of the studies (n = 18) were cross-sectional in design, where work status or work ability was measured at a single point in time, primarily at the time of study enrollment. The other two studies were retrospective in design, including one case-control study[193] and one retrospective cohort study.[181] No prospective studies, where changes in physical and/or cognitive function over time were considered in relation to changes in work status or ability, were identified for this review.

Twenty papers describing 18 studies used work status (yes/no or full-time, part-time, unemployed, retired, housewife) as a proxy measure for work ability among individuals with MS.[172-189,192,193] The remaining two[190,191] attempted to incorporate several aspects of work ability as a study outcome: the Hyllested criteria. The remainder of this section is organized by

types of measurement tools used to examine inability to work: Hyllested criteria, EDSS/DSS, cognitive measures, use of mobility aids, MS disease subtype, job type/characteristics, and self-report.

Hyllested criteria. As indicated above, only two[190,191] of the 20 included studies sought to determine ability to work among individuals with MS beyond the measurement of work status. Findings from these studies are reported separately (Table 14) from other studies that employed similar methods of measuring physical and mental functioning. Two cross-sectional studies conducted in Israel by Rozin et al. (1975[191] and 1982[190]) used similar methods for determining work ability among selected groups of individuals with MS ages 17 to 50 years. Interviews were conducted by social workers in the study participants' homes where demographic and occupational information was collected, as well as information about desire to be trained and employed. Subjects were evaluated by neurologists to determine degree of disability using a scale similar to the EDSS (described below) called the Hyllested criteria, which ranges from 0 (no functional disability, no residual signs) to 6 (bedridden, incontinent, requires constant supervision), with the mid-level score of 3 defined as moderate disability with work impairment sufficient to require a lighter job. Using these data, study participants were categorized into one of three groups: (1) Group A - completely handicapped with no rehabilitation potential; (2) Group B - potential for vocational rehabilitation, but unemployed or currently employed, but needs rehabilitation services for continuation of employment; or (3) Group C - currently working without need of rehabilitation intervention. All Group B patients underwent additional tests to evaluate their functioning potential by a rehabilitation physician, occupational therapist, and psychologist. Study participants were also categorized into types of disability (physical, mental, or both); however, it is unclear how researchers measured mental disability. Furthermore, it is unclear if physical disability was determined strictly on the basis of the Hyllested criteria or if additional information was used. (The earlier study by Rozin et al. [1975][191] addresses additional aspects of employment by examining disability type and level by job type, discussed in greater detail under "Job type/characteristics," below.)

Group A participants who were handicapped without rehabilitation potential were more likely to be disabled due to a decrease in physical or physical and mental function, with few being disabled strictly due to a decrease in mental function. Both studies[190,191] observed that about half of Group C (fully employed without need of vocational rehabilitation) were physically disabled and ranked as being either mild to moderately disabled on the Hyllested scale. Subjects in Group B (those who would benefit from vocational rehabilitation) were more likely to have moderate to severe physical disability. Although these patients had significant physical limitations, they were still considered to be individuals who would benefit from vocational rehabilitation and capable of working.

The obvious advantages of these studies include the consideration of work ability beyond work status, as well as the examination of both physical and mental function among the same sample population with regard to work ability, which most other studies did not report. However, a limitation of these methods is that researchers used current work status to determine ability to work, which could possibly bias the outcome of their evaluation. If a study participant was not working and expressed no desire to work, but was actually capable of performing a job, they may have been classified as someone who is not a candidate for vocational rehabilitation. Additional limitations include the omission of detailed information about how mental function was measured. These studies were also limited by small sample sizes, and data collected about education and marital status were not included as possible confounders in multivariate analyses.

Because these were cross-sectional studies, the levels of physical and mental functioning were measured at the time of the study and not at the time when study participants ceased employment. The timing between impaired function and inability to work was not established.

EDSS/DSS. Three cross-sectional studies (Table 15)[174,180,188] and one case-control study[193] used the EDSS, and two cross-sectional studies[183,187] used the DSS to assess ability to work among individuals with MS. The EDSS (and its earlier version, the DSS) is a clinical tool commonly used for rating neurological impairment in individuals with MS.[194] Clinicians determine a patient's EDSS level by first assigning a separate grade for eight functional systems including pyramidal, cerebellar, bowel and bladder, cerebral, brain stem, sensory, visual, and other functions. A composite of grades is then used to determine an individual's EDSS score ranging from 0 (normal neurological exam) to 10.0 (death due to MS).[194] The level of function for each of the eight systems is considered for EDSS score; however, assignment of a level is superseded by an individual's ability to ambulate (e.g., free from mobility aids vs. need for mobility aids), possibly giving more weight to ambulation than the other seven functional systems. For example, individuals with MS who are able to walk without ambulatory aid would receive a score of 0 through 4.5, whereas a need for constant bilateral assistant (e.g., canes, crutches or braces) would predetermine an individual to receive a score of 6.5. Although mental function is factored into the EDSS scoring system as one of eight systems, it is not considered independently of ambulation at any EDSS level.

As detailed in Table 15, a lower frequency of employment was consistently observed in groups with higher EDSS levels in all three cross-sectional studies. Unemployment among study participants with an EDSS ranging from 3 to 6 was reported to be approximately 42 percent,[174] 52 percent,[180] and 72 percent,[188] respectively, while employment among lower EDSS levels (≤ 2.5) was 37 percent, 42 percent, and 51 percent, respectively. Unemployment was most common among individuals with higher levels of EDSS (≥ 6.5). A case-control study[193] observed that mean EDSS levels were significantly different between unemployed cases ($\bar{0}$ = 5.4; standard deviation [SD] = 0.1) and employed controls ($\bar{0}$ = 4.5; SD = 0.1) with MS ($p = 0.01$). This is only a 1-point difference on the EDSS scale, but 4.5 and 5.4 straddle the scale's demarcation of work ability, with 4.5 defined as "able to work a full day" and 5.5 defined as "disability severe enough to preclude full daily activities."[194] These findings may reflect the timing of the neurological exam to assess EDSS, which was conducted at the outset of the study and not at the point when employment ceased. Physicians may not have been blinded to study participants' work status at the time of the exam, possibly biasing their evaluation.

Hammond et al. (1996)[183] conducted a large (n = 2099) cross-sectional study in Australia and reported that after adjusting for age, men with moderate DSS levels (4-6) were almost three times more likely to be unemployed (prevalence ratio [PR], 2.7; 95 percent CI, 2.1 to 3.6), and women were four times more likely to be unemployed (PR, 4.0; 95 percent CI, 2.7 to 5.8) compared to men and women (respectively) with lower DSS levels (0-3). Men and women with severe DSS (7-9) were also more likely to be unemployed (men PR, 17.9; 95 percent CI, 7.5 to 41.5; women PR, 24.6; 95 percent CI, 8.0 to 76.1) when compared to this same group. The second study[187] observed that a 1-point increase in DSS was associated with a seven percent decrease in the likelihood of being employed, and being male increased the probability of employment by 11 percent after controlling for numerous factors such as age, sex, education, marital status, and parenthood.

Findings from these studies suggest that individuals with higher EDSS/DSS levels are more likely to report not working. The three cross-sectional studies that examined EDSS had small

sample sizes such that adjustment of prevalence ratios for other aspects associated with work ability was not possible. Extrapolation of these findings is limited because they focus only on a single dimension of work ability.

Studies by Larocca et al. (1982)[187] and Hammond et al. (1996)[183] included multivariate analyses where adjusted estimates were reported; however, no measures of cognitive impairment or job characteristics and responsibilities were considered. Again, these studies were cross-sectional, and the assessment of EDSS during enrollment in the study failed to establish the timing between impaired physical function and inability to work.

From a more global perspective, a semantic issue with EDSS deserves mention. Level 5.5 denotes disability severe enough to preclude full daily activities. It is not clear to what degree clinicians equate this EDSS-based activity preclusion with being incapable of working, without exploring other aspects of work ability such as cognitive function and employer accommodations. Conversely, cognitive impairment sufficient to impair work capacity would not typically be reflected in the EDSS score.[189]

Cognitive measures. Three studies primarily examined cognitive function and work status among patients with MS (Table 16). Two of these[172,189] administered a battery of cognitive tests, while the third[177] collected data on cognitive function (attention/concentration, planning/organizing, retrospective and prospective memory) and ambulatory assistance through a self-report survey. The former studies examined a broad spectrum of function including verbal skills, memory, visuospatial perception, problem solving, and attention and concentration. In addition to these tests, Beatty et al. (1995)[172] also administered the Ambulation Index (which is highly correlated with the EDSS, r = 0.96). Ambulation, short-term memory, delay recall, age, and verbal ability were found to explain 49 percent of the variance in employment status. Patients who were still working attained significantly higher scores on most of the individual measures of cognitive performance and were impaired on significantly fewer cognitive domains. Rao et al. (1991)[189] reported that cognitively impaired patients were also less likely to be employed compared to individuals who were cognitively intact, but information on which specific cognitive tests (or impairments) were associated with employment was not reported, and level of physical function was not considered in the analyses. Self-perceived cognitive deficit and need for mobility assistance were also associated with unemployment, as were fewer years of education and age.[177] However, occupational level (socioeconomic index), number of people living at home, and duration of illness did not impact employment status. A study by Genevie et al. (1987)[179] also considered self-reported cognitive function in combination with physical function and other symptoms, but details of the types of cognitive limitations were not described (see Evidence Table 4 in Appendix F for details of study limitations).

One additional study focused on self-reported expressive communication disorder, and study participants were asked if the communication disorder interfered with employment.[173] Employment status among those with self-reported communication problems was less compared to the entire study sample. Methodological problems (described in Evidence Table 4 in Appendix F) prevented further interpretation of this study.

Common sense suggests that impaired cognitive function has the potential to seriously impact work ability. However, the three studies described in Table 16 do not provide the evidence needed to determine the type and/or level of cognitive impairment when an individual with MS is no longer able to work. Unlike the studies by Rao et al. (1991)[189] and Edgely et al. (1991),[177] Beatty et al. (1995)[172] provided far more detail about the specific cognitive tests that were associated with not working. In addition, these researchers also considered level of

ambulation in combination with cognitive function and demographic characteristics. Since only a global measure of variance was provided it is difficult to interpret the strength of association between each of these domains (cognitive function, level of ambulation, demographic characteristics) and work ability. The 1991 study by Rao et al.[189] did provide details about the types of tests that were administered, but used a global measure of "intact versus not intact" to examine work ability. The method of self-report of cognitive function used by Edgley et al. (1991)[177] has limitations in that someone with impairment may not be able to objectively measure their own level of cognitive function. Finally, the temporal relationship between cognitive impairment and cessation of work among study participants was not captured in these cross-sectional studies.

Mobility aids. The number and type of mobility aids study participants used was measured in two studies[176,186] as a proxy measure for degree of disability. Kornblith et al. (1986)[186] developed a three-level Mobility Dysfunction Index (MDI) ranging from no assistance needed (Level 1), to any combination of cane, walker, leg brace, etc. (Level 2), to use of a wheel chair for more than half the time in- or outdoors (Level 3). A 1-point increase in MDI decreased the probability of males working by 24.3 percent, while it decreased the likelihood employment for females by 15.4 percent, leading investigators to conclude that mobility was a major determinant of employment, while age and duration of disease were minor. Dyke et al. (2000)[176] considered the number of mobility aids used and reported that only 20 percent of the variance in employment among a sample of women was accounted for by the number of mobility aids used, age, and education.

Use of certain mobility aids (e.g., wheelchair) can certainly provide a measure of degree of physical disability, as well as indicate the possible level to which the disease progression has hindered physical function, but Dyke et al. (2000)[176] considered only the number of aids used. A limitation of using the number of mobility aids to measure degree of disability is that it most likely is not sensitive enough to detect changes in other aspects of disease status and mental function, and it certainly does not capture job requirements. Desk jobs that require only sitting may enable someone who uses a wheelchair, but is not cognitively impaired, to continue working.

Disease subtype. Although there is great variability in the course of MS, three subtypes of disease are generally recognized: (1) relapsing-remitting; (2) primary progressive; and (3) secondary progressive.[195] The terms of these subtypes have changed over time due to refinements made within each classification, which are reflected in the different terms used in the following studies. One cross-sectional study[184] and one case-control study[193] compared MS patients' current work status with disease subtype. Both studies reported a higher frequency of employment among study participants with relapsing-remitting compared to primary progressive[184] and relapsing-progressive MS.[193] These findings are consistent with the greater degree of disability typically noted among individuals with progressive MS;[196] however, the analyses for both of these studies were crude and did not consider other factors associated with ability to work, except for Jacobs et al. (1999),[184] which attempted to control for age by restricting analyses to individuals less than 60 years of age. Furthermore, disease subtype was not measured until enrollment into the study. The disadvantage of using disease subtype for determining work ability is that the range of cognitive and/or physical function within each classification can vary tremendously. Furthermore, these studies do not provide the needed information for the measurement of physical and/or cognitive function that results in cessation of employment.

Job type/characteristics. Six studies (Table 17) either focused primarily on job type or work characteristics[181,192,193] or included information about occupation as a secondary aim in their study.[183,187,191] Although the purpose of this review was to summarize information about measurements of physical and/or mental function among individuals with MS associated with inability to work, examining job requirements provides an indirect measure of the physical and/or mental levels of function needed to sustain employment.

In a case-control study conducted by Verdier-Talliefer et al. (1995)[193] several job characteristics were examined for their relationship with unemployment among MS patients. After adjusting for age, sex, type of disease, and level of education, an elevated odds of unemployment was observed among study participants whose jobs required physical strength (odds ratio [OR], 7.6; 95 percent CI, 3.2 to 18.2), manual precision (OR 3.1; 95 percent CI, 1.6 to 6.3), and frequent moves (OR, 2.5; 95 percent CI, 1.3 to 4.9). Furthermore, the odds of unemployment decreased when the job was a "desk job" (OR, 0.3; 95 percent CI, 0.1 to 0.5), or one that required sitting (OR, 0.3; 95 percent CI, 0.1 to 0.7). When all of the demographic and job characteristics were considered together in a multivariate model, work in the public sector was protective against unemployment (OR, 0.4; $p < 0.05$), and work requiring physical strength increased the odds of unemployment (OR, 4.5; $p < 0.001$). Analyses stratified by sex revealed that factors associated with unemployment for men involved a rigid work schedule (OR, 17.1; $p < 0.01$), while for women unemployment was strongly associated with work requiring physical strength (OR, 4.5; $p < 0.05$). These findings are consistent with those of Scheinberg et al. (1980),[192] who observed that currently employed (n = 51) study participants were more likely to hold jobs that were clerical (35.3 percent) or professional (37.2 percent) as opposed to skilled (13.7 percent) or unskilled (2.0 percent) labor. An early study by Rozin et al. (1975)[191] categorized study participants into groups according to their level of function and ability to work, described in greater detail above. This study crudely assessed changes in employment from the time of diagnosis to the time of the study. Study participants included in Group B (unemployed, but had the potential for vocational rehabilitation or employed, but needed rehabilitation services to continue employment) were more likely to remain in clerical and professional type jobs, compared to those in skilled and unskilled labor. Furthermore, those in Group C (currently working without need of rehabilitation intervention) were able to remain in the workplace, although they shifted employment from labor-intensive jobs to clerical or professional. Authors note that of the 131 clients with working potential, only 18 percent indicated that they stopped work because of MS, but provided no additional information about why study participants left work. Again, the limitations of this study are its small sample size and the lack of consideration of additional factors that influence ability to work. Grønning et al. (1990)[181] reported consistent findings that heavy work was predictive of early unemployment; however, this study had serious limitations with regard to how jobs were categorized into heavy versus light work (see Evidence Table 4 in Appendix F).

Two studies did not focus primarily on job characteristics in the analyses, but did provide commentary about it. LaRocca et al. (1982)[187] reported that a significant portion of the variance in employment status was unexplained by typical demographic characteristics such as age, education, and occupation, but was explained by more subjective measures of workplace characteristics, social support, and coping style. Unfortunately, additional information about workplace characteristics was not provided. Dyck et al. 2000[176] commented that 17 percent of the women in their study reported that they quit work because they were unable to negotiate reduced work hours with their managers.

From what we know about the possible physical and cognitive limitations associated with MS, as well as the resulting fatigue and other symptoms, it is not surprising that unemployment is more common among individuals whose jobs required physical exertion. The strength of the case-control study by Verdier-Talliefer et al. (1995)[193] is that it considered numerous working conditions that increased or decreased the odds of unemployment. The remaining studies provided descriptive information that was parallel with findings reported by Verdier-Talliefer et al. (1995).[193] Unfortunately, none of these studies systematically examined whether employers' willingness or ability to provide workplace accommodations or flexible work schedules fostered continued employment.

Self-report. Several studies provided descriptive information about conditions or situations that influenced individuals with MS to cease employment (Table 18). Physical difficulty, ambulation problems, visual difficulties, emotional problems, and fatigue were reasons for ceasing employment among participants in two studies[177,192] who indicated that they left work because of MS. In addition, both studies reported that a significant percentage of women (37.4 percent and 26 percent, respectively) indicated leaving for reasons other than MS, including marriage and/or pregnancy. Among individuals who remained at work, fatigue was reported as the most common symptom impeding work performance or restricting the work that could be done in two cross-sectional studies.[176,182] An additional study not included in Table 18[178] reported that 10 percent (n = 30) of study participants indicated that they quit work because of fatigue. Although these findings do not involve specific clinical tests to determine the presence or absence of cognitive or physical impairment, qualitative data like these are useful for shaping quantitative data analyses, as well as shaping future research.

Environmental Factors and Work Ability

Introduction

This section describes the evidence pertaining to Question 5: *Among individuals with MS, how does elevated temperature or other environmental factors impair the capacity to work?* The precise scope of this question was defined in collaboration with the project's technical advisory panel and representatives of SSA. This process led to consensus that temperature was the sole environmental factor that warranted investigation. We therefore focused specifically on evidence regarding the associations between thermal (ambient or climatic temperature) conditions in the work environment and the work capacity, work status, or disability status of patients with MS. It was recognized that occupational physical activity might be a modifier of the effect of environmental temperature.

The importance assigned to temperature effect in MS is based on longstanding clinical impressions that excessive or high heat conditions may be associated with transient worsening of symptoms and/or function in some patients with MS.[197,198] We did not attempt to assess the quality of the evidence underlying such clinical impressions, nor did we investigate possible mechanisms whereby ambient and/or body temperature might act physiologically to affect MS.[199-201] We also did not examine treatment modalities based on thermal sensitivity in relation to Question 5; rather, randomized controlled trials of cooling garments and other temperature-lowering interventions were considered for inclusion under Question 3b (symptomatic treatments).

A key issue for SSA disability determination in MS would seem to be assessment of reported functional or activity limitations due to worsening symptoms or decreases in functional capacity that are temporally associated with particular activity demands or the physical environments attendant to certain jobs. If such worsening were consistent and had significant adverse impact, the associated demand or situation might be considered a "critical job demand" for some jobs (i.e., the limiting point of a potentially significant mismatch between a person's work capacity and the job requirements). Another research question of interest to SSA might be whether environmental temperature conditions characteristic of particular workplaces or jobs are associated with different rates of MS work disability.

Results

A single research study met the inclusion criteria for this question (see Evidence Table 5 in Appendix F).[182] Other candidate articles were typically excluded due to a lack of data regarding work capacity, work status, or disability status variables. In considering some of the excluded interventional studies aimed at short-term reduction of individual body temperature,[199,201-203] it was clear that an unacceptable degree of extrapolation would be required to relate the conclusions of these studies to work demands or circumstances of likely relevance to SSA.

The single included article,[182] a questionnaire survey, also has significant limitations in its applicability to SSA-relevant issues. It does, however, suggest that some MS patients perceive temperature as a factor that can either impede (high temperature) or enhance (cool temperature) work performance. This cross-sectional study divided 508 respondents with MS into four self-reported work status categories. Table 19 summarizes subjects' responses to open-ended questions regarding impediments to and enhancers of work/chore performance. Independent raters coded the actual responses into several categories. Table 19 includes only temperature-related conditions/situations and those endorsed by all four work groups. Overall, 53 work-impeding categories were identified, with 22 of those being endorsed by at least five percent of respondents. For work-enhancement, 27 total categories were identified, with 17 being endorsed by at least five percent of respondents.

Chapter 4. Discussion

The goals of this review relate to examining the evidence in the medical literature for data that can guide policy for determining disability in patients with multiple sclerosis (MS). We found at least some evidence with which to address four of the five major topic areas. Although the literature in general and certain studies in particular suffer from limitations, reasonably strong conclusions can be drawn in some areas. The evidence for each topic is summarized below and is followed by a summation of knowledge gaps and recommendations for future research.

Discussion of Evidence

Reliability of Criteria for Diagnosing MS (Questions 1a and 1b)

The recently proposed McDonald criteria for diagnosing MS are well supported by two types of evidence. First, two studies show that between 73 and 94 percent of patients presenting with clinically isolated syndrome (CIS) who go on to develop clinically definite MS (CDMS) over 1-4 years of follow up could be diagnosed with MS according to the McDonald criteria. Furthermore, the specificity of these criteria is reasonably high, ranging from 83 to 87 percent. Second, many studies support the magnetic resonance imaging (MRI) component of the McDonald criteria, by showing a strong and consistent association between the number of T2 lesions on MRI and the subsequent development of CDMS among patients with CIS or optic neuritis. Thus the McDonald criteria appear to have substantial evidence for validity and offer the obvious potential advantage of resulting in an earlier diagnosis of MS than the Poser criteria permit.

The McDonald criteria have been criticized for their complexity in comparison with previous criteria; however, we found data that demonstrate that the McDonald criteria yield a good overall diagnostic reliability, at least as good as the previous Poser criteria. However, widespread adoption of the new criteria could result in deterioration of this reliability. Barkhof et al. (1997)[39] demonstrated that among neurologists inter-rater reliability of MRI diagnosis significantly improves with increased level of training. Non-neurologists are unlikely to be able to achieve the same level of MRI agreement and are therefore unlikely to be able to maintain this level of agreement with the McDonald criteria as a whole. Further research on the inter-rater reliability of these criteria in broader clinical settings would be helpful to determine the quality of MS diagnosis.

While these data may be sufficient to secure a place in clinical practice for the McDonald criteria, certain difficulties arise in applying these criteria retrospectively from medical record review for the process of determining disability. At the present time most patients have not been diagnosed according to the specific application of the McDonald criteria. Therefore, they may have medical records that do not clearly delineate the nature and timing of their specific MRI changes in a manner that conforms to the McDonald criteria.

Predictors of Physical and Mental Impairments at 12 Months (Question 2)

The ability to predict future course of MS has been an active area of MS research; however, most studies examining disease course do so over quite long time periods of 5 to 20 years. We found a paucity of data describing changes in neurological or other impairments over 9-24 months, which we used to approximate the 12-month time horizon dictated by statutory requirements. Clinical characteristics have been the best studied, with four reports providing evidence for this review. While clinical features do not individually provide reliable guidance on prognosis, multivariate predictive models based on relatively easy-to-obtain features may have better performance. However, the reliability and validity of these predictive models has not been evaluated and thus their value for predicting disability has yet to be determined.

In contrast to their value in predicting development of CDMS among patient with CIS, imaging studies do not appear to provide especially useful prognostic data among patients with MS. The absence of lesions on sequential MRI studies is associated with a lower probability of an exacerbation in the ensuing month, and long-term prediction of health outcomes needed in the context of disability assessments has not been shown to be possible. Somewhat more promising strategies for predicting outcome of MS patients is the use of laboratory markers, such as apolipoprotein E (APOE) $\in$4 allele, interleukin-2 (IL-2) levels, or intrathecal immunoglobulin-M (IgM) synthesis, although the current level of evidence is best considered preliminary. These reports may provide the rationale for further validation studies, but are not standard practice and their practical impact is thus limited.

A single study of quality-of-life measures as predictors of long-term outcome was suggestive, especially considering the persistence of the association after adjusting for clinical characteristics. In addition to the uncertain generalizability of these results, such measures could have substantial reliability problems in the context of disability assessment.

Notably, no study was identified that examined the relationship between various factors and subsequent mental impairment.

Disease-modifying Therapies and Long-term Improvement (Question 3a)

Most of the data presented suggest that few patients improve on therapy. Those few who do improve generally do so only in the range of 1.0 point on the Expanded Disability Status Scale (EDSS). We found no data regarding improvement in work ability and no data that would correlate a 1.0-point improvement in EDSS with improvement in work ability. The significance of a 1.0-point EDSS improvement varies depending on baseline EDSS score (because the scale is non-linear), but the improvement data available are not generally stratified according to baseline EDSS score. With regard to work ability, the significance of the available data on clinical improvement is unclear. We found no data that quantified individual patient improvement with regard to cognitive function or quality-of-life measures.

In considerations regarding the determination of disability, the ability of a therapy to reduce mean exacerbation rates is of unclear significance. We have considered this issue out of concern that despite any given level of physical dysfunction, one might consider that an individual with frequent relapses may have impaired job performance solely on the basis of exacerbations. The

data presented in Table 6 (see Chapter 3) document that with any of the current therapies, mean reductions in relapse rates are generally less than one relapse per year.

The data examined in this evidence review do not support the conclusion that the current therapies are likely to result in substantial improvement in a significant proportion of patients with MS. This finding is consistent with expert opinion and demonstrated by the inherent design of current clinical trials, that is, the use of lack of decline in EDSS scores as the primary outcome measure. The present state of therapy is generally regarded as allowing for modest reduction in progression of MS – particularly in the relapsing-remitting patient population – but is not generally expected to result in significant long-term improvement. The rare exception is most likely in patients with relapsing disease who are progressing rapidly and undergo aggressive immunosuppressive therapy.

In general, the studies reviewed were not designed to answer the question we have asked. Indeed, individual patient improvement is not a common expectation of these trials. The authors believe that, despite the relative lack of data, the conclusions from the data examined do reflect the state of the current therapies. We believe that the data available document that individual patient improvement is an uncommon result of the current therapies. Further studies of currently available therapies would be unlikely to yield different conclusions; however, the recent trend of combining treatments in MS could yield different results. Combinations of currently available therapies and new therapies now under investigation may result in greater potential for individual patient improvement in neurological status.

Symptom Management and Improvement (Question 3b)

Treatment aimed at alleviation of symptomatic manifestations of MS, rather than the underlying disease, could have an important role in maximizing functioning among people with MS. Among the six areas we investigated, the degree of impairments and the effectiveness of the treatments varied. We review the conclusions and discuss the limitations and implications for further research by sub-topic below.

Spasticity. Although drugs such as baclofen, diazepam, dantrolene, and tizanidine are often used to reduce spasticity in MS, the research evidence for a beneficial therapeutic effect is inconsistent. This may be due, in part, to measurement issues. Spasticity is a difficult parameter to measure; too much muscle tone interferes with function due to spams and rigidity (resistance to movement); too little muscle tone can also interfere with function due to weakness. In some patients, a certain degree of elevated muscle tone in certain muscle groups can be desirable.

We had additional difficulty in estimating the clinical relevance of improvements that were reported, even when those changes were statistically significant. Many studies that dichotomized patients into "improved" versus "unimproved" failed to provide a definition or threshold of what changes represented "improvement." Nonetheless, the relatively high baseline EDSS scores of patients enrolled in spasticity trials and unimpressive results of treatment suggest that anti-spasticity treatment is unlikely to have a clinically important impact on patients' functional status, and is, thus, unlikely to impact disability determination per se. Furthermore, all of these drugs are limited by poor tolerability at therapeutic doses. Our findings were consistent with another recent systematic review.[204] Better measurement tools may be required in order to confirm the clinical impression that widely used anti-spasticity drugs such as baclofen, tizanidine, and dantrolene are more effective than placebo. Given current measurement

techniques, it is not surprising that active-treatment comparison studies fail to show clinically important differences among these drugs.

Rehabilitation. Physiotherapy interventions failed to influence impairments as measured by EDSS. These interventions were, however, associated with measurable changes in functional status. Improvements in health (handicap) were observed in the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) and several other measures. It is interesting that the historically first randomized controlled trial (RCT) of rehabilitation was not designed to assess the effectiveness of the intervention, but to evaluate whether less costly outpatient rehabilitation was as effective as inpatient rehabilitation.[139] Only more recently have trials been conducted that were designed to assess the value of rehabilitation compared to controls. Except for one study of supervised exercise,[143] the interventions employed in these studies were multifaceted, and it is difficult to attribute beneficial effects to particular components of the interventions. However, three other trials focused on non-physiotherapy interventions, which may be part of a rehabilitation program.[141,146,147] Two of these studies found changes in health measures (SF-36) not unlike those seen in physiotherapy-based rehabilitation interventions; however, these studies did not include measures of impairments or function.

Depression. Depression treatments, including psychotherapy, behavioral therapy, and certain drug therapies, can lead to measurable improvements in mood. There are fewer data linking treatment of depression to improvements in other symptoms (such as fatigue or cognitive impairments) or other outcomes (such as functional status or quality of life). The changes demonstrated in instruments designed to measure depression were not small but, still, the link to improved functional status and, further, to ability to work was not demonstrated in these studies per se. To do so would require extrapolation from studies of treatment of depression in non-MS populations.

Fatigue. Amantadine appears to have some ability to alleviate fatigue in MS, as demonstrated in statistically significant differences in some outcomes in several trials; however, the clinical significance of these effects is likely small. Pemoline has been less often studied and shows results suggesting some effect. There is little support for the efficacy of 4-aminopyridine. Modafinil has shown promising results in phase-II trials,[205] but has not yet been evaluated in a double-blind RCT. Measurement of fatigue is limited by a definition that spans several domains, leading to difficulty with validation. Further research on new pharmacological therapies (such as modafinil) and development of additional data on the validity of instruments for fatigue measurement and their sensitivity to change would be helpful directions for future research.

Voiding dysfunction. Desmopressin was highly effective at reducing urine volume and also consistently effective at reducing urinary frequency. This was demonstrated to translate into improvements in uninterrupted sleep hours and in fewer episodes of incontinence. Physical treatments, including both pelvic floor rehabilitation and use of a handheld vibrator during micturition, were also shown to reduce urinary symptoms compared with control. Only studies of pelvic floor rehabilitation measured impact on symptom-related handicap. These studies showed clear improvements in symptoms, but provided less clear data on how improvements in urinary symptoms impact other areas of health, and no data on how these symptomatic improvements might impact work ability.

Many interventions commonly used for urinary disorders in MS have not been studied in randomized controlled trials of MS patients. Commonly used interventions for which no RCTs have been performed among MS patients include anticholinergic and antimuscarinic drugs,

behavior modification, and intermittent or indwelling urinary catheterization. Data supporting their use comes from trials in other populations or from case reports/series in MS.

Cognitive dysfunction. None of the treatments studied has had a consistent measurable effect on cognitive performance in MS; however, the question has been little studied and indirectly studied, in the sense that most data on cognitive effects are inferred from studies aimed at treatment of fatigue or depression. One study suggested that fatigue symptoms do not correlate with cognitive impairment, although they do correlate with symptoms of depression.[159] Future studies would benefit from more precise delineation of study population based on screening for cognitive performance deficits within a relatively narrow and defined range; this would likely improve the chances of finding a treatment effect and also make clearer the population for whom the results would be applicable.

Association of Clinical Findings with Work Ability (Question 4)

Findings and limitations. There is a significant gap between what is included in the literature and the research evidence using objective measures for determining ability to work. Although objective physical and cognitive measures have been developed, their application in the occupational literature is sparse. Furthermore, assessment of how symptoms such as pain and fatigue impact work ability was essentially absent.

In epidemiologic research we draw conclusions from the body of existing work and never from a single study. There are criteria that aid in the judgment of causality called the Bradford-Hill Criteria,[206] which include strength of association, consistency of findings, temporality, dose-response relationship, biological plausibility, coherence, and specificity. After applying several of these criteria to the pool of information in this review we conclude that the research findings presented here are insufficient to demonstrate that a causal relationship between specific physical and/or cognitive measures and work ability has been established. The reported findings did display some consistency across studies. For example, individuals who had higher EDSS levels or low cognitive function were more likely to report not working. However, the strength of association across these studies was not clearly demonstrated, as most studies reported frequencies or crude estimates of association. Several studies consisted of small sample sizes, which hindered researchers from calculating risk estimates that were adjusted for potential biases such as age, education, level of employer assistance, job type, and desire to work. In addition, most studies considered only physical function or cognitive function, when both can hinder employment. A dose-response relationship of selected functional measures and degree of work capacity was not established. Because the majority of studies were cross-sectional, a temporal relationship between impaired function and inability to work was not established. Impaired function may not have occurred until after the study participants had ceased employment.

Although the bulk of these studies are descriptive in nature, they are useful for generating hypotheses for future studies to examine the causal relationship between impaired function and work ability. Some patterns that are noteworthy and should be considered when designing future studies to examine the risk of inability to work related to impaired function and adverse symptoms are as follows:

- The study outcome of work ability that extended beyond the definition of work status was informative for determining possible vocational rehabilitation potential for moderately to severely disabled individuals.

- As EDSS level increased, the frequency of reporting "not working" also increased. This same pattern was observed for the Hyllested criteria. However, there was considerable overlap between ability to work and EDSS level. Degree of disability or impaired physical function did not solely determine work ability.
- Level of cognitive impairment resulting in work inability was not adequately determined; however, the combination of both physical and cognitive measures proved necessary when assessing ability to work.
- Use of mobility aids and disease subtype as proxy measures for function provided very little information that was useful. Extrapolation of these definitions has the potential to lead to various interpretations, resulting in limited application of findings.
- Individuals with jobs that required less physical exertion were more likely to report remaining employed. These findings supported studies that measured both physical and cognitive function directly.
- The impact of fatigue on work ability was captured only through self-report. Direct measures of fatigue did not appear in the included studies.

In conclusion to the findings presented here it is important to discuss a significant limitation of observational research as it relates to determining if an individual with MS is able to work. Population-based epidemiologic research is useful for determining patterns, trends, and causal relationships between exposures and disease outcomes among groups of individuals, but in prior studies[207,208] researchers have demonstrated that risk factors or combinations of risk factors included in a statistical model serve as poor screening tools at the individual level. In the case of MS, future epidemiologic studies may indicate that certain physical or cognitive function tests are strongly associated with inability to work; however, extrapolation of these findings for the purpose of predicting work ability at the individual is not possible.

Future research. Future research about work ability among individuals with MS can shed a great deal of light on factors that foster or hinder employment. Work ability involves numerous medical and non-medical factors that have been discussed in great detail. In light of the gaps in the current literature, it would be advantageous to design future research endeavors to simultaneously address the following domains:

1) *Objective clinical data:* Collect data on clinical measures, such as disease subtype, that the Social Security Administration (SSA) typically uses when determining disability among individuals with MS. Data collection should be tailored to gather information from medical records that SSA deems relevant to its process.
2) *Physical/cognitive/symptom measures:* Objective measures of physical and cognitive function, as well as symptoms such as fatigue and pain. Consider the tools that have been well established and tested for measuring these types of impairments. As previously noted, the use of well-established tools in the occupational literature has been sparse with regard to MS.
3) *Work ability measures:* The measurement of work ability should be extended beyond the definition of work status to include examination of skill level, education level, career interests, willingness to work, and vocational rehabilitation potential.
4) *Occupational requirements/employer accommodations:* Assess job responsibilities and employer's willingness to provide accommodations in tandem with work ability measures. Current occupational requirements may not match with current level of function.
5) *Demographics:* Age, sex, education level, marital status.

6) *Family responsibilities/support:* Family demographics, income, responsibilities, number of children, and number of elderly parents who need care.
7) *Subjective reports from individuals with MS:* Qualitative information about hindrances and enhancers of work, including characteristics specific to the job or workplace and symptoms related to MS.
8) *Subjective reports from employers:* Qualitative information about how employers are able to provide accommodations and support for workers who have significant and/or intermittent fatigue, pain, and other symptoms related to MS. Gather information about how employers accommodate workers who also have physical and/or cognitive limitations, as well as information about conditions or situations where they cannot provide accommodations.

We suggest that a series of case-control studies be conducted, as well as a prospective cohort. For both these study designs, we suggest that resources already available through MS research centers across the country be used. A recent report by the Institute of Medicine[209] describes certain limitations of research based in MS centers, but indicates that multisite research of this sort is valuable for conducting epidemiologic studies requiring a large number of patients with MS. Conducting a series of studies at several centers in the US could provide consistent evidence across numerous populations and geographic regions. Furthermore, data needed about employment history and disease progression may already be collected for established patients enrolled in ongoing studies. It is recommended that SSA collaborate with the National Multiple Sclerosis Society when selecting sites for this research.

Although it would be ideal to conduct a prospective cohort study for the purpose of establishing a temporal relationship between impaired function and work inability, this could take considerable time and money. We recommend initially a series of case-control studies where cases (defined as individuals with MS who are no longer employed) and controls (defined as individuals with MS who are still employed) are compared on the numerous domains described above. This should provide SSA with more detailed information about the types of clinical measures it currently deems relevant for determining work ability. Sample size was an issue in almost every study included in the review. Sample sizes should be large enough to detect true differences between groups, especially when considering cognitive function. Furthermore, the sample size should be large enough so that subtype of disease can be appropriately considered through stratified analyses. The pattern of disease progression varies between disease subtypes in ways that could influence employment. For example, patients with relapsing-remitting MS may not be able to remain steadily employed because of the erratic and unpredictable nature of disease exacerbations, whereas individuals with primary progressive MS may have a more predictable disease course that does not intermittently interfere with work. Although there is significant overlap of symptoms between the current disease subtypes, ability to work may vary considerably between them.

The case-control studies should be advantageous for examining the timing or sequence of clinical information and physical and cognitive function testing prior to cessation of employment. Demographic information would most likely be available as well. However, information surrounding employment issues, triggers for leaving work, obstacles or enhancers to work, and employers' willingness to help may not be available. In order to capture this information, especially around the time that an individual with MS decides to leave work, we recommend that researchers conduct a prospective cohort study. Incident cases of MS must be captured and followed over time so that changes in physical and cognitive function can be

examined in relation to ability to work. Ideally, incident or fairly recent cases where the individual is still employed should be captured for follow up. As previously indicated, it would be ideal for researchers to build on prospective studies that are already ongoing. Information needed for this study could be added to what is already being collected for other studies.

The qualitative data collected through focus groups, personal interviews, and surveys have proven invaluable for guiding quantitative analyses. Information gathered from individuals with MS, as well as their employers, could provide a great deal of information about the types of accommodations that are useful and effective. Furthermore, companies may struggle with providing accommodations, especially with an individual who has frequent relapses.

Several study limitations have been highlighted in this review, as well as patterns of findings, which should be considered when developing future research. Future studies that consider the multiple factors influencing work can lead to generating unbiased risk estimates of inability to work among individuals with MS. In the development phase of these studies, it is imperative that SSA be involved in determining the types of data to be collected. Data collection should reflect the information that SSA deems important when making decisions about ability to work.

Findings in the context of other literature on work and MS. Several of the studies included in this review reported findings or trends about their study populations that reflect what is already known or established in the literature about issues surrounding employment independent of MS and vice-versa.

The onset of MS occurs between ages 15 to 50 years for approximately 90 percent of cases.[210] Thus, MS strikes individuals during peak years of education, training, and employment. Labor market analyses by the Bureau of Labor Statistics[211] reported that, in general, higher levels of education enhance labor force participation, and severely disabled individuals are more likely to participate in the labor force if they have a college degree (57 percent) compared to disabled individuals with less than 4 years of high school (17.3 percent), high school completion (31.2 percent), and some college (39.1 percent).[211]

The incidence of disease is twice as high among women as among men.[195] MS impacts women not only during peak years of employment, but also during peak reproductive and childbearing years. Attachment to the workforce among first-time pregnant women in the US is influenced by several factors including age, education, years of work experience, and whether or not they were employed and established in their careers prior to the onset of pregnancy.[212] The domestic responsibilities that follow pregnancy influence employment as well: compared to unmarried women without children, both married mothers and single mothers commit far fewer hours to the workforce (although the differences have declined significantly over the past two decades).[213] Some of the studies included here concurred with these findings in that women reported leaving work for reasons unrelated to MS, but related to domestic responsibilities.[191] It can be especially challenging to distinguish between the impact of MS and the responsibilities of childrearing among women when examining ability to work. Some studies recognized these sex differences by controlling for them in their analyses.[183,186,187]

Symptoms associated with MS vary between individuals, but can include fatigue, ataxia, dementia, optic neuritis, bladder urgency and incontinence, spasticity, pain, and sexual dysfunction.[195] As reported above, fatigue was the most common reason individuals with MS reported ceasing employment;[177] however, fatigue, like pain, is very subjective and difficult to measure (see discussions of Question 3b in this and previous chapters).

The importance of employer involvement in providing accommodations for disabled individuals was nationally endorsed in 1990 with the enactment of the Americans with

Disabilities Act (ADA). In an earlier study by Mitchell (1981)[214] two-thirds of male postal workers with MS received work accommodations with respect to their MS related work capacity, which enabled them to remain at work. With the ADA in place for more than a decade, and MS representing the third most common neurological diagnosis that SSA receives,[1] the paucity of information in the literature about how employers have enabled individuals with MS to remain at work exists is unfortunate.

Environmental Factors and Work Ability (Question 5)

Current clinical wisdom about thermal sensitivity in some MS patients is based not on large controlled research studies but rather on a combination of many decades of clinical observations, case reports, small trials of thermal challenge outcomes, and reports of beneficial therapeutic effects of body cooling. The present report, while not directly addressing the question, provides no basis for rejecting such clinical observations that excessive heat can have an adverse temporary effect on the well-being and symptoms of some MS patients.

With regard to work impairment, limitation, or disability related to temperature conditions, we found remarkably little research that met our inclusion criteria. This should probably not be surprising. The difficulties of conducting population-based research on work capacity in patients with MS are reflected in the discussion of Question 4. Given this reality, researching temperature as an independent determinant of functional capacity would be particularly challenging.

There remain important questions about what proportion of MS patient populations may be thermo-sensitive, to what degree, and why?[197,200] As to temperature sensitivity significant enough to impede work, this report found only one includable report.[182] This study has significant limitations in its generalizabililty to a Social Security Disability Insurance (SSDI) applicant pool due to a number of issues, including the fact that the assessment of thermal sensitivity was completely subjective. The low percentage of respondents citing thermal factors in this study suggests that exposure to heat is not among major perceived critical job demands.

Of interest, there is little or no report of thermal factors in other studies that might have identified perceptions of workplace temperature[193] or self-reported thermal sensitivity[177,185,192] as variables that impede work or affect employment status.

It is possible that most MS research has focused at a more primary symptom level (e.g., affective lability, numbness, speech, fatigue, cognition, ambulation, vision, incontinence) without addressing more subtle factors, such as temperature, that may exacerbate symptoms. Forced-choice questionnaires, for example, may not include an option to report thermal sensitivity.[179]

We conclude that answers to Question 5 remain mostly unknown. The evidence provides no basis for generalizations such as maximum appropriate working temperature levels unique to MS patient populations. The one included report confirmed that some MS patients perceive heat to impede their work capacity. It is not likely that medical data in SSDI application files in the current era will include objective diagnostic test results identifying MS patients who respond adversely to heat challenges.[215] However, subjective patient reports may describe such associations with or without clinician comment or correlation with objective clinical status measures. Although not necessarily founded on randomized controlled trial data, current clinical impression seems to hold that ambient and/or exercise-induced body temperature effects may

bear a relationship to MS symptom status in some patients, perhaps more so than is thought to be the case for chronic disease states in general.

Knowledge Gaps and Future Research Recommendations

This report has identified several gaps in current knowledge that can direct future research. Regarding diagnosis of MS, the available studies evaluating the validity and reliability of the recent McDonald criteria,[5] though few in number, are strong and consistent. The evidence reviewed suggests that diagnosis of MS using MRI data as implemented in the McDonald criteria has good validity compared with ultimate clinical diagnosis; further research is needed on the prognosis of patients diagnosed with MS using McDonald criteria, especially with regard to the ability of clinical or radiographic features to predict clinical outcomes.

Regarding prognostic studies, most studies report prognosis over long periods of time, over which MS shows inexorable progression. Shorter-term studies demonstrate a high degree of variability, and few factors seem to predict near-term prognosis. Studies of prognosis are needed that focus on the early disease course (an inception cohort) defined by McDonald criteria; such studies may be more fruitful at identifying prognostic factors than previous research has been. Data of this sort may be most efficiently gathered in the course of disease-modifying treatment trials, which are also a high priority in this population.

Regarding treatment issues, while differences in relapse rates and EDSS scores between control groups and groups receiving disease-modifying agents have been modest, reductions in disease activity as measured by MRI have been marked; the long-term significance of this reduction is not yet clear. Whether the failure to show differences in clinical outcomes is a limitation of the EDSS, the efficacy of the experimental agents, or the follow-up time is uncertain. Further treatment studies are needed that (1) target earlier disease (as diagnosed by McDonald criteria) and (2) are large enough and long enough to correlate MRI response with clinical response. Furthermore, while disease-modifying drug treatment trials have focused on physical function outcomes, this choice of outcome measure may preclude evaluating whether these treatments prevent or slow the development of cortical atrophy, which may correlate better with disability in MS.

Regarding symptomatic treatment issues, of the six symptomatic areas we explored, several were well covered. Spasticity drug treatments have been well studied, although the clinical relevance of the major outcome measure used in these studies, the Ashworth Scale, has been questioned. Further research on spasticity should be directed at evaluating functional status outcomes rather than muscle tone outcomes; and while drug treatments may be important, greater attention should be directed toward physical therapy, rehabilitation, and behavioral approaches instead of, or in addition to, drug treatments.

Treatment of fatigue has also focused on drug treatments, which have been largely unsuccessful. A new drug agent, modafinil, is currently under study, and may prove more useful; however, further research in non-drug approaches instead of, or in addition to, drug treatment may be necessary.

Mental and psychological functioning in MS has rarely been the target in intervention trials, although mood and cognitive disorders have been shown to be prevalent in MS. Further attention is warranted toward measurement of these impairments with the goal of developing

outcome measures for disease-modifying drug treatment trials or symptom-directed intervention trials.

The major clinical interventions in urinary management in MS were little studied in MS patients specifically; it is unclear whether further research on groups of subjects with MS would be fruitful.

Regarding ability to work, this report highlights significant evidence and information gaps concerning:

- patterns of MS patient reports regarding functional limitations;
- information commonly collected in medical encounters with MS patients (and therefore available to SSA);
- knowledge about the impact on performance of specific work tasks of commonly objectified parameters such as coordination, strength, and vision, and especially of factors such as fatigue or cognitive dysfunction, which are either difficult to measure or are less commonly assessed in detail; and
- effective research methods for categorizing job or task demands in such a way as to isolate those demands that are likely to be "critical" for an SSDI applicant with MS.

In the context of these gaps, it may be productive to pursue research approaches that simultaneously address four domains:

- subjective reports (this domain is not sufficient alone for SSDI determination purposes);
- objective clinical data (ideally of the sort commonly encountered in medical records);
- in-depth objective measures (which may be available and not widely applied clinically, but which may be used with subsets of subjects to explore correlation with other domains); and
- work status measures (ideally longitudinal, with stratifications based on work demands).

Such an approach may apply to thermal sensitivity as well, with some additional specification and focus. Parallel assessment of concomitant ambient temperature, physical exertion, and core body temperature would address key relevant physiological exposure factors. Outcome measures could include the domains outlined above, for example:

- self-perceived well-being and level of symptoms such as fatigue;
- clinical parameters such as walking speed or muscle strength;
- in-depth measures such as potentially associated biomarkers or physiological parameters;[199,200] and
- work status measures, including absenteeism and disability benefits use.

Obviously, considerable caution would be required for subject safety related to heat exposure.[216,217] Such a research approach would be relatively complex and expensive, but might provide relevant information in the arenas of basic science and clinical care, and to a broad range of agencies, employers, and insurers dealing with MS work capacity issues.

Generating research results of practical relevance to SSA would, in some ways, be an even more demanding goal. The range of potential job situations in question for SSDI determinations always has the potential to extend beyond the claimant's own or previous occupation to a wide range of substantial gainful employment possibilities.[218] Heat exposure may well be an MS-related critical job demand in the context of various degrees of outdoor physical labor in warm climates. However, it seems likely that less physically demanding work in temperature-controlled job environments would frequently be the relevant job capacity circumstance by which SSDI applications were ultimately determined. Therefore, it may be necessary to use a narrower range of exposure and outcome variables in order to address the actual questions that might arise in the SSDI process. Such restrictions may limit a study's power to demonstrate

associations or effects. The likely value to SSA of such an effort may well be influenced by an awareness of the frequency of and the particular circumstances surrounding SSDI determination situations in which thermal sensitivity is a critical determinant of the process outcome. Historical SSDI information may shed light on those particular permutations of ambient workplace temperature and physical demands that have commonly represented a critical or significant question in SSDI determinations.

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Table 1. Results of title-and-abstract screening and full-text article review

Articles identified:	1487
Abstracts:	
Included	739
Excluded	748
Full-text articles:	
Included	168
Excluded	571

Table 2. Included full-text articles by research question

Question 1a *(diagnostic reliability of McDonald criteria)*	13
Question 1b *(inter-rater reliability of diagnosis with McDonald and Poser criteria)*	2
Question 2 *(predictors of physical and mental impairments at 12 months)*	12
Question 3a *(disease-modifying therapies and long-term improvement)*	51
Question 3b *(symptom management and improvement)*	68
Question 4 *(association of clinical findings with work ability)*	22
Question 5 *(environmental factors and work ability)*	1
Total	168*

* Note: One article was included for both Question 4 and Question 5

Table 3. Data supporting the validity of MRI components of the McDonald criteria

Study	Diagnosis	Time to diagnosis of CDMS	Para-clinical test(s)	Findings associated with CDMS	Proportion developing CDMS	SN	SP
Barkhof et al. 1997[22]	CIS	Median follow up (with range): 9 mo (1-48 mo) for patients with CDMS (n = 33); 39 mo (23-96 mo) for patients without CDMS (n = 41)	MRI	No. of T2 lesions ≥ 9 No. of abnormal MRI criteria:* 0 1 2 3 4 Specific MRI criteria: Final model Paty et al. 1988[35] Fazekas et al. 1988[36]	24/30 (80%) 16% 11% 54% 75% 87%	73% 82% 88% 88%	80% 78% 54% 54%
Brex et al. 2001[23]	CIS	1-year follow up (n = 68)	MRI	T2 lesions Enhancing lesions T2 lesion at baseline and new T2 lesion Enhancing lesion at baseline and new enhancing lesion	16/48 (33%) 11/21 (52%) 15/27 (56%) 7/10 (70%)	89% 61% 83% 39%	36% 80% 76% 94%
CHAMPS Study Group 2002[24]	CIS	18-month follow up (n = 190)	MRI	No. of T2 lesions: 2-4 5-8 9-12 13-21 22-34 > 35 No. of enhancing lesions: 0 1 > 1 > 2	 20% 15% 33% 33% 26% 20% 23% 33% 43% 52%		
Comi et al. 2001[25]	CIS	2 years (n = 241)	MRI	No. of T2 lesions: 0-8 > 8	NR (OR, 3.64; 95% CI, 1.3 to 10.2; p = 0.014)		

Table 3. Data supporting the validity of MRI components of the McDonald criteria (continued)

Study	Diagnosis	Time to diagnosis of CDMS	Para-clinical test(s)	Findings associated with CDMS	Proportion developing CDMS	SN	SP
Filippi et al. 1994[28]	CIS	Mean follow up, 63 months (n = 89)	MRI	Initial MRI normal Initial lesion load > 1.23 cm^3 Initial MRI abnormal, but lesion load < 1.23 cm^3	2/32 (6%) 19/21 (90%) 17/31 (55%)		
Morrissey et al. 1993[30]	CIS	5-year follow up (n = 89)	MRI	No. of lesions: 0 1 2-3 4-10 > 11	 2 (6%) 1 (17%) 12 (67%) 12 (92%) 16 (80%)		
Optic Neuritis Study Group 2001[32]	Optic Neuritis	5-year follow up (n = 388)	MRI	No. of lesions: 0 1 2 > 3	 16% 44% 26% 51%		
O'Riordan et al. 1998[31]	CIS	10-year follow up (n = 81)	MRI	No. of asymptomatic lesions at baseline MRI: 0 1 2-3 4-10 > 10	 3/27 (11%) 1/3 (33%) 14/16 (87%) 13/15 (87%) 17/20 (85%)		
Sastre-Garriga et al. 2003[33]	CIS (brainstem syndrome)	12-month follow up (n = 51)	MRI CSF EPs	Abnormal MRI Abnormal CSF-OCB Abnormal EPs Specific MRI criteria: Paty et al. 1988[35] Fazekas et al. 1988[36] Barkhof et al. 1997[22]	17/46 (37%) 11/25 (44%) 10/29 (34%) 16/32 (50%) 16/33 (48%) 14/27 (52%)	94% 100% 89% 89% 78%	42% 42% 52% 48% 61%

*Abnormal MRI criteria: ≥ 1 gadolinium-enhancing lesions, ≥ 1 juxtacortical lesions, ≥ 3 periventricular lesions, and ≥ 1 infratentorial lesions.

Abbreviations: CDMS = clinically definite multiple sclerosis; CI = confidence interval; CIS = clinically isolated syndrome; CSF = cerebrospinal fluid; EPs = evoked potentials; mo = month(s); MRI = magnetic resonance imaging; No. = Number; OCB = oligoclonal bands; OR = odds ratio; SN = sensitivity; SP = specificity

Table 4. Studies validating the McDonald criteria

Study	Diagnosis	Time from onset of symptoms	Time to diagnosis of CDMS	Sensitivity	Specificity	PPV	NPV	Accuracy
Dalton et al. 2002[27]	CIS	3 months (n = 79)	1 year	0.73	0.87	0.58	0.93	0.84
		1 year (n = 50)	3 years	0.94	0.83	0.77	0.96	0.87
Tintoré et al. 2003[34]	CIS	1 year (n = 86)	49 months (mean follow up)	0.74	0.86	NR	NR	0.80

Abbreviations: CDMS = clinically definite multiple sclerosis; CIS = clinically isolated syndrome; NPV = negative predictive value (predictive value of a negative test result); NR = not reported; PPV = positive predictive value (predictive value of a positive test result)

Table 5. Kappa statistics for multiple raters using Poser and McDonald criteria

Poser criteria		**McDonald criteria**	
Diagnosis of MS (all categories):	0.57	Diagnosis of MS (all categories):	0.57
Clinically definite MS:	0.39	MS:	0.57
Clinically probable MS:	0.37	Possible MS:	0.49
Dissemination in time:	0.69	-	
Dissemination in space:	0.46	-	

Abbreviation: MS = multiple sclerosis

Table 6. Relapse rate outcomes from placebo-controlled RCTs of disease-modifying therapies

Study	Therapy	Relapse rate parameter	Active	Placebo	Difference	P-value
Achiron et al. 1998[53]	IV IgG	ARR:				
		Baseline	1.85	1.55	0.30	0.34
		Year 1	0.75	1.80	1.05	0.0002
		Year 2	0.42	1.42	1.0	0.0009
Fazekas et al. 1997a[63] Fazekas et al. 1997b[64]	IV IgG	ARR:				
		Year 1	0.49	1.30	0.81	0.011
		Year 2	0.42	0.83	0.41	0.006
Cohen et al. 2002[59]	IFNβ-1a	ARR	0.20	0.30	0.10	0.008
Jacobs et al. 1996[76] Rudick et al. 1997[97] Fischer et al. 2000[65] Jacobs et al. 2000[75] Rudick et al. 2000[96]	IFNβ-1a	ARR	0.67	0.82	0.15	0.04
SPECTRIMS Study Group 2001[100]	IFNβ-1a	ARR	0.50	0.71	0.21	0.001
European Study Group on Interferon beta-1b in Secondary Progressive MS 1998[62]	IFNβ-1b	ARR	0.44	0.64	0.20	0.0002
IFNB Multiple Sclerosis Study Group 1993[72] IFNB Study Group 1995[73] IFNB Study Group 1996[74] Pliskin et al. 1996[92]	IFNβ-1b	ARR:				
		Year 1	0.96	1.44	0.48	
		Year 2	0.85	1.18	0.33	
		Year 3	0.66	0.92	0.26	
		Year 4	0.67	0.88	0.21	
		Year 5	0.57	0.81	0.24	
PRISMS Study Group 1998[93] Liu et al. 1999[82] Liu et al. 2002[84] Patten et al. 2001[89]	IFNβ-1a	Relapse rate, not annualized, ~ 2 years	1.73	2.56	0.83	
Bastianello et al. 1994[54]	Mitoxantrone	Mean RR	0.54	1.67	1.13	0.014
Millefiorini et al. 1997[86]	Mitoxantrone	No. of relapses	0.89	2.62	1.73	0.0002
Johnson et al. 1995[78] Weinstein et al. 1999[103] Liu et al. 2000[83] Johnson et al. 1998[77]	Glatiramer	ARR	0.59	0.84	0.25	NR
Goodkin et al. 1991[68]	Azathioprine	ARR:				
		Year 1	0.74	1.17	0.43	0.16
		Year 2	0.30	0.79	0.49	0.05
Romine et al. 1999[95]	Cladribine	Relapse rates, annualized (?)	0.77	1.67	0.90	NR

Abbreviations: ARR = annual relapse rate; IFNβ-1a = interferon β-1a; IFNβ-1b = interferon β-1b; IV IgG = intravenous immunoglobulin-G; No. = Number; NR = not reported; RCTs = randomized controlled trials; RR = relapse rate

Table 7. Improvements in physical function (EDSS) in placebo-controlled RCTs of disease-modifying therapies

Study	Therapy	Definition(s) of improvement (change in EDSS)	Active	Placebo	Difference
Achiron et al. 1998[53]	IV IgG	-1.0 point over 2 years	31%	14%	17%
Fazekas et al. 1997a[63] Fazekas et al. 1997b[64]	IV IgG	-1.0 point over 2 years	31%	14%	16%
Cohen et al. 2002[59]	IFNβ-1a	Improvement not defined	7.5%	7.3%	0.2% (NS)
Jacobs et al. 1996[76] Rudick et al. 1997[97] Fischer et al. 2000[65] Jacobs et al. 2000[75] Rudick et al. 2000[96]	IFNβ-1a	-1.0 point (not sustained) -0.5 point (not sustained) -1.0 point (sustained) -0.5 point (sustained)	19.3% 15.7% 18.2% 25.5%	11.5% 11.5% 8.9% 16.1%	8.2% 4.2% 9.7% 9.4%
Patti et al. 1999[90]	nIFNβ	-0.5 or -1.0 point: Relapsing-remitting Secondary progressive	 52% 40%	 3% 5%	 49% 35%
Johnson et al. 1995[78] Weinstein et al. 1999[103] Liu et al. 2000[83] Johnson et al. 1998[77]	Glatiramer	-1.0 point: 2-year trial Extension trial	 24.8% 27.2%	 15.2% 15.0%	 9.6% 12.2%
Bornstein et al. 1987[55]	Glatiramer	-1.0 point over 2 years -2.0 points over 2 years -3.0 points over 2 years	20.0% 12.0% 0	8.7% 0 4.4%	11.4% 12.0% -4.4%
Ghezzi et al. 1989[67]	Azathioprine	Improvement not defined: Relapsing Relapsing-progressive	 16% 5%	 0 7%	 16% (NS) -2% (NS)
Goodkin et al. 1991[68]	Azathioprine	Improvement on EDSS or 9HPT	22.2%	20%	2.2%
van de Wyngaert et al. 2001[102]	Mitoxantrone	Improvement not defined	35%	22%	13% (NS)
Canadian Cooperative Multiple Sclerosis Study Group 1991[58]	Cyclo-phosphamide	-1.0 point sustained for: 1 year 2 year Final	 6% 6% 4%	 2% 0 2%	 4% 6% 2%
Canadian Cooperative Multiple Sclerosis Study Group 1991[58]	Plasma exchange	-1.0 point sustained for: 1 year 2 year Final	 8% 3% 2%	 2% 0 2%	 6% 3% 0
Khatri et al. 1985[80]	Plasma exchange	> 1.0 point at 11 months: ≥ 3 points 2 points 1 point	 10% 13% 13%	 0 3% 14%	 10% 10% -1%

Abbreviations: 9-HPT = 9-Hole Peg Test; EDSS = Expanded Disability Status Scale; IFNβ-1a = interferon β-1a; IV IgG = intravenous immunoglobulin-G; nIFNβ = natural interferon-β; NS = not statistically significant; RCTs = randomized controlled trials

Table 8. Randomized controlled trials of symptomatic treatments for spasticity

Treatment	Study	Baseline EDSS	No. of patients started (completed)	Outcomes/Results
Baclofen PO (to 80 mg/d) vs. Placebo *Crossover*	Feldman et al. 1978[109]	NR	33	Spasm frequency ($p < 0.05$) Resistance to movement ($p < 0.05$) Clonus (knee) ($p < 0.001$) Ambulation (p = NS) Transfer activity (p = NS) Spastic limb pain (p = NS) Use of spastic limb (p = NS) Functional assessment (Barthel) (p = NS)
Baclofen PO (to 80 mg/d) vs. Placebo	Sachais et al. 1977[129]	NR	166 (106)	Flexor spasm severity ($p < 0.02$) Ankle clonus (p = NS) ADL (p = NS) Overall disability (p = NS)
Baclofen PO (to 45 mg/d) vs. Placebo *Crossover*	Ørsnes et al. 2000[124]	5.0 (median) 3.5-6.0 (range)	14	Voluntary power (0-5 scale) (p = NS) Ashworth Scale (p = 0.33) Tendon reflexes (p = 0.14) EDSS & Ambulation Index (p = NS) NRS (p = NS) MSIS (p = NS)
Baclofen PO (to 80 mg/d) vs. Placebo	Levine et al. 1977[117]	NR	19 (18)	Ashworth Scale (p = NS)
Baclofen PO (to 60 mg/d) vs. Placebo *Crossover*	Sawa et al. 1979[130]	NR	21 (18)	Muscle tone (p = NR)
Baclofen PO (to 20 mg/d) vs. Stretching exercises + baclofen vs. Stretching exercises vs. Placebo *Crossover*	Brar et al. 1991[105]	NR	38 (30)	Spasticity: Cybex flexion scores ($p < 0.05$; baclofen and combination vs. placebo) Ashworth Scale ($p = 0.1$; combination vs. placebo) Self-rated questionnaire of functional abilities (p = NR)
Baclofen intrathecal vs. Placebo *Crossover*	Penn et al. 1989[125]	NR	20 (10 MS)	Ashworth Scale ($p < 0.0001$) Spasm score ($p < 0.0005$)
Tizanidine PO (to 36 mg/d) vs. Placebo	Smith et al. 1994[133]	NR	257 (159)	Ashworth Scale (p = 0.46) Spasm response (p = 0.03) Clonus response (p = NS)
Tizanidine PO (to 36 mg/d) vs. Placebo	UK Tizanidine Trial Group 1994[137]	NR	187 (155)	Ashworth Scale ($p < 0.004$) Spasm frequency (p = NS) Muscle strength (p = NS) EDSS (p = NS) Tendon reflexes Intermediate motor skills (p = NS) Upper limb function (p = NS) Impact on physical therapy (p = NS) Impact on nursing care (p = 0.09)

Table 8. Randomized controlled trials of symptomatic treatments for spasticity (continued)

Treatment	Study	Baseline EDSS	No. of patients started (completed)	Outcomes/Results
Gabapentin PO 2700 mg vs. Placebo *Crossover*	Cutter et al. 2000[107]	6.0-9.0 (range)	22 (21)	Spasm frequency scale (p = 0.0001) Spasm severity scale (p = NS) Interference with function scale (p = 0.02) Painful spasm scale (p = NS) Global assessment scale (p = 0.003) Modified Ashworth Scale (p = 0.0005) EDSS (p = NS)
Gabapentin PO 400 mg vs. Placebo *Crossover*	Mueller et al. 1997[121]	NR	15	Visual Faces Scale rating of pain and spasticity (p = 0.008) Ashworth Scale (p = 0.007) Clonus (p = 0.1) Reflex withdrawal to pain (p = NS) EDSS (p = 0.03)
Dantrolene PO (to 350 mg/d) vs. Placebo *Crossover*	Gambi et al. 1983[111]	NR	24 (22)	Hip flexor movement (p = NS) Spasticity scale (p < 0.05) Muscular strength (p = NS) Clonus (p = NS) Knee and ankle tendon reflexes scale (p = NS)
Delta-9-THC vs. Cannabis sativa extract vs. Placebo	Zajicek et al. 2003[138]	NR	630 (611)	Muscle tone (p=0.4) Pain (p=0.003; favoring active treatments) Subjective spasticity (p=0.01) 10-meter walk (p=0.015; favoring delta-9-THC)
Delta-9-THC vs. Cannabis sativa extract vs. Placebo *Crossover*	Killestein et al. 2002[115]	6.2 ± 1.2 (mean ± SD)	16	MSFC score (p = 0.09; favoring placebo) 9-HPT (p = 0.02; favoring placebo) EDSS (p = NS) Muscle tone (p = NS) SF-36 mental health subscale (p = 0.02) and psychological status domain (p = 0.02) Other parameters (p = NS)
Progabide PO (to 45 mg/kg/d) vs. Placebo *Crossover*	Rudick et al. 1987[128]	6.3 ± 1.7 (mean ± SD)	32 (25)	Ashworth Scale (p < 0.01) EDSS (p = NS) 8-meter walk (p = 0.62) Spasm frequency (p = 0.28) Reflex scores (p = 0.20) Strength (p = 0.77) Various functional tasks (p = NS)
Progabide PO (14.3-32.7 mg/kg/d) vs. Placebo *Crossover*	Mondrup et al. 1984[119,120]	NR	17 (14)	Spasticity (0-4 scale) (p < 0.01) Spasms (p < 0.01) Reflex response (p < 0.01, patellar; p = NS, Achilles) Flexor reflexes (p = NS) Muscle strength (p = NS) Spasm frequency (p < 0.05) Spasm pain (p = NS)

Table 8. Randomized controlled trials of symptomatic treatments for spasticity (continued)

Treatment	Study	Baseline EDSS	No. of patients started (completed)	Outcomes/Results
Botulinum toxin IM vs. Placebo	Hyman et al. 2000[114]	7.5 (median [estimated])	74 (60)	Hip abduction (p = NS) Modified Ashworth Scale (p = NS) Spasm frequency (p = NS) Hygiene assessment (p = NR)
Botulinum toxin IM vs. Placebo *Crossover*	Snow et al. 1990[135]	8.0-9.5 (range)	10 (9)	Spasticity score (Ashworth Scale + spasm frequency) (p = 0.009) Hygiene score (p = 0.02)
Threonine PO (7.5 g/d) vs. Placebo *Crossover*	Hauser et al. 1992[112]	4.7 ± 1.5 (mean ± SD)	26 (21)	Spasticity (clinician scale) (p = 0.04) Spasticity (patient scale) (p = 0.18)
Threonine PO 6 g/d vs. Placebo *Crossover*	Lee et al. 1993[116]	7.4 (mean) 2-9 (range)	41 (33)	Spasticity score (based on Ashworth) (p = NR) Barthel Index (p = NS) EDSS (p = NS)
Electrical neuromuscular stimulation vs. Sham stimulation	Livesley 1992[118]	NR	40 (39)	Spasticity, active movement, and function (p = NS) Subjective evaluation (p = NR)
Magnetic stimulation vs. Sham stimulation	Nielsen et al. 1996[123]	NR	38	Ashworth Scale (p = NR) Tendon reflexes (p = NR) Patient's self-score for ease of daily activities (p = NS)
Tizanidine PO (to 32 mg/d) vs. Baclofen PO (to 80 mg/d) *Crossover*	Bass et al. 1988[104] Rice 1989[126]	NR	66 (48)	Spasticity (6-point ordinal scale) (p = NS) Strength (7-point ordinal scale) (p = NS) EDSS (p = NS) Pedersen functional disability scale (p = NR) Overall evaluation (patient, clinician) (p = NR)
Tizanidine PO (to 36 mg/d) vs. Baclofen PO (to 80 mg/d)	Smolenski et al. 1981[134]	NR	21	Muscle strength (p = NR) Ashworth Scale (p = NR) Spasms scale (p = NR)
Tizanidine PO (to 24 mg/d) vs. Baclofen PO (to 60 mg/d)	Eyssette et al. 1988[108]	NR	100	Flexor spasms (p = NS) Muscle tone (p = NS)
Tizanidine PO (to 24 mg/d) vs. Baclofen PO (to 60 mg/d) *Crossover*	Hoog-straten et al. 1988[113]	6.1 ± 0.8 (mean ± SD)	16 (11)	Ashworth Scale (p = NS) EDSS (p = NS) Functional systems (p = NS) Isometric strength (p = NS)
Tizanidine PO (to 16 mg/d) vs. Baclofen PO (to 40 mg/d) *Crossover*	Newman et al. 1982[122]	NR	36 (26)	Ashworth Scale (p = NS) EDSS (p = NS) Pedersen functional disability scale (p = NS)

Table 8. Randomized controlled trials of symptomatic treatments for spasticity (continued)

Treatment	Study	Baseline EDSS	No. of patients started (completed)	Outcomes/Results
Tizanidine PO (to 35 mg/d) vs. Baclofen PO (to 90 mg/d)	Stien et al. 1987[136]	NR	40 (38)	Ashworth Scale (p = NS) EDSS (p = NS) Pedersen functional disability scale (p = NS) Overall evaluation (p = NS)
Tizanidine PO (to 18 mg/d) vs. Diazepam PO (to 22.5 mg/d)	Rinne 1980[127]	NR	30 (26)	Ashworth Scale (p = NS)
Baclofen PO (30-60 mg/d) vs. Diazepam PO (15-30 mg/d) *Crossover*	Cartlidge et al. 1974[106]	NR	40 (34)	Ashworth Scale (p = NS) Subjective impression (p = NS)
Baclofen PO (30-120 mg/d) vs. Diazepam PO (10-40 mg/d) *Crossover*	From et al. 1975[110]	NR	17	Ashworth Scale (p = NR) Spasms (p = NS) Clonus (p = NS) Urine retention, incontinence (p = NR) Walking (p = NR)
Dantrolene PO (25 or 75 mg, 4 times per day) vs. Diazepam PO (to 2 or 5 mg, 4 times per day) *Crossover*	Schmidt et al. 1975[131,132]	5.5 (mean)	46 (42)	10- item exam evaluating spasticity, clonus, hyperreflexia, muscle stiffness, cramping (p = NR) Subjective evaluation (p = NR)

Abbreviations: 9-HPT = 9-Hole Peg Test; ADL = activities of daily living; d = day(s); EDSS = Expanded Disability Status Scale; g = gram(s); IM = intramuscular; kg = kilogram(s); mg = milligram(s); MRD = Minimal Record of Disability; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; MSIS = MS-Impairment Scale; No. = Number; NR = not reported; NRS = Neurologic Rating Scale; NS = not statistically significant; PO = per os (by mouth); SD = standard deviation; SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey; THC = tetrahydrocannabinol

Table 9. Randomized controlled trials of rehabilitation interventions

Treatment	Study	Baseline EDSS	No. of patients started (completed)	Outcomes/Results
Inpatient rehab (3 mo) vs. Outpatient rehab	Francabandera et al. 1988[139]	NR	84 (73)	ISS ($p < 0.05$) Need for home assistance ($p = 0.17$)
Inpatient rehab (20 d) vs. Wait-list control	Freeman et al. 1997[140]	6.5 (median) 5-9 (range)	70 (66)	EDSS (p = NS) FIM motor score ($p < 0.001$) LHS ($p = 0.01$)
Inpatient rehab (3 wk) vs. Home exercise program	Solari et al. 1999[145]	5.5 (median) 3-7 (range)	50 (45)	FIM ($p < 0.01$) EDSS (p = NS) SF-36 (p = NS)
Outpatient rehab (6 wk) vs. Self-exercise treatment	Patti et al. 2002[142]	6.2 (mean) 4-8 (range)	111 (106)	Fatigue Impact Scale ($p < 0.001$) EDSS (p = NS) SET ($p < 0.001$) BDI ($p < 0.001$) SF-36 ($p < 0.05$ on all subscales)
Home PT (8 wk) vs. Outpatient PT vs. No PT *Crossover*	Wiles et al. 2001[148]	6.0 (median) 4-6.5 (range)	42 (40)	Rivermead mobility index ($p < 0.001$, each active treatment vs. control) Balance time ($p = 0.004$; $p = 0.001$) Walk A ($p < 0.003$; $p = 0.002$) 9-HPT ($p = 0.01$; $p = 0.08$) Global mobility ($p < 0.001$; $p < 0.001$)
Supervised exercise (15 wk) vs. No treatment	Petajan et al. 1996[143]	3.4 ± 1.0 (mean $\pm$ SD)	54 (46)	FSS (p = NS) SIP physical dimension subscale ($p < 0.05$) EDSS (p = NS) ISS (p = NS) VO_{2max} ($p < 0.01$) POMS (p = NS)
Home-based management (rehab, nursing, education, psychological support, social services) vs. Usual care	Pozzilli et al. 2002[144]	5.9 ± 1.5 (mean $\pm$ SD)	201 (188)	FSS (p = NS) FIM (p = NS) SF-36 ($p < 0.05$ for bodily pain, general health, social function and emotional role subscales, and physical and mental component scores) EDSS (p = NS) MMSE (p = NS) STAXI (p = NS) STAI (p = NS) CDQ ($p = 0.11$)
Professionally guided self-care vs. No treatment	O'Hara et al. 2002[141]	NR	183 (169)	SDDR subscale O ($p = 0.6$) SDDR subscale E ($p = 0.04$) SF-36 ($p < 0.05$ on mental health and vitality subscales)
Education in health behaviors and lifestyle change vs. Usual care	Stuifbergen et al. 2003[146]	NR	142 (113)	SF-36 ($p < 0.05$ for bodily pain and mental health subscales) Self-efficacy ($p < 0.01$) Barriers scale (p = NS) PRQ (p = NS) HPLP-II ($p < 0.01$)

Table 9. Randomized controlled trials of rehabilitation interventions (continued)

Treatment	Study	Baseline EDSS	No. of patients started (completed)	Outcomes/Results
Multifaceted outpatient intervention (educational, behavioral) vs. Usual care	Wassem et al. 2003[147]	3.4 (mean) 0-9 (range)	27 (16)	Fatigue (p = 0.09) Sleep disturbance (p = 0.07) Pain (p = NS) Sum of symptom severity (p = 0.03) SEAB (p = 0.55) PAIS-SR (p = 0.72)

Abbreviations: 9-HPT = 9-Hole Peg Test; BDI = Beck Depression Inventory; CDQ = Clinical Depression Questionnaire; d = day(s); EDSS = Expanded Disability Status Scale; FIM = Functional Independence Measure; FSS = Fatigue Severity Scale; HPLP-II = Health Promoting Lifestyle Profile-II; ISS = Incapacity Status Scale; LHS = London Handicap Scale; MMSE = Mini Mental State Examination; mo = month(s); No. = Number; NR = not reported; NS = not statistically significant; PAIS-SR = Psychosocial Adjustment to Illness Scale-Self-Report; POMS = Profile of Mood States; PRQ = Personal Resources Questionnaire; PT = physiotherapy; SD = standard deviation; SDDR = Standard Day Dependency Record; SEAB = Self-Efficacy for Adjustment Behaviors Scale; SET = Tempelaar Social Experience Checklist; SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey; SIP = Sickness Impact Profile; STAI = State-Trait Anxiety Inventory; STAXI = State-Trait Anger Expression Inventory; VO_{2max} = maximum oxygen consumption with exercise; wk = wk(s)

Table 10. Randomized controlled trials of treatments for depression

Treatment	Study	Baseline EDSS	No. of patients started (completed)	Outcomes/Results
Psychotherapy vs. Active control (current events discussion group) vs. Passive control (no treatment)	Crawford et al. 1985[149]	NR	32	MMPI Depression-30 scale (p = 0.025) IECS (p = 0.005) ASQ (p = NS) SES (p = NS)
CBT vs. Wait-list control	Larcombe et al. 1984[151]	NR	21 (19)	BDI (p < 0.01) HRSD (p < 0.01) Significant-Other Rating Scale (p < 0.01) Worst mood (p < 0.05) Best mood (p = NS) Average mood (p = NS)
CBT + relaxation vs. Wait-list control	Foley et al. 1987[150]	6 (mean) 1-8 (range)	41 (36)	BDI (p < 0.05) STAI-S (p < 0.05) STAI-T (p = NS) Hassles Scale (p < 0.05) PFC (p < 0.05)
Cognitive remediation (CBT + memory aids) vs. Active control (support group)	Mendoza et al. 2001[152]	NR	20	BDI (p = NS)
CBT vs. Support group (SEG) vs. Sertraline (200 mg/d)	Mohr et al. 2001[153]	2.4 (mean) 0-8 (range)	63 (52)	BDI CBT vs. SEG (p = 0.003) Sertraline vs. SEG (p = 0.05) CBT vs. sertraline (p = NS) HRSD CBT vs. SEG (p = 0.02) Sertraline vs. SEG (p = 0.45) CBT vs. sertraline (p = 0.13)
CBT (telephone-administered) vs. Control (usual care)	Mohr et al. 2000[154]	NR	32 (23)	POMS Depression-Dejection scale (p < 0.003, completers; p < 0.01, ITT population)
Amitriptyline vs. Placebo	Schiffer et al. 1985[155]	NR	17 (12)	Improvement in number of episodes of pathological laughing or crying; BDI; HRSD (p = 0.011)
Desipramine + psychotherapy vs. Placebo + psychotherapy	Schiffer et al. 1990[156]	4.6 (mean)	32 (28)	Clinical improvement in psychosocial function (p = 0.05) BDI (p = 0.16) HRSD (p = 0.02)

Abbreviations: ASQ = Anxiety Scale Questionnaire; BDI = Beck Depression Inventory; CBT = cognitive behavioral therapy; d = day; EDSS = Expanded Disability Status Scale; HRSD = Hamilton Rating Scale for Depression; IECS = Internal-External Control Scale; ITT = intention-to-treat; mg = milligram(s); MMPI = Minnesota Multiphasic Personality Inventory; No. = Number; NR = not reported; NS = not statistically significant; PFC = Problem-Focused Coping score from Ways of Coping Checklist; SEG = supportive-expressive group therapy; SES = Self-Esteem Scale; PFC = Problem-Focused Coping score from the Ways of Coping Checklist; POMS = Profile of Mood States; STAI-S = State-Trait Anxiety Inventory-State; STAI-T = State-Trait Anxiety Inventory-Trait

Table 11. Randomized controlled trials of treatments for fatigue

Treatment	Study	Baseline EDSS (Mean ± SD)	No. of patients started (completed)	Outcomes/Results
Amantadine (100 mg twice per day x 3 wk) vs. Placebo	Canadian MS Research Group 1987[157]	4.3 ± 1.9	115 (109)	Change in VAS fatigue score (p = NS) Most affected activity VAS (p < 0.05) ADL total score (p = 0.09)
Amantadine (100 mg twice per day x 4 wk) vs. Placebo	Cohen et al. 1989[158]	4.0 ± 1.4	29 (22)	Fatigue score (p = 0.58)
Amantadine (100 mg twice per day x 6 wk) vs. Pemoline vs. Placebo	Krupp et al. 1995[161]	2.9 ± 0.9	119 (93)	MS-FS A vs. placebo (p = 0.04) P vs. placebo (p = 0.4) FSS A vs. placebo (p = NS) P vs. placebo (p = 0.8)
Amantadine (100 mg twice per day x 6 wk) vs. Pemoline vs. Placebo	Geisler et al. 1996[159]	2.6 ± 0.7	45	SDMT A vs. placebo (p < 0.05) P vs. placebo (p = NR) Digit Span (p = NS) Selective Reminding Test (p = NS) Benton Visual Retention Test (p = NS) Finger Tapping Test (p = NS)
Pemoline vs. Placebo	Weinshenker et al. 1992[163]	3.6 ± 2.0	46 (41)	EDSS (p = NS) Fatigue VAS (p = NS) Fatigue 4-point scale (p = 0.06)
Transdermal histamine/caffeine vs. Placebo	Gillson et al. 2002[160]	NR	29 (26)	MFIS (p < 0.02) 25-foot timed walk (p =NS) 9-HPT (p = NS) PASAT (p = NS)
4-aminopyridine vs. Placebo	Rossini et al. 2001[162]	6.2 ± 0.8	54 (49)	FSS (p = 0.19) EDSS (p = NS)

Abbreviations: 9-HPT = 9-Hole Peg Test; ADL = activities of daily living; EDSS = Extended Disability Status Scale; FSS = Fatigue Severity Scale; MFIS = Modified Fatigue Impact Scale; mg = milligram(s); MS = multiple sclerosis; MS-FS = MS-Specific Fatigue Scale; No. = Number; NR = not reported; NS = not statistically significant; PASAT = Paced Auditory Serial Addition Test; SD = standard deviation; SDMT = Symbol Digit Modalities Test; VAS = visual analog scale; wk = week(s)

Table 12. Randomized controlled trials of treatments for voiding dysfunction

Treatment	Study	Baseline EDSS	No. of patients started (completed)	Outcomes/Results
Desmopressin nasal spray (20 mcg/d) vs. Placebo nasal spray	Fredrikson 1996[164]	NR	27 (22)	No. of voidings in 6 hr ($p < 0.05$) No. of voidings in 24 hr (p = NS)
Desmopressin nasal spray (20 mcg/d) vs. Placebo nasal spray	Hilton et al. 1983[165]	NR	16	Subjective benefit in nocturia ($p < 0.01$) Daytime urinary frequency (p = NS) Nighttime urinary frequency ($p < 0.001$)
Desmopressin nasal spray (20 mcg/d) vs. Placebo nasal spray	Hoverd et al. 1998[166]	NR	28 (24)	Daytime urinary frequency ($p = 0.008$) Nighttime urinary frequency ($p = 0.26$) Urine volume in 6 hr ($p = 0.006$) Urine volume in 24 hr ($p = 0.052$)
Desmopressin nasal spray vs. Placebo nasal spray	Kinn et al. 1990[167]	NR	13 (12)	No. of voidings in 6 hr ($p < 0.05$) No. of voidings in 24 hr (p = NS) Urine volume in 6 hr ($p < 0.05$)
Desmopressin nasal spray (10 mcg/d) vs. Placebo nasal spray	Valiquette et al. 1996[170]	6.7 (mean) 2.5-8.5 (range)	17 (11)	Nights with nocturia ($p < 0.01$) Incontinence ($p = 0.08$) Frequency of nocturia ($p < 0.01$) Uninterrupted sleep hours ($p < 0.01$)
Abdominal vibration vs. Abdominal pressure vs. No treatment	Prasad et al. 2003[168]	NR	30 (28)	No. of patients with no incontinence in 72 hr (p = NR) No. of voidings in 72 hr (p = NR) Post-void residual volume: Vibration vs. placebo ($p = 0.002$) Vibration vs. pressure ($p = 0.059$)
Pelvic floor rehabilitation (biofeedback + exercise) vs. No treatment	Vahtera et al. 1997[169]	4.4 (mean) 1-6.5 (range)	80	Incontinence ($p < 0.05$) Nocturia ($p < 0.05$) Frequency of UTIs (p = NS) Urinary symptom-related handicap ($p < 0.05$)

Abbreviations: d = day(s); EDSS = Extended Disability Status Scale; hr = hour(s); mcg = microgram(s); No. = Number; NR = not reported; NS = not statistically significant; UTIs = urinary tract infections

Table 13. Included studies by type of measure used and type of function considered (physical, mental, other)

Type of measure used	Type(s) of function considered	Study
Hyllested criteria, etc.	Physical and mental	Rozin et al. 1975[191] Rozin et al. 1982[190]
Expanded Disability Status Scale (EDSS) and Disability Status Scale (DSS)	Physical	Canadian Burden of Illness Study Group 1998a[174] Grima et al. 2000[180] Hammond et al. 1996[183] LaRocca et al. 1982[187] Miller et al. 2000[188] Verdier-Taillefer et al. 1995[193]
Mobility aids	Physical	Dyck et al. 2000[176] Kornblith et al. 1986[186]
Job characteristics	Physical, mental, symptoms	Dyck et al. 2000[176] Grønning et al. 1990[181] LaRocca et al. 1982[187] Rozin et al. 1975[191] Scheinberg et al. 1980[192] Verdier-Taillefer et al. 1995[193]
Cognitive function	Mental/cognitive and physical	Beatty et al. 1995[172] Beukelman et al. 1985[173] Edgley et al. 1991[177] Genevie et al. 1987[179] Rao et al. 1991[189]
Disease subtype	–	Jacobs et al. 1999[184] Verdier-Taillefer et al. 1995[193]
Self-report	Physical, mental, symptoms	Dyck et al. 2000[176] Edgley et al. 1991[177] Freal et al. 1984[178] Gulick et al. 1989[182] Scheinberg et al. 1980[192]

Table 14. Studies by Rozin et al.[190,191] measuring ability to work among individuals with MS

Rozin et al. 1975[191]	**Rozin et al. 1982[190] (Series I and II combined)**
1) Study participants (n = 172) initially grouped: n = 41 – Group A: Completely handicapped with no rehabilitation potential n = 37 – Group B: Potential for vocational rehabilitation, but unemployed or currently employed, but needs rehabilitation services for continuation of employment n = 94 – Group C: Currently working, holding previous jobs, or changed jobs without intervention of rehabilitation **2) Type of MS disability by group:** No disability: NR – Group A NR – Group B 50% – Group C Physical disability due to MS: 39% – Group A 81% – Group B 41% – Group C Physical and mental disability due to MS: 56% – Group A 19% – Group B 3% – Group C Mental disability due to MS: NR – Group A NR – Group B 1% – Group C Other causes of disability not connected with MS: 5% – Group A NR – Group B 5% – Group C	**1) Study participants (n = 299) initially grouped:** n = 71 – Group A: Completely handicapped with no rehabilitation potential n = 53 – Group B: Potential for vocational rehabilitation, but unemployed or currently employed, but needs rehabilitation services for continuation of employment n = 175 – Group C: Currently working, holding previous jobs, or changed jobs without intervention of rehabilitation **2) Type of MS disability by group:** No disability: NR – Group A 3% – Group B 29% – Group C Physical disability due to MS: 59% – Group A 75% – Group B 61% – Group C Physical and mental disability due to MS: 30% – Group A 11% – Group B 6% – Group C Mental disability due to MS: 1% – Group A 2% – Group B 1% – Group C Other causes of disability not connected with MS: 7% – Group A 2% – Group B 1% – Group C MS and other causes of disability: 3% – Group A 7% – Group B 2% – Group C

Table 14. Studies by Rozin et al.[190,191] measuring ability to work among individuals with MS (continued)

Rozin et al. 1975[191]	Rozin et al. 1982[190] (Series I and II combined)
3) Hyllested criteria of disability: Group A (no rehabilitation potential) (n = 41) 0% – Mild (0-2) 0% – Moderate (3-4) 100% – Severe (5-6) Group B (vocational rehabilitation needed among unemployed and employed) (n = 37) 0% – Mild (0-2) 57% – Moderate (3-4) 43% – Severe (5-6) Group C (working) (n = 94) 70% – Mild (0-2) 30% – Moderate (3-4) 0% – Severe (5-6)	**3) Hyllested criteria of disability:** Group A (no rehabilitation potential) (n = 71) 15% – Mild (0-2) 38% – Moderate (3-4) 46% – Severe (5-6) Group B (vocational rehabilitation needed among unemployed and employed) (n = 53) 36% – Mild (0-2) 51% – Moderate (3-4) 13% – Severe (5-6) Group C (working) (n = 175) 74% – Mild (0-2) 25% – Moderate (3-4) 0.6% – Severe (5-6)

Abbreviations: MS = multiple sclerosis; NR = not reported

Table 15. Cross-sectional studies examining current employment status and EDSS level among individuals with MS

Canadian Burden of Illness Study Group 1998a[174]	**Grima et al. 2000[180]**	**Miller et al. 2000[188]**
EDSS ≤ 2.5 (n = 62): 37% - Full-time 13% - Part-time 29% - Unemployed 13% - Other	EDSS 1-2 (n = 78): 44% - Full-time 14% - Part-time 15% - Not working due to MS 27% - Not working, other reasons	EDSS 0-3.0 (n = 113): 42.0% - Full-time 20.5% - Part-time 37.5% - None
EDSS 3-6: (n =68) 28% - Full-time 10% - Part-time 44% - Unemployed 18% - Other	EDSS 3-6: (n = 75) 15% - Full-time 8% - Part-time 51% - Not working due to MS 13% - Not working, other reasons 4% - NR	EDSS 3.5-6.5 (n = 131) 15.4% - Full-time 10.0% - Part-time 74.6% - None
EDSS ≥ 6.5: (n = 68) 4% - Full-time 6% - Part-time 57% - Unemployed 32% - Other	–	EDSS 7.0-8.5 (n = 56) 8.9% - Full-time 5.4% - Part-time 85.7% - None

Abbreviations: EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; NR = not reported

Table 16. Cognitive function and work status among individuals with MS

Study, number of subjects	Cognitive function measures	Primary findings
Beatty et al. 1995[172] N = 102 38 employed 64 retired	Categories: ▪ Verbal ability (SILS Vocabulary Test) ▪ Naming (Boston Naming Test) ▪ Visuospatial (Perception-LOT) ▪ Attention/Concentration (Digit Span) ▪ Information processing (Speed, SDMT, FAS) ▪ Category fluency ▪ Memory (STM–Correct, NMT-Delay, SRT-Total, SRT-Delay Recall, SRT-Delay Recognition) ▪ Problem solving/abstraction (SILS-Abstraction, SILS-Conceptual Quotient, WCST-Categories, WCST-% Perseverative Responses) ▪ Ambulatory Index (score 1-6) (highly correlated with EDSS: r = 0.96) ▪ Beck Depression Index	Significant differences between workers and non-workers were observed on all measures except Digit Span, LOT, and WCST-% Perseverative Response 49% of the variance in employment status was explained by walking ability, age, two measures of memory, and one test of verbal fluency Partial R^2 ▪ Ambulation index: 0.25 ▪ STM (short term memory): 0.13 ▪ SRT (delay recall/memory): 0.04 ▪ Age (29-62 years): 0.03 ▪ FAS (verbal ability/letter fluency): 0.03
Edgley et al. 1991[177] N = 602	PDQ score – sum of 4 subscales: 1. attention/concentration 2. planning/organizing 3. retrospective memory 4. prospective memory (each subscale ranked 0-4: 0 = never 1 = rarely 2 = sometimes 3 = often 4 = almost always) Mobility assistance: 1. no ambulatory problems 2. a bit unsteady 3. need cane/brace 4. wheelchair 5. can't walk	PDQ score (mean [SD]): Unemployed: 1.6 (0.7) Employed: 1.4 (0.7) $p < 0.001$ Mobility assistance (mean [SD]): Unemployed: 3.1 (1.2) Employed: 2.2 (1.0) $p < 0.001$ "A significant multivariate main effect for employment status was obtained. Compared to individuals who were employed, unemployed individuals had more mobility problems (indicated above), obtained higher scores on the self-report PDQ (indicated above), had fewer years of education. Occupational level, number of people living at home and illness duration did not impact employment status."
Rao et al. 1991[189] N = 100 52 intact 48 impaired	A battery of 36 tests were used to evaluate the following: Dementia Screen (MMS) Verbal Intelligence (WAIS-R) Memory Immediate Memory Recent Memory Remote Abstract Reasoning Attention/Concentration Language Visuospatial Perception 100 MS patients were grouped as being either intact or impaired	From the Environmental Status Scale (ESS), one of seven domains – Actual Work Status – was compared to cognitive impairment (yes/no) Mean score of ESS scale (range 0-4) for Actual Work Status was lower (approximately 1.8) for cognitively impaired versus intact (approximately 2.8; $p < 0.01$)

Table 16. Cognitive function and work status among individuals with MS (continued)

Abbreviations: EDSS = Expanded Disability Status Scale; ESS = Environmental Status Scale; FAS = letter fluency test (saying as many words as possible that begin with F, A, and S, 60 seconds each); LOT = Line Orientation Test; MMS = Mini-Mental State; MS = multiple sclerosis; N = number of subjects; NMT = New Map Test; PDQ = Perceived Deficit Questionnaire; SD = standard deviation; SDMT = Symbol Digit Modalities Test; SILS = Shipley Institute of Living Scale; SRT = Selective Reminding Test; STM = Short Term Memory Test; WCST = Wisconsin Card Sorting Test; WAIS-R = Wechsler Adult Intelligence Scale-Revised

Table 17. Job type/characteristics and current work status among individuals with MS

Study	Findings
Grønning et al. 1990[181]	Univariate analyses of time to unemployment: Non-remittent MS vs. remittent ($p < 0.001$) Heavy vs. light work ($p < 0.01$) Male vs. female ($p < 0.05$) Age > 30 at onset ($p < 0.01$) Multivariate analyses, when disease subtype was not considered, occupation (heavy work) and age (> 30 years) were predictive of early unemployment
Hammond et al. 1996[183]	"Authors noted that trade and farm workers were less likely to be in paid employment than professional or clerical workers as their level of disability increased." (Researchers provided no data to support this statement.)
LaRocca et al. 1982[187]	84% of variability in employment status was unexplained by age, sex, education, marital status, occupation, and parenthood However, variability in employment status was explained by factors such as premorbid personality, coping style, characteristics of the workplace, and social support systems. Authors suggested that these findings contribute to the probability of a patient with MS staying at work. (Researchers provided no data to support this statement.)
Scheinberg et al. 1980[192]	Job category of currently employed subjects (n = 51): 35.3% - Clerical 23.5% - Professional 13.7% - Semi-professional 13.7% - Skilled labor 7.8% - Managerial 2.0% - Unskilled labor 3.9% - Other
Verdier-Taillefer et al. 1995[193]	Job characteristics and odds of unemployment (odds ratio [95% CI]): Desk job - 0.3 (0.1 to 0.5) Sitting position - 0.3 (0.1 to 0.7) Possibility of obtaining specific arrangements - 0.4 (0.2 to 0.8) Travel time > 30 minutes - 1.7 (0.9 to 3.2) Daily work > 8 hours - 2.6 (1.2 to 5.7) Accessibility problems - 1.9 (0.9 to 4.0) Work requirements and odds of unemployment (odds ratio [95% CI]): Close attention - 0.9 (0.4 to 1.8) Good memory - 0.7 (0.3 to 1.5) Physical strength - 7.6 (3.2 to 18.2) Manual precision - 3.1 (1.6 to 6.3) Rigid work schedule - 2.2 (1.1 to 4.6) Decision making - 1.7 (0.7 to 3.4) Frequent moves - 2.5 (1.3 to 4.9)

Table 17. Job type/characteristics and current work status among individuals with MS (continued)

Study	Findings
Rozin et al. 1975[191]	Study participants were initially grouped into A, B, or C (described below), followed by examination of changes in work status/job type Changes in work status are from onset of MS to time of study in 1971; work type by predetermined work groups Group A (n = 41): Completely handicapped with no rehabilitation potential Unskilled labor: 18% – onset of MS 0% – at time of study Skilled, semiskilled, service: 27% – onset of MS 0% – at time of study Clerical, professional, student: 37% – onset of MS 0% – at time of study Housewives: 2% – onset of MS 0% – at time of study Not working: 6% – onset of MS 100% – at time of study Group C (n = 94): Currently working, holding previous jobs, or changed jobs without intervention of rehabilitation Unskilled labor: 22% – onset of MS 8% – at time of study Skilled, semiskilled, service: 18% – onset of MS 17% – at time of study Clerical, professional, student: 40% – onset of MS 37% – at time of study Housewives: 12% – onset of MS 38% – at time of study Not working: 8% – onset of MS 0% – at time of study Group B (n = 37): Potential for vocational rehabilitation, but unemployed or currently employed, but needs rehabilitation services for continuation of employment Unskilled labor: 28% – onset of MS 3% – at time of study Skilled, semiskilled, service: 31% – onset of MS 3% – at time of study Clerical, professional, student: 31% – onset of MS 21% – at time of study Housewives: 5% – onset of MS 8% – at time of study Not working: 5% – onset of MS 65% – at time of study Authors note that “of the 131 clients with working potential (groups B and C), only 18% stopped working because of MS”

Abbreviations: CI = confidence interval; MS = multiple sclerosis

Table 18. Self-report on why individuals with MS continued or terminated employment

Study	Findings
Dyck et al. 2000[176]	Factors contributing to maintaining employment – 44% of currently employed women were limited in the kind and amount of work they could do because of MS including: NR - fatigue "most common" 16% - difficulty with standing and stairs 15% - walking 12% - writing 11% - memory/concentration 17% no longer working indicated "inability to negotiate reduced work hours" with their manager as reason for quitting work
Edgley et al. 1991[177]	Study participants who indicated that they quit working because of MS symptoms were asked an open-ended question about types of symptoms (n = 313; 78% of sample) 41% - Ambulation problems 39% - Fatigue 12% - Memory problems 10% - Emotional problems 12% - Visual difficulties 6% - Coordination problems 2% - Pain 1% - Incontinence 22% left for reasons unrelated to MS. Women (26%) were significantly more likely than men (11%) to cite reasons unrelated to MS as the primary cause of unemployment ($\chi^2 = 9.3$, $P < 0.01$)
Gulick et al. 1989[182]	Ranked comparison of conditions/situations that impede work performance (data on housewives and retired participants not described here): Fatigue: Employed: 50% Unemployed: 25% Tremors: Employed: NR Unemployed: 10% Walking: Employed: 12% Unemployed: NR Use of wheelchair: Employed: NR Unemployed: 10% Standing: Employed: 8% Unemployed: 12% Restricted mobility: Employed: NR Unemployed: 9% Numbness: Employed: 8% Unemployed: 5% Stiffness: Employed: 5% Unemployed: NR

Table 18. Self-report on why individuals with MS continued or terminated employment (continued)

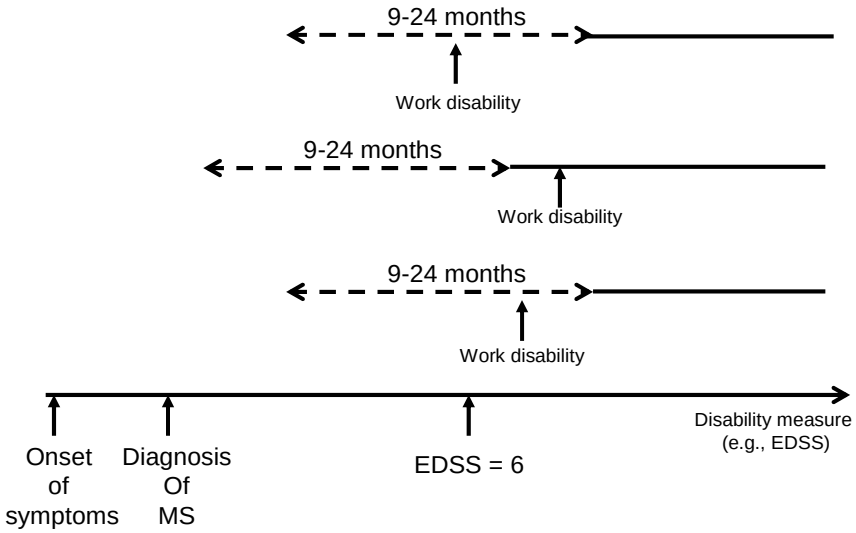
Study	Findings
Scheinberg et al. 1980[192]	Among those having left employment, the most common reason for leaving among multiple reasons given by 182 subjects (categories not mutually exclusive): 52.7% - Physical difficulty 15.9% - Visual difficulty 12.1% - Transportation difficulty 9.3% - Fatigue 1.3% - Emotional difficulty 37.4% - Other (mainly marriage and/or pregnancy)

Abbreviations: MS = multiple sclerosis; NR = not reported

Table 19. Conditions/situations impeding or enhancing performance of work/chores

	Employed outside home	Homemaker	Unemployed	Retired
Conditions/situations *impeding* performance of work/chores (% of respondents citing)				
Fatigue	50%	51%	25%	25%
Balance	10%	16%	11%	19%
Vision	12%	9%	11%	7%
High temperature	7%	6%	-	-
Conditions/situations *enhancing* performance of work/chores (% of respondents citing)				
Intermittent rest	21%	22%	12%	19%
Assistance with tasks	18%	22%	22%	11%
Adaptive aids	16%	18%	12%	26%
Self-pacing	13%	11%	12%	13%
Cool temperature	-	8%	-	6%
Positive attitude	6%	5%	5%	6%

Figure 1. Temporal relationship of pre-disability evaluation and occurrence of work disability



The experiences of three individuals over a 9- to 24-month time frame are depicted. Variability in the point at which an individual becomes unable to work is shown by the variable position of the arrow labeled "work disability." Variability in the time of assessment of prognostic data is depicted by variation in the position of the left-pointing arrow. Variability in the duration of follow up is depicted by variation in the position of the right-pointing arrow. Abbreviations: EDSS = Expanded Disability Status Scale; MS = multiple sclerosis.

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Listing of Excluded Studies

All excluded articles listed below were reviewed in their full-text versions. Following each reference, in italics, is the primary reason for exclusion and the question (Q) for which the article was considered. If no Q is indicated, then the article was excluded a priori from the study for the reason given. *Reasons for exclusion pertain only to the usefulness of articles for this study and are not intended as criticisms of the articles per se.* "DA" indicates exclusion at the data abstraction stage. For reference, the questions are:

Question 1a: What is the reliability of new McDonald criteria (incorporating supplementary information form radiologic and laboratory studies including MRI, VEP, and CSF analyses) compared with long-term follow-up diagnosis of clinically definite MS according to the Poser criteria?

Question 1b: What is the inter-rater reliability of diagnosis of MS according to Poser or McDonald criteria among neurologists or between neurologists and non-neurologist physicians?

Question 2: What clinical indicators, including particularly time-course of impairments, predict physical or mental impairment at 12 months?

Question 3a: Among patients with MS, do current disease-modifying treatments result in long-term improvements in physical or mental outcomes compared to placebo or usual care?

Question 3b: Among patients with MS, do treatments aimed at symptom management result in improvements in physical or mental outcomes compared to usual care?

Question 4: Among individuals with MS, what physical, mental, laboratory, or radiographic findings have been associated with inability to work?

Question 5: Among individuals with MS, how does elevated temperature or other environmental factors impair the capacity to work?

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Adams HP, Wagner S, Sobel DF, et al. Hypointense and hyperintense lesions on magnetic resonance imaging in secondary-progressive MS patients. Eur Neurol 1999;42(1):52-63. *Exclude-Q2-no predictor with outcome*

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Barkhof F. The clinico-radiological paradox in multiple sclerosis revisited [review]. Curr Opinion Neurol 2002;15(3):239-45. *Exclude-Q2-no long-term follow up*

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List of Acronyms/Abbreviations

9-HPT	9-Hole Peg Test
ADA	Americans with Disabilities Act
AHRQ	Agency for Healthcare Research and Quality
APOE	apolipoprotein E
BDI	Beck Depression Inventory
BRB-N	Brief Repeatable Battery
CI	confidence interval
CIS	clinically isolated syndrome
CSF	cerebrospinal fluid
CDMS	clinically definite multiple sclerosis
CT	computed tomography
Delta-9-THC	delta-9-tetrahydrocannabinol
DSS	Disability Status Scale
EDSS	Expanded Disability Status Scale
EPC	Evidence-based Practice Center
FIM	Functional Independence Measure
GNDS	Guy's Neurological Disability Scale
IgG	immunoglobulin-G
IgM	immunoglobulin-M
IL-2	interleukin-2
IV	intravenous
MDI	Mobility Dysfunction Index
MeSH	Medical Subject Headings
MFIS	Modified Fatigue Impact Scale
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
MS-FS	MS-Specific Fatigue Scale
NA	not applicable
NR	not reported
PASAT	Paced Auditory Serial Addition Test
PR	prevalence ratio
OR	odds ratio
QOL	quality of life
RCT	randomized controlled trial
SD	standard deviation
SDMT	Symbol Digit Modalities Test
SF-36	Medical Outcomes Study 36-Item Short-Form Health Survey
SSA	Social Security Administration
SSDI	Social Security Disability Insurance
VEP	visual evoked potential

APPENDIXES

to

“Criteria to Determine Disability Related to Multiple Sclerosis”

Prepared by the Duke Evidence-based Practice Center
(Contract #290-02-0025)

Appendix A. Excerpts from: Social Security Administration Office of Disability. *Disability Evaluation Under Social Security, 2003.* SSA Pub. No. 64-039. Social Security Administration: Baltimore, MD.

Section below has been excerpted from:
Social Security Administration Office of Disability. Disability Evaluation Under Social Security, 2003. SSA Pub. No. 64-039. Social Security Administration: Baltimore, MD, pp. 92-99.

11.00 Neurological

A. Epilepsy. In epilepsy, regardless of etiology, degree of impairment will be determined according to type, frequency, duration, and sequelae of seizures. At least one detailed description of a typical seizure is required. Such description includes the presence or absence of aura, tongue bites, sphincter control, injuries associated with the attack, and postictal phenomena. The reporting physician should indicate the extent to which
description of seizures reflects his own observations and the source of ancillary information. Testimony of persons other than the claimant is essential for description of type and frequency of seizures if professional observation is not available.

Under 11.02 and 11.03, the criteria can be applied only if the impairment persists despite the fact that the individual is following prescribed antiepileptic treatment. Adherence to prescribed antiepileptic therapy can ordinarily be determined from objective clinical findings in the report of the physician currently providing treatment for epilepsy. Determination of blood levels of phenytoin sodium or other antiepileptic drugs may serve to indicate whether the prescribed medication is being taken. When seizures are occurring at the frequency stated in 11.02 or 11.03, evaluation of the severity of the impairment must include consideration of the serum drug levels. Should serum drug levels appear therapeutically inadequate, consideration should be given as to whether this is caused by individual idiosyncrasy in absorption or metabolism of the drug. Blood drug levels should be evaluated in conjunction with all other evidence to determine the extent of compliance. When the reported blood drug levels are low, therefore, the information obtained from the treating source should include the physician's statement as to why the levels are low and the results of any relevant diagnostic studies concerning the blood levels. Where adequate seizure control is obtained only with unusually large doses, the possibility of impairment resulting from the side effects of this medication must also be assessed. Where documentation shows that use of alcohol or drugs affects adherence to prescribed therapy or may play a part in the precipitation of seizures, this must also be considered in the overall assessment of impairment level.

B. Brain tumors. The diagnosis of malignant brain tumors must be established, and the persistence of the tumor should be evaluated, under the criteria described in 13.00 B and C for neoplastic disease.

In histologically malignant tumors, the pathological diagnosis alone will be the decisive criterion for severity and expected duration (see I 1.05A). For other tumors of the brain, the

severity and duration of the impairment will be determined on the basis of symptoms, signs, and pertinent laboratory findings (11.05B).

C. Persistent disorganization of motor function in the form of paresis or paralysis, tremor or other involuntary movements, ataxia and sensory disturbances (any or all of which may be due to cerebral, cerebellar, brain stem, spinal cord, or peripheral nerve dysfunction) which occur singly or in various combinations, frequently provides the sole or partial basis for decision in cases of neurological impairment. The assessment of impairment depends on the degree of interference with locomotion and/or interference with the use of fingers, hands and arms.

D. In conditions which are episodic in character, such as multiple sclerosis or myasthenia gravis, consideration should be given to frequency and duration of exacerbations, length of remissions, and permanent residuals.

E. Multiple sclerosis. The major criteria for evaluating impairment caused by multiple sclerosis are discussed in Listing 11.09. Paragraph A provides criteria for evaluating disorganization of motor function and gives reference to 11.0413 (11.04B then refers to 11.000). Paragraph B provides references to other listings for evaluating visual or mental impairments caused by multiple sclerosis. Paragraph C provides criteria for evaluating the impairment of individuals who do not have muscle weakness or other significant disorganization of motor function at rest, but who do develop muscle weakness on activity as a result of fatigue.

Use of the criteria in 11.09C is dependent upon (1) documenting a diagnosis of multiple sclerosis, (2) obtaining a description of fatigue considered to be characteristic of multiple sclerosis, and (3) obtaining evidence that the system has actually become fatigued. The evaluation of the magnitude of the impairment must consider the degree of exercise and the severity of the resulting muscle weakness.

The criteria in 11.09C deal with motor abnormalities which occur on activity. If the disorganization of motor function is present at rest, paragraph A must be used, taking into account any further increase in muscle weakness resulting from activity.

Sensory abnormalities may occur, particularly involving central visual acuity. The decrease in visual acuity may occur after brief attempts at activity involving near vision, such as reading. This decrease in visual acuity may not persist when the specific activity is terminated, as with rest, but is predictably reproduced with resumption of the activity. The impairment of central visual acuity in these cases should be evaluated under the criteria in Listing 2.02, taking into account the fact that the decrease in visual acuity will wax and wane.

Clarification of the evidence regarding central nervous system dysfunction responsible for the symptoms may require supporting technical evidence of functional impairment such as evoked response tests during exercise.

F. Traumatic brain injury (TBI). The guidelines for evaluating impairments caused by cerebral trauma are contained in 11.18. Listing 11.18 states that cerebral trauma is to be evaluated under 11.02, 11.03, 11.04, and 12.02, as applicable.

TBI may result in neurological and mental impairments with a wide variety of posttraumatic symptoms and signs. The rate and extent of recovery can be highly variable and the long-term outcome may be difficult to predict in the first few months post-injury. Generally, the neurological impairment (s) will stabilize more rapidly than any mental impairment (s). Sometimes a mental impairment may appear to improve immediately following TBI and then worsen, or, conversely, it may appear much worse initially but improve after a few months. Therefore, the mental findings immediately following TBI may not reflect the actual severity of your mental impairment (s). The actual severity of a mental impairment may not become apparent until 6 months post-injury.

In some cases, evidence of a profound neurological impairment is sufficient to permit a finding of disability within 3 months post-injury. If a finding of disability within 3 months post-injury is not possible based on any neurological impairment (s), we will defer adjudication of the claim until we obtain evidence of your neurological or mental impairments at least 3 months' post-injury. If a finding of disability still is not possible at that time, we will again defer adjudication of the claim until we obtain evidence at least 6 months post-injury. At that time, we will fully evaluate any neurological and mental impairments and adjudicate the claim.

11.01 Category of Impairments, Neurological

11.02 Epilepsy - convulsive epilepsy (grand mal or psychomotor), documented by detailed description of a typical seizure pattern, including all associated phenomena; occurring more frequently than once a month, in spite of at least 3 months of prescribed treatment. With:

A. Daytime episodes (loss of consciousness and convulsive seizures) or

B. Nocturnal episodes manifesting residuals which interfere significantly with activity during the day.

11.03 Epilepsy -- nonconvulsive epilepsy (petit mal, psychomotor, or focal) documented by detailed description of a typical seizure pattern, including all associated phenomena, occurring more frequently than once weekly, in spite of at least 3 months of prescribed treatment. With alteration of awareness or loss of consciousness and transient postictal manifestations of unconventional behavior or significant interference with activity during the day.

11.04 Central nervous system vascular accident. With one of the following more than 3 months post-vascular accident:

A. Sensory or motor aphasia resulting in ineffective speech or communication; or

B. Significant and persistent disorganization of motor function in two extremities, resulting in sustained disturbance of gross and dexterous movements, or gait and station (see 11.000).

11.05 Brain tumors

A. Malignant gliomas (astrocytoma - grades III and IV, glioblastoma multiforme), medulloblastoma, ependymoblastoma, or primary sarcoma; or
B. Astrocytoma (grades I and II), meningioma, pituitary tumors, oligodendroglioma, ependymoma, clivus chordoma, and benign tumors. Evaluate under 11.02, 11.03, 11.04A or B, or 12.02.

11.06 Parkinsonian syndrome with the following signs: Significant rigidity, bradykinesia, or tremor in two extremities, which, singly or in combination, result in sustained disturbance of gross and dexterous movements, or gait and station.

11.07 Cerebral palsy. With: *A. IQ of 70*

or less; or

B. Abnormal behavior patterns, such as destructiveness or emotional instability; or

C. Significant interference in communication due to speech, hearing, or visual defect; or

D. Disorganization *of* motor function as described in 11.04B.

11.08 Spinal cord or nerve root lesions, due to any cause with disorganization of motor function as described in 11.04B.

11.09 Multiple sclerosis. With:

A. Disorganization of motor function as described in 11.04B; or

B. Visual or mental impairment as described under the criteria in 2.02, 2.03, 2.04, or 12.02; or

C. Significant, reproducible fatigue of motor function with substantial muscle weakness on repetitive activity, demonstrated on physical examination, resulting from neurological dysfunction in areas of the central nervous system known to be pathologically involved by the multiple sclerosis process.

11.10 Amyotrophic lateral sclerosis. With:

A. Significant bulbar signs; or

B. Disorganization of motor function as described in 11.04B. ***11.11 Anterior***

poliomyelitis. With:

A. Persistent difficulty with swallowing or breathing; or B. Unintelligible

speech; or

C. Disorganization of motor function as described in 11.04B. ***11.12***

Myasthenia gravis. With:

A. Significant difficulty with speaking, swallowing, or breathing while on prescribed therapy; or

B. Significant motor weakness of muscles of extremities on repetitive activity against resistance while on prescribed therapy.

11.13 Muscular dystrophy with disorganization of motor function as described in 11.04B.

11.14 Peripheral neuropathies. With disorganization of motor function as described in 11.04B, in spite of prescribed treatment.

11.15 (Reserved)

11.16 Subacute combined cord degeneration (pernicious anemia) with disorganization of motor function as described in 11.04B or 11.15B, not significantly improved by prescribed treatment.

11.17 Degenerative disease not listed elsewhere, such as Huntington's chorea, Friedreich's ataxia, and spino-cerebellar degeneration. With:

A. Disorganization of motor function as described in I 1.04B; or B. Chronic brain

syndrome. Evaluate under 12.02.

11.18 Cerebral trauma.

Evaluate under the provisions of 11.02, 11.03, 11.04, and 12.02, as applicable.

11.19 ***Syringomyelia.*** With:

A. Significant bulbar signs; or

B. Disorganization of motor function as described in 11.04B. **12.00**

Section below has been excerpted from:
Social Security Administration Office of Disability. Disability Evaluation Under Social Security, 2003. SSA Pub. No. 64-039. Social Security Administration: Baltimore, MD, pp. 39-40.

2.01 Category of Impairments, Special Senses and Speech

2.02 Impairment of Visual Acuity. Remaining vision in the better eye after best correction is *20/200* or less.

2.03 Contraction of Peripheral Visual Fields in the Better Eye.

A. To 10^0 or less from the point of fixation; or

B. So the widest diameter subtends an angle no greater than *20* degrees; or *C. To 20* percent

or less visual field efficiency.

2.04 Loss of visual efficiency. The visual efficiency of the better eye after best correction is 20 percent or less. (The percent of remaining visual efficiency is equal to the product of the percent of remaining visual acuity efficiency and the percent of remaining visual field efficiency.)

2.05 (Reserved)

2.06 ***Total Bilateral Ophthalmoplegia.***

2.07 Disturbance of Labyrinthine- Vestibular Function (Including Meniere's disease), characterized by a history of frequent attacks of balance disturbance, tinnitus, and progressive loss of hearing. With both A and B

A. Disturbed function of vestibular labyrinth demonstrated by caloric or other vestibular tests; and

B. Hearing loss established by audiometry.

Section below has been excerpted from:
Social Security Administration Office of Disability. Disability Evaluation Under Social Security, 2003. SSA Pub. No. 64-039. Social Security Administration: Baltimore, MD, pp. 112-114

12.01 Category of Impairments - Mental

12.02 ***Organic Mental Disorders:*** Psychological or behavioral abnormalities associated with a dysfunction of the brain. History and physical examination or laboratory tests demonstrate the presence of a specific organic factor judged to be etiologically related to the abnormal mental state and loss of previously acquired functional abilities.

The required level of severity for these disorders is met when the requirements in both A and B are satisfied, or when the requirements in C are satisfied.

A. Demonstration of a loss of specific cognitive abilities or affective changes and the medically documented persistence of at least one of the following:

1. Disorientation to time and place; or

2. Memory impairment, either short-term (inability to learn new information), intermediate, or long-term (inability to remember information that was known sometime in the past); or

3. Perceptual or thinking disturbances (e.g., hallucinations, delusions); or 4. Change in

personality; or

5. Disturbance in mood; or

6. Emotional lability (e.g., explosive temper outbursts, sudden crying, etc.) and impairment in impulse control; or

7. Loss of measured intellectual ability of at least 15 I.Q. points from premorbid levels or overall impairment index clearly within the severely impaired range on neuropsychological testing, e.g., Luria-Nebraska, Halstead-Reitan, etc;

AND

B. Resulting in at least two of the following:

1. Marked restriction of activities of daily living; or

2. Marked difficulties in maintaining social functioning; or

3. Marked difficulties in maintaining concentration, persistence, or pace; or 4. Repeated episodes

of decompensation, each of extended duration; OR

C. Medically documented history of a chronic organic mental disorder of at least 2 years' duration that has caused more than a minimal limitation of ability to do basic work activities, with symptoms or signs currently attenuated by medication or psychosocial support, and one of the following:
1. Repeated episodes of decompensation, each of extended duration; or

2. A residual disease process that has resulted in such marginal adjustment that even a minimal increase in mental demands or change in the environment would be predicted to cause the individual to decompensate; or

3. Current history of 1 or more years' inability to function outside a highly supportive living arrangement, with an indication of continued need for such an arrangement.

12.03 ***Schizophrenic, Paranoid and Other Psychotic Disorders:*** Characterized by the onset of psychotic features with deterioration from a previous level of functioning.

The required level of severity for these disorders is met when the requirements in both A and B are satisfied, or when the requirements in C are satisfied.

A. Medically documented persistence, either continuous or intermittent, of one or more of the following:

1. Delusions or hallucinations; or

2. Catatonic or other grossly disorganized behavior; or

3. Incoherence, loosening of associations, illogical thinking, or poverty of content of speech if associated with one of the following:

a. Blunt affect; or

b. Flat affect; or

c. Inappropriate affect;

OR

4. Emotional withdrawal and/or isolation.

Appendix B. Search Strategies

Search Strategy #1: Employment
Database: MEDLINE <1966 to April Week 4 2003>
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1. multiple sclerosis/
2. multiple sclerosis.tw.
3. exp myelitis, transverse/
4. transverse myelitis.tw.
5. optic neuritis.tw.
6. exp optic neuritis/
7. or/1-6
8. disability evaluation/ or work capacity evaluation/
9. exp EMPLOYMENT/
10. "Activities of Daily Living"/
11. or/8-9
12. or/8-10
13. 7 and 11
14. limit 13 to (human and english language)
15. 7 and 10
16. 15 not 13
17. limit 16 to (human and english language)

Search #2: Reliability of diagnostic criteria for MS
Database: MEDLINE <1966 to April Week 4 2003>

1	multiple sclerosis/di (4293)
2	mcdonald.mp. (344)
3	multiple sclerosis/ (20934)
4	Reproducibility of Results/ or Observer Variation/ or Psychometrics/ (102929)
5	poser.mp. (116)
6	reliability.mp. (37919)
7	4 or 6 (126832)
8	or/1-2,5 (4705)
9	7 and 8 (149)
10	2 or 5 (457)
11	10 and 3 (102)
12	or/1,11 (4350)
13	7 and 12 (143)
14	from 13 keep 1-143 (143)

Search #3: Effectiveness of treatment for fatigue in MS
Database: MEDLINE <1966 to April Week 4 2003>

1	multiple sclerosis.tw. (20468)
2	exp Multiple Sclerosis/ (21587)
3	Fatigue/ (8057)
4	fatigue.tw. (21592)
5	Amantadine/ (2571)
6	amantadine.tw. (1889)
7	Pemoline/ (408)
8	exp Aminopyridines/ (6784)
9	4-aminopyridine.tw. (3341)
10	3,4-diaminopyridine.mp. (385)
11	exp Potassium Channel Blockers/ (6598)

12 Antidepressive Agents/ or exp Antidepressive Agents, Tricyclic/ or Sertraline/ or Fluoxetine/ or Fluvoxamine/ or Paroxetine/ or exp Serotonin Uptake Inhibitors/ or ssri.mp. or exp Antidepressive Agents, Second-Generation/ (70859)
13 Central Nervous System Stimulants/ (5345)
14 modafinil.mp. (202)
15 or/5-14 (90835)
16 or/1-2 (24958)
17 15 and 16 (189)
18 or/3-4 (25266)
19 18 and 16 (367)
20 17 and 19 (45)
21 from 20 keep 1,3-4,6-7,15,19,26 (8)
22 from 17 keep 1-189 (189)

Search #4: Other symptom therapy and disease-modifying therapies
Database: MEDLINE <1966 to June Week 3 2003>

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1 randomized controlled trials/ (29246)
2 random allocation/ (48831)
3 double-blind method/ (74469)
4 single-blind method/ (7355)
5 randomized controlled trial.pt. (176910)
6 1 or 2 or 3 or 4 or 5 (252007)
7 animal/ (3458955)
8 human/ (8124713)
9 7 and 8 (776249)
10 7 not 9 (2682706)
11 6 not 10 (237650)
12 clinical trial.pt. (360658)
13 exp clinical trials/ (147492)
14 (clin$ adj trial$).tw. (71615)
15 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (71153)
16 placebos/ (23020)
17 placebo$.tw. (79266)
18 random$.tw. (263309)
19 research design/ (37382)
20 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (621803)
21 20 not 10 (578657)
22 comparative-study/ (1052532)
23 exp evaluation studies/ (462029)
24 follow-up studies/ (269186)
25 prospective-studies/ (162165)
26 (control$ or prospectiv$ or volunteer$).tw. (1344071)
27 22 or 23 or 24 or 25 or 26 (2709523)
28 27 not 10 (2072206)
29 21 not 11 (350750)
30 28 not (21 or 11) (1666124)
31 19991$.em. (119004)
32 200$.em. (1786129)
33 or/31-32 (1905133)
34 Anti-Dyskinesia Agents/ or Muscle Relaxants, Central/ or Baclofen/ or MUSCLE SPASTICITY/ or spasticity.mp. or Spasm/ or Botulinum Toxin Type A/ or Botulinum Toxins/ (19461)
35 Diazepam/tu [Therapeutic Use] (3612)
36 exp DEPRESSION/dh, dt, rh, th [Diet Therapy, Drug Therapy, Rehabilitation, Therapy] (10148)
37 exp REHABILITATION/ or exp REHABILITATION CENTERS/ or exp REHABILITATION, VOCATIONAL/ (139505)
38 bladder, neurogenic/ or urination disorders/ or exp urinary incontinence/ or urinary retention/ (24827)
39 or/34-38 (193826)
40 exp multiple sclerosis/ or multiple sclerosis.mp. (25332)
41 39 and 40 (1544)
42 11 and 41 (111)
43 29 and 41 (150)
44 30 and 41 (319)

45 11 and 40 and 33 (277)
46 42 or 45 (359)
47 limit 46 to english language (331)

Search #5: Predictive value of McDonald diagnostic criteria and components
Database: MEDLINE <1966 to April Week 4 2003>

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1 multiple sclerosis/di (4293)
2 mcdonald.mp. (344)
3 multiple sclerosis/ (20934)
4 2 and 3 (15)
5 Magnetic Resonance Imaging/ (103327)
6 3 and 5 (2359)
7 follow-up studies/ (265132)
8 6 and 7 (182)
9 prospective studies/ (158042)
10 6 and 9 (88)
11 8 or 10 (246)
12 "sensitivity and specificity"/ (98408)
13 2 and 12 (3)
14 12 and 1 (171)
15 or/4,11,13-14 (408)
16 or/4,8,13-14 (352)
17 15 not 16 (56)
18 from 15 keep 1-408 (408)
19 Reproducibility of Results/ or Observer Variation/ or Psychometrics/ (102929)
20 poser.mp. (116)
21 19 and 20 (4)
22 19 and 2 (5)
23 19 and 1 (112)
24 Evoked Potentials, Visual/ (8416)
25 3 and 7 and 24 (37)
26 oligoclonal bands.mp. (535)
27 Cerebrospinal Fluid/ (9812)
28 3 and 7 and 27 (4)
29 3 and 7 and 26 (15)
30 or/15,21-23,25,28-29 (529)
31 limit 30 to (human and english language) (465)
32 from 31 keep 1-465 (465)

Appendix C. Instructions for Title and Abstract Screening

Rate each citation as "include" or "exclude" If article doesn't meet criteria but you think it may provide useful background data or be a useful source to identify relevant articles (e.g. a recent on topic review article) then mark it as "include".

Bear in mind the following questions and criteria. You do not need to indicate the question for which the citation is included.

Question 1:

(a) What is the reliability of new McDonald criteria (incorporating supplementary information form radiologic and laboratory studies including MRI, VEP, and CSF analyses) compared with long-term follow-up diagnosis of clinically definite MS according to the Poser criteria?

- Patients with suspected MS
- Compare new McDonald criteria with clinical diagnosis (based on clinical follow-up)
- At least 20 patients

(b) What is the inter-rater reliability of diagnosis of MS according to Poser or McDonald criteria among neurologists or between neurologists and non-neurologist physicians?

- Multiple physicians assess diagnosis of MS on same actual or simulated patients.

Question 2:

What clinical indicators, including particularly time-course of impairments, predict physical or mental impairment at 12 months?

- Patients with suspected MS
- Studies must have follow-up patients for at least 12 months and provide data in the 9-24 month time frame (studies that provide 5-year outcomes for example, would be too distant from the mandated 12-month or permanent time frame for SSA disability determination).
- Ideally, studies should have large numbers of patients, a population-based incidence cohort, and describe the clinical course in enough detail to assess the physical and mental abnormalities at around 12 months after baseline assessment (this does not need to be 12-months from time of diagnosis). Pragmatically, several types of studies might be useful.

1. Large population based cohorts that are not necessarily incidence cohorts.
2. Smaller studies with careful longitudinal follow-up at defined time points (e.g. RCTs)
3. Retrospective case series
4. Case-control studies comparing patients with continued impairments at 12-months to patients with recovery from exacerbations.

Question 3:

(a) Among patients with MS, do current disease-modifying treatments result in long-term improvements in physical or mental outcomes compared to placebo or usual care?

- Study design must be randomized controlled trial
- No restriction on study population's degree of impairment (i.e. low EDSS ok)
- Duration of study must be at least 12 months
- Outcomes of interest would include measures of physical functioning (e.g. EDSS), cognitive functioning, and work/employment outcomes at 12 months or more, as well as relapse rate.

(b) Among patient with MS, do treatments aimed at symptom management result in improvements in physical or mental outcomes compared to usual care?

- Symptom management includes:
  * Bladder management (but not short-term UTI)
  * Spasticity treatment
  * Fatigue treatment eg. exercise
  *Depression treatment
  *Comprehensive rehabilitation programs
- Study design must be randomized controlled trial
- Populations with impairments severe enough that they would clearly meet the current medical listing criteria (eg. EDSS≥6) may be excluded
- Outcomes of interest would include measures of physical or mental functioning that are either generic, or specific to the symptom treated, as well as work/employment outcomes.
- Duration of study may be less than 12 months (at least 3 weeks)

Question 4:

Among individuals with MS, what physical, mental, laboratory, or radiographic findings have been associated with inability to work?

- Study design may include cohort or case control studies or small series (ethnographic studies) and may be cross-sectional or longitudinal.
- Study must describe the association between work/employment status (by self-reported inability to work, work status, or by determination of disability) and certain physical or mental findings
- would generally use univariate or multivariable analysis to determine association between work ability and a variety of physical or mental findings.
- We will not be exclusive with regard to the physical or mental findings considered.

Question 5:

Among individuals with MS, how does elevated temperature or other environmental factors impair the capacity to work?

- Elevated temperature (heat, hot environmental temperature, work conditions that might lead to elevated body temperature [eg. clothing]) is the only environmental issue that is particularly relevant to MS.
- Study must describe work/employment status (by self-reported inability to work, work status, or by determination of disability)

Appendix D. Decision Rules for Full-text Screening

Version 3: June 5, 2003

GENERAL:
Study relevant to at least one of 5 key research questions?
- If yes, then include
- If no, then exclude

PATIENTS:
Are most of all of the patients in this study adult (over 17 years old)?
- If yes, then include
- If no, then exclude

Have some or all of the patients been diagnosed with possible, probable or definite MS?
- If yes, then include
- If no, then exclude

If the study includes a mixed population (MS + other underlying disease), then include if at least one of the following criteria are met:
- Reports results separately for MS population
- Explicitly states there is no difference in outcome between MS and other population
- MS population represents overwhelming majority (>90%) of total population

Otherwise, exclude.

QUESTION 1a:
Does study describe prospective validation of McDonald criteria or equivalent (MRI, VEP, or CSF analyses) according to long-term follow-up diagnosis of clinically-definite MS (according to Poser criteria)?

Exclude article if:

- Not a McDonald criterion (see attached Table 3 from McDonald article)
- Not a longitudinal study
- No long-term diagnosis of clinically definite MS
- Not standard MRI technology such as magnetization transfer. Note: "Standard" MRI technologies include increased T2 images, enhancement, or flare.

Otherwise, include. (Retrospective studies are okay if they include a McDonald criterion).

QUESTION 1b:
Does study describe inter-rater reliability (IRR) of MS diagnosis according to Poser or McDonald criteria among neurologists or between neurologists and non-neurologist physicians?

Exclude article if:

- Reports IRR for MRI techniques other than T2 or gadolinium enhancing. For example, volume and magnetization transfer would be excluded.

Otherwise, include.

QUESTION 2:
Does study describe the association of clinical indicators (signs, laboratory or other objective findings including clinical course, number or frequency of exacerbations) with physical/mental health impairment (e.g., EDSS, cognitive function, fatigue, 6-minute walk, depression scale) 9-24 months later? MUST BE LONGITUDINAL STUDIES; NO CROSS-SECTIONAL STUDIES.

Exclude article if:

- No longitudinal follow-up (e.g., cross-sectional design).
- Time frame is too long (>24 mo) or too short (< 9 months). Article must report data for some point in time between 9 and 24 months.
- No candidate predictors of outcome are considered, i.e., signs, lab, or other objective findings, including clinical course.
- No assessment of physical or mental health outcomes.

Otherwise, include.

QUESTION 3:
Does study address question of efficacy of a treatment aimed at modifying the disease or alleviating a symptomatic manifestation of MS?

Exclude article if:

- Not a RCT

For disease modifying treatments:
Exclude article if:

- Not a "current" treatment, e.g. other than: beta interferon (Avonex, Betaseron, Rebif), glatiramer acetate (Copaxone), mitoxantrone (Novantrone), glucocorticoids.
  Apply this exclusion to disease modifying treatments only.
- Wrong time-frame, that is, too long (> 24 mo) or too short (< 9 mo)
  Apply this exclusion to disease modifying treatments only.
- Outcome measure is NOT a measure of improvement in physical or mental function (e.g., proportion of patients with improved EDSS ≥ 1 point). NOTE: Lack of progression is not sufficient for this purpose.

Otherwise, include.

For symptom management treatments:
Exclude article if:

- Not a long-term symptom management treatment, such as bladder management, spasticity; fatigue treatment (e.g. exercise); depression treatment; comprehensive rehabilitation program. Short-term symptom management (e.g., UTI treatment) would be excluded.

Otherwise, include.

QUESTIONS 4-5:
Does the study report direct or indirect measures of ability to work aimed at MS patients?

- If yes, then include
- If no, then exclude.

Note: "Indirect" measures would include self-reported information such as employment status; measuring performance of non-work tasks (e.g., 6-min walks, ADL) does not meet our definition of "indirect" measures of ability to work.

Appendix E. Evidence Table/Data Abstraction Templates

Question 1a: What is the reliability of new McDonald criteria (incorporating supplementary information from radiologic and laboratory studies including MRI, VEP, and CSF analyses) compared with long-term follow-up diagnosis of clinically definite MS according to the Poser criteria?

Study	Study Design	Patients	Clinical Presentation	Additional Data Used for Diagnosis [Abstractor please complete]	Results [Abstractor please complete]	Comments/Quality Scoring [Abstractor please complete]
StudyID	Prospective/ Retrospective cohort study Case-control study Duration of follow up: Location:	*Prospective studies:* Total no. at start: Dropouts: Completed: *Retrospective studies:* N = (with indication of time point) *Both types of studies:* Age:	[Essentially inclusion criteria; see left hand column of McDonald table]	1) MRI [indicate type of MRI; type of findings reported/analyzed; and frequency of repeat scans, if any] 2) CSF [indicate how test conducted and how "abnormal" defined] 3) VEP [indicate how test conducted and how "abnormal" defined]	[Describe data for each predictor/test considered. Report both relative measures (Hazard ratios, etc.) and absolute rates (e.g., percentages of patients with/without positive CSF who met Poser criteria at long-term follow up; sensitivity and specificity may also be reported); focus should be primarily on absolute rates. Bear in mind that data may be reported for more than one long-term follow-up time point.] 1) 2) 3) 4) 5) 6)	[IF ARTICLE SHOULD BE EXCLUDED, PLEASE EXPLAIN WHY HERE] [COMMENT ON BIASES, ETC. AFFECTING CLINICAL INTERPRETATION – please indicate when points discussed here were raised by authors themselves (e.g., "investigators noted that study was under-powered")] [Please comment here on closeness of fit between clinical presentation and additional test data described in study and specific McDonald criteria.] QUALITY ASSESSMENT: Patients evaluated using Poser criteria regardless of results on initial tests?: Yes/No/Unclear Follow up > 80%?: Yes/No/NR/NA (retrospective cohort study or case-control study) This article is relevant to (please delete as appropriate): Question 1a Question 1b Question 2 Question 3a Question 3b Question 4 Question 5

Question 1b: What is the inter-rater reliability of diagnosis of MS according to Poser or McDonald criteria among neurologists or between neurologists and non-neurologist physicians?

Study	Study Design	Patients & Physicians	Patients' Clinical Presentation	Diagnostic Criteria and Data Available	Results [Abstractor please complete]	Comments/Quality Scoring [Abstractor please complete]
StudyID	Cross-sectional diagnostic test study Multicenter/ Single-center Setting: Location:	*Patients:* N = Age: *Physicians:* N = (broken down by specialty type)	[Essentially inclusion criteria; see left hand column of McDonald table]	1) Diagnostic criteria used: Poser/McDonald/Other 2) Data available for diagnosis (clinical data, neuro exam, MRI, CSF, VEP, lab tests, other):	[Describe data on agreement/ disagreement on MS diagnosis between evaluating physicians. If possible, report raw data needed to complete 2x2-type table, as well as agreement statistics (kappa scores, sensitivity, specificity, simple agreement, etc.).]	[IF ARTICLE SHOULD BE EXCLUDED, PLEASE EXPLAIN WHY HERE] [COMMENT ON BIASES, ETC. AFFECTING CLINICAL INTERPRETATION – please indicate when points discussed here were raised by authors themselves (e.g., "investigators noted that study was under-powered")] [Please comment here on closeness of fit between clinical presentation and additional test data described in study and specific McDonald or Poser criteria.] [Please note authors' speculations (if any) about possible sources/causes of observed agreement/disagreement.] QUALITY ASSESSMENT: Evaluating physicians blinded to one another's diagnosis?: Yes/No/Unclear Did study sample include an appropriate spectrum of patients (not just "difficult" cases)?: Yes/No/Unclear This article is relevant to (please delete as appropriate): Question 1a Question 1b Question 2 Question 3a Question 3b Question 4 Question 5

Question 2: What clinical indicators, including particularly time-course of impairments, predict physical or mental impairment at 12 months?

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Possible Predictors Considered	Results	Comments/Quality Scoring
StudyID	Inclusion: [MS dx, definite/probable, relapse frequency, EDSS] Exclusion:	Retrospective/ Prospective; population-based/ not population-based; cohort study (incl. RCTs)/ case series/ case-control study Duration of follow up:	*Prospective studies:* Total no. at start (if different diagnostic categories, give subtotals by diagnosis): Completed: Dropouts: *Retrospective studies:* N = (with indication of timepoint) *Both types of studies:* Age: Baseline measures of physical and mental functioning:	1) 2) 3) 4) 5) 6)	[Describe data for each predictor considered. Report both relative measures (Hazard ratios, etc.) and absolute rates (e.g., percentages of men and women with EDSS > 6 at 12 mo), but focus primarily on absolute rates. Bear in mind that data may be reported for more than one time point in the 9- to 24-mo time frame of interest to us.] 1) 2) 3) 4) 5) 6)	IF ARTICLE SHOULD BE EXCLUDED, PLEASE EXPLAIN WHY HERE COMMENT ON BIASES, ETC AFFECTING CLINICAL INTERPRETATION (including dropout rate) – please indicate when points discussed here were raised by authors themselves (e.g., "investigators noted that study was under-powered") QUALITY ASSESSMENT: Study described as "population-based"?: Yes/No Sample of patients assembled at a *common* point in the course of their disease?: Yes/No/Unclear Sample of patients assembled at an *early* point in the course of their disease?: Yes/No/Unclear Follow up > 80%?: Yes/No/NR/NA (retrospective cohort or case-control study) Outcomes assessed using a widely used scale?: Yes/No Outcomes assessed in a blind fashion?: Yes/No/Unclear If subgroups with different prognoses identified: a) was there adjustment for important prognostic factors? Yes/No/Unclear/NA b) was there independent validation?: Yes/No/Unclear/NA This article is relevant to (please delete as appropriate): Question 1a Question 1b Question 2 Question 3a Question 3b Question 4

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Possible Predictors Considered	Results	Comments/Quality Scoring
						Question 5

Question 3a: Among patients with MS, do current disease-modifying treatments result in long-term improvements in physical or mental outcomes compared to placebo or usual care?

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results [Abstractor please complete]	Comments/Quality Scoring [Abstractor please complete]
StudyID	Inclusion: [MS dx, definite/probable, relapse frequency, EDSS] Exclusion:	RCT (parallel-group, open-label/double-blind, single-center/ multicenter) Duration of study treatment/follow up: Provider specialty: Location:	No. of patients randomized: [if different diagnostic categories, give subtotals by diagnosis] Dropouts: Completed: Age: Baseline EDSS: Baseline relapse rate:	1) Agent, route, dose 2) 3)	[If outcome/data not reported, type "NR." For each outcome, please report quantitative data (e.g., means ± SD or proportions [numbers of patients/total]) and statistical significance (with direction of effect). Please specify time points at which outcomes measured (9-24 mo).] 1) Physical functioning (primarily EDSS): Definition of "improvement": Proportion of patients with "improvement": Other (non-improvement) outcomes [list outcome measures, do not report data]: 2) Relapse frequency: Definition of "relapse": Definition of "improvement" [includes decrease in relapse rate]: Proportion of patients with "improvement": Other (non-improvement) outcomes [report non-improvement data on relapse rates; otherwise simply list outcome measures]: 3) Cognitive functioning [describe scale/ instrument used]: Definition of "improvement": Proportion of patients with "improvement": Other (non-improvement) outcomes [list outcome measures, do not report data]: 4) Work or employment outcomes: Definition of "improvement":	[IF ARTICLE SHOULD BE EXCLUDED, PLEASE EXPLAIN WHY HERE] [COMMENT ON BIASES, ETC. AFFECTING CLINICAL INTERPRETATION (including dropout rate) – please indicate when points discussed here were raised by authors themselves (e.g., "investigators noted that study was under-powered")] QUALITY ASSESSMENT: Described as "randomized"? Yes/No Method of randomization clearly described? Yes/No Concealment of allocation? Yes/No/Unclear Described as "double-blind"? Yes/No Patients blinded? Yes/No/Unclear Investigators blinded? Yes/No/Unclear Outcome assessors blinded? Yes/No/Unclear No. of withdrawals in each group stated? Yes/No This article is relevant to (please delete as appropriate): Question 1a Question 1b Question 2 Question 3a Question 3b Question 4 Question 5

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results [Abstractor please complete]	Comments/Quality Scoring [Abstractor please complete]
					Proportion of patients with “improvement”: Other (non-improvement) outcomes [list outcome measures, do not report data]: 5) Quality of life [describe scale/ instrument used]: Definition of “improvement”: Proportion of patients with “improvement”: Other (non-improvement) outcomes [list outcome measures, do not report data]: 6) Adverse events (no. of pts reporting AEs, most common AEs [especially when significant between-group difference], and no. of dropouts due to AEs):	

Question 3b: Among patients with MS, do treatments aimed at symptom management result in improvements in physical or mental outcomes compared to usual care?

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results [Abstractor please complete]	Comments/Quality Scoring [Abstractor please complete]
StudyID	Inclusion: [MS dx, definite/probable, relapse frequency, EDSS] Exclusion:	RCT (crossover/ parallel-group, open-label/ double-blind, single-center/ multicenter) Duration of study treatment/follow up: Provider specialty: Location:	No. of patients randomized: [if different diagnostic categories, give subtotals by diagnosis] Dropouts: Completed: Age: Baseline EDSS:	1) Agent, route, dose 2) 3) If crossover, was washout period described?	[If outcome/data not reported, type "NR." For each outcome, please report quantitative data (e.g., means ± SD or proportions [numbers of patients/total]) and statistical significance (with direction of effect). Please specify time points at which outcomes measured (earlier time points acceptable).] 1) Symptom-specific functional status/ quality-of-life outcomes [describe scale/instrument used]: Definition of "improvement": Proportion of patients with "improvement": Other (non-improvement) outcomes [list outcome measures, do not report data]: 2) Physical functioning (primarily EDSS): Definition of "improvement": Proportion of patients with "improvement": Other (non-improvement) outcomes [list outcome measures, do not report data]: 3) Cognitive functioning [describe scale/ instrument used]: Definition of "improvement": Proportion of patients with "improvement": Other (non-improvement) outcomes [list outcome measures, do not report data]: 4) Work or employment outcomes: Definition of "improvement":	[IF ARTICLE SHOULD BE EXCLUDED, PLEASE EXPLAIN WHY HERE] [COMMENT ON BIASES, ETC. AFFECTING CLINICAL INTERPRETATION (including dropout rate) – please indicate when points discussed here were raised by authors themselves (e.g., "investigators noted that study was under-powered")] QUALITY ASSESSMENT: Described as "randomized"? Yes/No Method of randomization clearly described? Yes/No Concealment of allocation? Yes/No/Unclear Described as "double-blind"? Yes/No Patients blinded? Yes/No/Unclear Investigators blinded? Yes/No/Unclear Outcome assessors blinded? Yes/No/Unclear No. of withdrawals in each group stated? Yes/No *Crossover trials only:* Period or carry-over effects? Yes/No/Not discussed Washout period? Yes (give duration)/No No. of patients in each sequence clearly described? Yes/No Were patients who did not complete all of the periods excluded from the analysis? Yes/No/Unclear This article is relevant to (please delete as necessary): Question 1a Question 1b Question 2

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results [Abstractor please complete]	Comments/Quality Scoring [Abstractor please complete]
					Proportion of patients with “improvement”: Other (non-improvement) outcomes [list outcome measures, do not report data]: 5) Generic quality-of-life outcomes [describe scale/ instrument used]: Definition of “improvement”: Proportion of patients with “improvement”: Other (non-improvement) outcomes [list outcome measures, do not report data]: 6) Adverse events (no. of pts reporting AEs, most common AEs [especially when significant between-group difference], and no. of dropouts due to AEs):	Question 3a Question 3b Question 4 Question 5

Question 4: Among individuals with MS, what physical, mental, laboratory, or radiographic findings have been associated with inability to work?

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered [Please verify/edit as needed]	Results [Abstractor please complete]	Comments/Quality Scoring [Abstractor please complete]
StudyID	Inclusion: [MS dx, definite/ probable, relapse frequency, EDSS] Exclusion:	Retrospective/ Prospective/ Cross-sectional; population-based/ not population-based; cohort study (incl. RCTs)/ case series/ case-control study Location/recruitment: Data collection:	N = (if different diagnostic categories, give subtotals by diagnosis) Age: Baseline measures of physical and mental functioning: Baseline work status:	1) Physical: 2) Mental: 3) Laboratory: 4) Radiographic: 5) Other:	[Begin by indicating how work ability was assessed (stating explicitly whether the measure was direct or indirect). For each finding possibly associated with work ability, please report both relative measures of association (Hazard ratios, etc.) and absolute rates (e.g., percentages of patients with EDSS > or < 4 who reported that they are still employed), but focus primarily on absolute rates.] 1) 2) 3) 4) 5) 6)	[IF ARTICLE SHOULD BE EXCLUDED, PLEASE EXPLAIN WHY HERE] [COMMENT ON BIASES, ETC. AFFECTING CLINICAL INTERPRETATION – please indicate when points discussed here were raised by authors themselves (e.g., "investigators noted that study was under-powered")] QUALITY ASSESSMENT: Study described as "population-based"?: Yes/No Follow up > 80%?: Yes/No/NR/NA Work outcomes assessed using a widely used scale?: Yes/No Work outcomes assessed in a blind fashion?: Yes/No/Unclear If subgroups with different work ability identified: a) was there adjustment for important prognostic factors? Yes/No/Unclear/NA b) was there independent validation?: Yes/No/Unclear/NA This article is relevant to (please delete as appropriate): Question 1a Question 1b Question 2 Question 3a Question 3b Question 4 Question 5

Question 5: Among individuals with MS, how does elevated temperature or other environmental factors impair the capacity to work?

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Environmental Factors Considered [Abstractor please complete]	Results [Abstractor please complete]	Comments/Quality Scoring [Abstractor please complete]
StudyID	Inclusion: [MS dx, definite/probable, relapse frequency, EDSS] Exclusion:	Retrospective/ Prospective; population-based/ not population-based; cohort study (incl. RCTs)/ case series/ case-control study	N = (if different diagnostic categories, give subtotals by diagnosis) Age: Baseline measures of physical and mental functioning:	1) Elevated temperature: 2) Other (please specify):	[Begin by indicating how work ability was assessed (stating explicitly whether the measure was direct or indirect). For each environmental factor possibly associated with work ability, please report both relative measures of association (Hazard ratios, etc.) and absolute rates (e.g., percentages of patients in jobs with hot vs. cool working environments who reported that they are still employed), but focus primarily on absolute rates.]	IF ARTICLE SHOULD BE EXCLUDED, PLEASE EXPLAIN WHY HERE COMMENT ON BIASES, ETC AFFECTING CLINICAL INTERPRETATION (including dropout rate) – please indicate when points discussed here were raised by authors themselves (e.g., "investigators noted that study was under-powered")
					1)	QUALITY ASSESSMENT: Study described as "population-based"?: Yes/No Follow up > 80%?: Yes/No/NR/NA (retrospective cohort or case-control study)
					2)	Work outcomes assessed using a widely used scale?: Yes/No Work outcomes assessed in a blind fashion?: Yes/No/Unclear
					3)	If subgroups with different work ability identified: a) was there adjustment for important prognostic factors? Yes/No/Unclear/NA b) was there independent validation?: Yes/No/Unclear/NA
					4)	
					5)	This article is relevant to (please delete as appropriate): Question 1a Question 1b Question 2 Question 3a Question 3b
					6)	Question 4 Question 5

Appendix F. Evidence Tables

Evidence Table 1a. Diagnostic reliability of McDonald criteria

Study	Study Design	Patients	Clinical Presentation	Additional Data Used for Diagnosis	Results	Comments/Quality Scoring
Barkhof, Filippi, Miller, et al., 1997	Prospective cohort study Duration of follow up: Minimum of 2 yr; median follow up among patients not diagnosed with MS at end of study was 39 mo (range, 23-96 mo) Location: 3 sites in Europe (1 each in The Netherlands, Italy, and UK)	Total no. at start: 91 Dropouts: 17 (7 lost to follow up; 10 given definitive diagnosis other than MS and excluded from analysis) Completed: 74 Age: NR	Clinically isolated syndrome suggestive of MS and not attributable to other diseases; among those completing study (n = 74), presenting symptom was optic neuritis in 40 patients, spinal cord syndrome in 22, and brainstem/ cerebellum syndrome in 12	Baseline MRIs performed at a median of 4 wk (range, 1-20 wk) after onset of symptoms Clinically definite MS was diagnosed when clinical signs or symptoms developed in other areas of the central nervous system after a period of at least 1 month, and when other diagnoses had been excluded by appropriate clinical tests 1) MRI –not used in the diagnosis of clinically definite MS 2) CSF- not used in the diagnosis of clinically definite MS 3) VEP – not used in the diagnosis of clinically definite MS MRIs were analyzed during a single session by consensus of two observers who were unaware of the clinical findings	This study examined various MRI lesion characteristics and used regression analysis to determine the utility of each characteristic with regard to diagnosis. Because previous criteria have demonstrated significant sensitivity, but low specificity, the authors then developed a model with greater positive predictive value based on the results of regression analysis. 1) By regression analysis, the four dichotomized MRI parameters that demonstrated the greatest diagnostic utility were presence of 1 or more gadolinium-enhancing lesions, 1 or more infratentorial lesions, 1 or more juxtacortical lesions, and 3 or more periventricular lesions. The final regression model based on the presence of 3 or more of these 4 parameters demonstrated the following characteristics: Sensitivity – 82% Specificity – 78% Accuracy – 80% PPV – 75% NPV – 84%	This study is a thorough, prospective analysis of MRI characteristics with regard to their diagnostic utility, using prospective regression analysis to assess the predictive value of each parameter. On the basis of the findings, a model was developed using the four most predictive parameters. This model became the basis for the MRI criteria used in the McDonald criteria. This study thus does not directly assess the performance of the McDonald criteria, but serves as the basis for the MRI portion of the McDonald criteria. The only significant criticism is that the criteria are based on T2 lesions and gadolinium enhancement without analysis of FLAIR images, sagittal images, or images obtained from higher-strength magnets. These issues were appropriately addressed by the authors. QUALITY ASSESSMENT: Patients evaluated using Poser criteria regardless of results on initial tests?: Yes Follow up > 80%?: Yes

Evidence Table 1a. Diagnostic reliability of McDonald criteria (continued)

Study	Study Design	Patients	Clinical Presentation	Additional Data Used for Diagnosis	Results	Comments/Quality Scoring
Brex, Miszkiel, O'Riordan, et al., 2001	Prospective cohort study Duration of follow up: Median, 12 mo; range, 11-19 mo Location: London, UK	Total no. at start: 81 Dropouts: 13 Completed: 68 attended all 3 study visits and were included in analysis Age at presentation: Mean, 31; range, 17-50	Clinically isolated syndrome (defined as the occurrence of a presumed inflammatory demyelinating event of acute onset in the CNS in a patient with no history suggestive of an earlier demyelinating episode); presenting symptom was optic neuritis in 45 patients, brain stem syndrome in 16, spinal cord syndrome in 6, and optic tract lesion in 1; age 16-50 at presentation; appropriate investigations ruled out alternative diagnoses	Baseline MRIs performed at a median of 5 wk (range, 1-12 wk) after onset of symptoms MRI – performed as part of the initial baseline evaluation and again after 3 mo, with and without contrast enhancement Clinical assessment at 1 yr	1) Contrast enhancing lesion at baseline was the most predictive initial MRI characteristic with positive predictive value of 52%, specificity of 80%, and sensitivity of 61%. 2) A single T2 lesion on baseline scan had highest sensitivity (89%) but poor specificity (36%). 3) The combination of T2 lesions on baseline scan and new T2 lesions on follow-up scan yielded positive predictive value of 55%, sensitivity of 83%, and specificity of 76%. 4) The combination of enhancing lesions on T1 images of both examinations had the highest positive predictive value (70%) and specificity (94%), but had a very low sensitivity (39%).	This study does not directly assess the utility of MRI as specifically used in the McDonald criteria, but it contributes to the idea that MRI scans performed serially augment the clinical criteria of Poser. QUALITY ASSESSMENT: Patients evaluated using Poser criteria regardless of results on initial tests?: Yes Follow up > 80%?: Yes -- 84%
CHAMPS Study Group, 2002	Prospective cohort study Duration of follow up: 18 mo Location: 50 sites in the US and Canada	Total no. at start: 190 Dropouts: NR Completed: NR Age (mean ± SD): 33 ± 7 Patients were enrolled in an RCT comparing interferon beta-1a (30 µg weekly by IM injection; n = 193) vs. placebo (n = 190); all were	First occurrence of an isolated, well-defined neurological event consistent with demyelination and involving the optic nerve (unilateral optic neuritis; n = 97), spinal cord (incomplete transverse myelitis; n = 42), or brain stem or cerebellum (n = 51); ≥ 2 clinically silent T2-hyperintense brain MRI lesions (≥ 3 mm in size, at least one	Baseline MRI performed ≥ 4 days after patient completed initial IV corticosteroid therapy (commenced within 14 days of symptom onset and lasted 3 days), but while patient still receiving oral prednisone (lasted 15 days after IV therapy stopped); median time from onset of symptoms = 18 days, range = 8-39 days MRI – performed ≥ 4 days after initial corticosteroid therapy	1) Overall, 27% of patients (51/190) developed clinically definite MS by 18 mo. 2) The best predictive model for clinically definite MS by 18 mo consisted only of whether patients had ≥ 2 enhancing lesions. None of the other MRI characteristics at their optimized cut-points improved the model fit. 3) A higher percentage of those patients meeting the Barkhof criteria (≥ 9 T2 lesions) developed clinically definite MS (31%) by 18 mo than did patients who did not meet the criteria (16%) (RR = 1.94, 95% CI = 1.02 to 3.72). 4) The highest risk of clinically definite	This study does examine the impact of MRI data in the diagnosis of clinically definite MS – including various MRI criteria. It serves as background information regarding the utility of the addition of MRI criteria in the McDonald criteria. QUALITY ASSESSMENT: Patients evaluated using Poser criteria regardless of results on initial tests?: Yes Follow up > 80%?: Uncertain (dropouts not clearly reported

Evidence Table 1a. Diagnostic reliability of McDonald criteria (continued)

Study	Study Design	Patients	Clinical Presentation	Additional Data Used for Diagnosis	Results	Comments/Quality Scoring
		treated with a course of corticosteroids before the start of the trial. *Only placebo patients are considered in this publication.*	characteristic of MS [periventricular or ovoid]); onset of symptoms 14 days or less before start of IV corticosteroid and 27 days or less before randomization (see under "Patients"); age 18-50	(see above) and at 6, 12, and 18 months for those patients not meeting the primary study endpoint of clinically definite MS due to recurrence	MS was seen among those with ≥ 2 enhancing lesions, with 52% of these patients reaching clinically definite MS by 18 mo compared with 24% of those with < 2 enhancing lesions (RR = 2.16, 95% CI = 1.35 to 3.46).	
Comi, Filippi, Barkhof, et al., 2001	Prospective cohort study Duration of follow up: 2 yr Location: 57 sites in 14 European countries	Total no. at start: 309 Dropouts: 31 Completed: 278 Age: Mean, 28.5 Patients were enrolled in an RCT comparing interferon β-1a (22 µg weekly by SC injection; n = 154) vs. placebo (n = 155); patients were offered open-label interferon after conversion to clinically definite MS	Clinical syndrome indicating unifocal or multifocal involvement of the CNS; first neurological episode suggesting MS in the previous 3 mo; 1 or more abnormalities on neurological exam; positive brain MRI (presence of ≥ 4 white-matter lesions on T2-weighted scans *or* presence of ≥ 3 white-matter lesions if at least one of these was intratentorial or contrast enhancing); age 18-40	Baseline MRI performed as part of pre-study screening, within 3 mo of first neurological episode suggesting MS 1) MRI – performed as part of the initial baseline evaluation and again at 12 and 24 mo 2) CSF – performed only in those patients with initial manifestations suggestive of spinal cord lesion	1) 34% of patients treated with interferon β-1a (52/154) and 45% of patients treated with placebo (69/154) converted to clinically definite MS during the 2-yr study. 2) The only baseline clinical and MRI variables that were significantly predictive of outcome were multifocal onset (odds ratio 1.99 [95% CI, 1.14 to 3.46]; p = 0.015) and T2 lesion number > 8 (3.64 [1.30 to 10.2]; p = 0.014).	This was a placebo-controlled treatment trial in patients with clinically isolated syndromes. The study does include a small amount of data regarding the predictive value of initial evaluations in the diagnosis of MS. Although MRI was used prospectively, the report does not contain data regarding the diagnostic performance of serial MRI studies. This study therefore does not answer question 1a directly but provides some background information regarding the utility of MRI in the diagnosis of MS. QUALITY ASSESSMENT: Patients evaluated using Poser criteria regardless of results on initial tests?: Yes Follow up > 80%?: Yes – 90%

Evidence Table 1a. Diagnostic reliability of McDonald criteria (continued)

Study	Study Design	Patients	Clinical Presentation	Additional Data Used for Diagnosis	Results	Comments/Quality Scoring
Dalton, Brex, Jenkins, et al., 2002	Prospective cohort study Duration of follow up: Median, 12 mo (range, 11-16 mo) Location: London, UK	Total no. at start: 55 Dropouts: 0 Completed: 55 Age: Mean, 29.6; range, 21-41	Clinically isolated syndrome suggestive of MS, defined as a single event of acute onset in the CNS suggestive of demyelination. In study population, 38 had unilateral optic neuritis, 11 brain stem syndrome, 5 spinal cord syndrome, and 1 a hemianopia due to an MRI lesion in the optic tract. Exclusion criteria: History of neuro-logical symptoms suggestive of demyelination; age < 17 or > 50	Baseline MRIs conducted within 3 mo of onset of symptoms MRI – performed at baseline, 3 mo later, and approximately 1 yr after presentation	14/55 patients (25%) developed clinically definite MS and 4 (7%) probable MS according to Poser criteria during the 1-yr follow up. 27 of 55 patients met McDonald criteria for MS at 1 yr.	This study provides minimal data on the relative sensitivity of the Poser and McDonald criteria. This was not the primary purpose of the study, but it does demonstrate increased sensitivity of the McDonald criteria. MRI data focused on ventricular volume changes. QUALITY ASSESSMENT: Patients evaluated using Poser criteria regardless of results on initial tests?: Yes Follow up > 80%?: Yes – 100%
Dalton, Brex, Miszkiel, et al., 2002	Prospective cohort study Duration of follow up: 3 mo to 3 yr (follow up ongoing – see under "Patients," at right) Location: London, UK	Total no. at start: 119 Follow up ongoing at time of publication: 95 patients studied at 3 mo, 79 at 1 yr, and 50 at 3 yr Dropouts: 1 (died of asthmatic attack) Completed: Follow up ongoing; see above Age: Median at onset, 31; range, 16-50	Clinically isolated syndrome, defined as an acute isolated event affecting one region of the CNS and presumed to be demyelinating, with no previous history of possible demyelinating events. In study population, 87 had acute unilateral optic neuritis, 2 bilateral consecutive optic neuritis, 19 brain stem syndrome, 10 spinal cord syndrome, and 1 demyelinating optic	Baseline MRIs conducted within 3 mo of onset of symptoms MRI of the brain was performed at baseline, 3 mo, 1 yr, and 3 yr. MRI of the spinal cord was performed at baseline, 1 yr, and 3 yr.	1) Clinically definite MS was present in 7% of patients (7/95) at 3 mo, 20% (16/79) at 1 yr, and 38% (19/50) at 3 yr follow up. 2) Performance of the McDonald criteria at 3-mo evaluation for predicting the development of clinically definite MS at 1 yr: Sensitivity = 73% Specificity = 87% PPV = 58% NPV = 93% Accuracy = 84% 3) Performance of the McDonald criteria at 1-yr evaluation for predicting the development of clinically definite MS at 3 yr: Sensitivity = 94%	This study specifically evaluates the performance of the McDonald criteria in comparison with the Poser criteria. This is a preliminary report of a 3-yr study in which fewer than 80% of patients had completed the 1-yr evaluation. The study demonstrates a significant increase in sensitivity of the McDonald criteria. QUALITY ASSESSMENT: Patients evaluated using Poser criteria regardless of results on initial tests?: Yes Follow up > 80%?: No – at the time of this report the study was ongoing with fewer than 80% of patients having had 1-yr evaluations

Evidence Table 1a. Diagnostic reliability of McDonald criteria (continued)

Study	Study Design	Patients	Clinical Presentation	Additional Data Used for Diagnosis	Results	Comments/Quality Scoring
			tract lesion. Maximal symptoms and signs evident within 14 days of symptom onset. Alternative diagnoses excluded. Age 16-50.		Specificity = 83% PPV = 77% NPV = 96% Accuracy = 87%	
Filippi, Horsfield, Morrissey, et al., 1994	Prospective cohort study Duration of follow up: Mean ± SD, 63 ± 11 mo; range, 43-84 mo Location: London, UK	Total no. at start: 129 Dropouts: 40 of original cohort not included in this 5-yr follow up Completed: 89 re-examined and re-scanned at 5-yr follow up; 84 had complete data available (initial MRI unavailable at follow up for 5) Age at baseline presentation: Mean, 31; range, 13-50	Clinically isolated syndrome of the optic nerves (n = 40), brainstem (n = 16), or spinal cord (n = 28) suggestive of MS; syndrome fully developed within 14 days of symptom onset; age 10-50 at presentation; appropriate studies (including initial MRI) ruled out alternative diagnoses	Baseline MRIs were conducted within 60 days of onset of symptoms in 69/84 patients (82%), later in remaining 15 patients 1) MRI – repeat MRI scans were performed after a mean of 63 mo. Quantitative semi-automated computer assessment of T2 lesion load was performed in a manner shown to have an intrarater reproducibility of 6%. 2) Clinical examination – patients were re-examined after a mean of 63 mo with assessment of EDSS. MS was diagnosed solely on clinical grounds using Poser criteria.	1) During 5-yr follow up, 34 patients (40%) developed clinically definite MS: 18 of 40 (45%) with initial optic neuritis, 10 of 28 (36%) with initial spinal cord syndrome, and 6 of 16 (38%) with initial brainstem syndrome. 4 patients (5%) developed clinically probable MS – 2 with initial optic neuritis and one each with spinal cord or brainstem syndrome. 2) 52 patients with abnormal MRI at presentation with median total brain lesion volume 0.83 cm^3 (range, 0.09-52.41), with median infratentorial lesion volume of 0 cm^3 (range, 0-1.82) 3) Patients developing MS had significantly higher total and infratentorial lesion loads at presentation than those who did not: median total lesion volumes were 1.15 cm^3 (range, 0-52.41) versus 0 cm^3 (range, 0-25.6), $p < 0.0001$; the median infratentorial lesion volumes were 0 cm^3 (range, 0-1.82) versus 0 cm^3 (range, 0-0.59), $p < 0.0001$. 4) Lesion load of 1.23 cm^3 at presentation afforded the highest probability of separating patients developing MS from those who did not. Patients then divided into three groups: Group A - patients with total lesion volume ≥ 1.23 cm^3, Group B - patients with abnormal MRI but total lesion volume < 1.23 cm^3, and Group C - patients with normal MRI at baseline. Results:	The MRI criteria used here are similar to those used in the McDonald criteria but not precisely the same. This study supports the use of MRI findings in the diagnosis, but does not directly compare with the MRI criteria adopted in the McDonald criteria. Additional reports on this study population are provided in Morrissey, Miller, Kendall, et al., 1993; and O'Riordan, Thompson, Kingsley, et al., 1998, below. QUALITY ASSESSMENT: Patients evaluated using Poser criteria regardless of results on initial tests?: Yes Follow up > 80%?: Yes – 84%

Evidence Table 1a. Diagnostic reliability of McDonald criteria (continued)

Study	Study Design	Patients	Clinical Presentation	Additional Data Used for Diagnosis	Results	Comments/Quality Scoring
					Group A - 19 of 21 (90%) patients developed MS (18 clinically definite, 1 clinically probable) Group B - 17 of 31 (55%) developed MS (15 definite and 2 probable) Group C – 2 of 32 (6%) developed MS (1 definite and 2 probable) 5) 18 of 20 (90%) patients with infratentorial lesions developed MS (all clinically definite), whereas 44 of 64 (69%) without such lesions did not. 6) A significant correlation was found between total and infratentorial lesion load on the initial MRI (Spearman rank correlation coefficient = 0.649; $p < 0.0001$).	
Ghezzi, Martinelli, Torri, et al., 1999	Prospective cohort study Duration of follow up: Mean ± SD, 6.3 ± 2.2 yr; median, 5 yr Location: Gallarate, Italy	Total no. at start: 112 Dropouts: 10 lost to follow up Completed: 102 Age: Mean ± SD, 29.2 ± 9.0	Acute isolated optic neuritis	Baseline paraclinical tests performed within 6 mo of onset of optic neuritis; mean interval, 45 ± 24 days 1) MRI – performed at baseline only – details not delineated 2) CSF IgG Index was the parameter utilized; definition of abnormal not stated 3) VEP – Multiple Evoked Potential studies were performed at baseline. No details regarding technique were presented.	36% of patients (37/102) developed clinically definite MS in 2.3 ± 1.6 yr of follow up after initial attack of optic neuritis. Number of patients developing MS in relation to the results of paraclinical tests performed at baseline: MS+ MS- P-value 1) MRI: 0.0001 Negative 37 34 Positive 0 31 2) CSF: 0.19 Negative 22 29 Positive 12 31 3) VEP: 0.95 Negative 10 16 Positive 26 48 4) BAEP, median nerve SEP, and upper limb MEP: 0.7 Negative 2 7	This study evaluated the utility of paraclinical tests in predicting those patients with clinically isolated syndromes who would progress to develop clinically definite MS. The data presented provide background information regarding the utility of paraclinical tests, but do not directly evaluate the McDonald criteria in that the paraclinical tests were not applied in the same manner as used in the McDonald criteria. QUALITY ASSESSMENT: Patients evaluated using Poser criteria regardless of results on initial tests?: Yes Follow up > 80%?: Yes – 91%

Evidence Table 1a. Diagnostic reliability of McDonald criteria (continued)

Study	Study Design	Patients	Clinical Presentation	Additional Data Used for Diagnosis	Results	Comments/Quality Scoring
					Positive 17 31 5) BAEP, median and tibial nerve SEP: 0.02 Negative 9 5 Positive 6 21	
Morrissey, Miller, Kendall, et al., 1993	Prospective cohort study Duration of follow up: Mean, 63.6 mo; range, 43-84 mo Location: London, UK	Total no. at start: 132 Dropouts: 43 of original cohort not included in 5-yr follow up Completed: 89 re-examined and re-scanned at 5-yr follow up Age at baseline presentation: Mean, 31.3; range, 13-50	Clinically isolated syndrome of the optic nerves (n = 44), brainstem (n = 17), or spinal cord (n = 28) suggestive of MS; syndrome acute or subacute in onset; age 10-50 at presentation; appropriate studies (including initial MRI) ruled out alternative diagnoses	Baseline MRIs were conducted within 60 days of onset of symptoms in 74/89 patients (83%), later in remaining 15 patients 1) MRI – performed at baseline and a mean of 1.3 yr later and again at 5.3 yr – all scans were unenhanced 2) CSF – not performed in patients with clinically isolated optic neuritis, but was performed in patients with isolated spinal cord or brainstem syndromes	After 5 yr, progression to clinically definite MS occurred in 41 of 57 (72%) of patients who had had abnormal initial scans, but in only 2 of 36 (6%) patients whose initial scan was normal (P < 0.0001).	This study provides background information regarding the utility of MRI in the diagnosis of MS but does not utilize MRI in the same manner as the McDonald criteria and therefore does not answer Question 1a specifically. Additional reports on this study population are provided in Filippi, Horsfield, Morrissey, et al., 1994, above; and O'Riordan, Thompson, Kingsley, et al., 1998, below. QUALITY ASSESSMENT: Patients evaluated using Poser criteria regardless of results on initial tests?: Yes Follow up > 80%?: No – 67%
Optic Neuritis Study Group, 1997	Prospective cohort study Duration of follow up: 5 yr Location: 15 sites in the US	Total no. at start: 388 Dropouts: 47 Completed: 341 followed up for 5 yr Age (mean ± SD): 32 ± 7 Patients were participants in an RCT comparing IV methylprednisolone	Acute unilateral optic neuritis with visual symptoms of 8 days or less; no previous history of optic neuritis or ophthalmoscopic signs of optic atrophy in the affected eye; no evidence of a systemic disease other than MS that might be associated with the optic neuritis; no previous treatment	Baseline MRIs performed "on study entry" (within 8 days of onset of acute symptoms) MRI – brain MRI was performed at baseline according to standardized protocols	1) 27% of patients (106/388) developed clinically definite MS with 5 yr, and an additional 9% (35 patients) developed probable MS. 2) The presence of MRI abnormalities at the time of optic neuritis was the single most important predictor of the development of clinically definite MS by 5 yr. The probability of clinically definite MS was 16% in the 202 patients with no MRI abnormalities, 37% in the 60 patients with 1-2 MRI abnormalities, and 51% in the 89 patients with ≥ 3 MRI abnormalities.	This study provides background information regarding the utility of MRI in the diagnosis of MS, but the utilization of MRI did not include serial studies as is the case for the McDonald criteria, and therefore this report does not provide direct data on the performance of the McDonald criteria. QUALITY ASSESSMENT: Patients evaluated using Poser criteria regardless of results on initial tests?: Yes Follow up > 80%?: Yes – 88%

Evidence Table 1a. Diagnostic reliability of McDonald criteria (continued)

Study	Study Design	Patients	Clinical Presentation	Additional Data Used for Diagnosis	Results	Comments/Quality Scoring
		vs. oral prednisone vs. oral placebo	with corticosteroids for MS or for optic neuritis in the opposite eye; age 18-46 yr Patients with a diagnosis of clinically definite or probable MS were excluded			
O'Riordan, Thompson, Kingsley, et al., 1998	Prospective cohort study Duration of follow up: Mean, 9.7 yr Location: London, UK	Total no. at start: 129 Dropouts: 48 of original cohort not included in this 10-yr follow up Completed: 81 re-examined and re-scanned at 10-yr follow up Age at baseline presentation: Mean, 32.3; range, 17-49	Clinically isolated syndrome (defined as an acute or subacute episode suggestive of demyelination affecting the optic nerves [n = 42], brainstem [n = 16], or spinal cord [n = 23]); age 10-50 at presentation; appropriate studies (including initial MRI) ruled out alternative diagnoses	Not clear when baseline MRIs conducted 1) MRI – baseline and follow-up scans up to the 5-yr scans were performed on a 0.5 T scanner using SE2000/60 sequences. 10-yr scans were performed on a 1.5 T scanner and used conventional dual spin echo technique. All scans were evaluated only for the presence of hyperintense lesions. Scans were considered abnormal only if one or more asymptomatic lesions characteristic for demyelination were present. The number of lesions compatible with demyelination was recorded. All scans were read with the baseline and 5-yr scans side-by-side for comparison. 2) Diagnosis of MS was made solely on the basis of Poser criteria after 10 yr of follow up	1) Patients with a normal baseline MRI (n = 27): Only 3 patients (11%) progressed to clinically definite MS, all of whom had benign disease. 2 additional patients (7%) had clinically probable MS. Of these 5 patients, 4 had 10-yr follow-up MRIs and all had developed new lesions. 22 patients of these original 27 (81%) were still classified as having clinically isolated syndromes. 2) Patients with abnormal MRI at baseline (n = 54): After 10 yr, only 7 patients (13%) still had a diagnosis of clinically isolated syndrome, 2 patients (4%) had clinically probable MS, and 45 patients (83%) had progressed to clinically definite MS. Of those with clinically definite MS, 21 patients (39%) had benign disease, 11 patients (20%) relapsing/remitting disease with an EDSS of > 3, and 13 patients (24%) developed secondary progressive MS. For those with an abnormal baseline MRI, the presence of infratentorial lesions did not confer any greater risk for the subsequent development of clinically definite MS.	The MRI criteria used here are similar to those used in the McDonald criteria but not precisely the same. This study supports the use of MRI findings in the diagnosis, but does not directly compare with the MRI criteria adopted in the McDonald criteria. Additional reports on this study population are provided in Filippi, Horsfield, Morrissey, et al., 1994; and Morrissey, Miller, Kendall, et al., 1993, above. QUALITY ASSESSMENT: Patients evaluated using Poser criteria regardless of results on initial tests?: Yes Follow up > 80%?: No – 81 patients at 10-yr follow up of 129 patients in original cohort = 63%

Evidence Table 1a. Diagnostic reliability of McDonald criteria (continued)

Study	Study Design	Patients	Clinical Presentation	Additional Data Used for Diagnosis	Results	Comments/Quality Scoring
Sastre-Garriga, Tintoré, Rovira, et al., 2003	Prospective cohort study Duration of follow up: Mean, 37 mo Location: Barcelona, Spain	Total no. at start: 59 Dropouts: 8 (excluded because follow-up shorter than 12 mo) Completed: 51 Age: Mean at assessment, 29; range, 14-49	Episode of clinical brainstem dysfunction suggestive of inflammatory demyelination; clinical assessment within 3 mo of onset of symptoms; age < 50; other possible diagnoses excluded	Mean time between onset of symptoms and initial MRI 29 days 1) MRI – 1.0 or 1.5 T scanners including transverse proton density and T2-weighted conventional spin echo or fast spin echo, and T1-weighted spin echo. T1 images were repeated after administration of gadolinium. Sagittal T2 or transverse T2 FLAIR were also performed on most patients. A blinded neuroradiologist recorded the number and sites of abnormalities. The MRI diagnostic criteria of Paty, Fazekas, and Barkhof were then studied. 2) CSF – presence of oligoclonal bands were assessed, but not used in the diagnosis of MS 3) VEP – values of VEP and SEP results were assessed but not used in the diagnosis of MS	1) Paty MRI criteria: Sensitivity = 89% Specificity = 52% PPV = 50% NPV = 89% Accuracy = 65% 2) Fazekas MRI criteria: Sensitivity = 89% Specificity = 48% PPV = 48% NPV = 89% Accuracy = 63% 3) Barkhof MRI criteria: Sensitivity = 78% Specificity = 61% PPV = 52% NPV = 83% Accuracy = 67% 4) CSF – presence of oligoclonal bands: Sensitivity = 100% Specificity = 42% PPV = 44% NPV = 100% Accuracy = 63% 5) Evoked potential studies – no statistically significant differences for baseline VEP or SSEP parameters were found between patients who did and those who did not convert to MS	Clinical diagnosis of MS was made based on the occurrence of neurological symptoms lasting over 24 hr without the requirement of objective findings on neurological examination. This definition is more sensitive but less specific than most clinical criteria in use, including the Poser criteria. Additionally, this study evaluated the ability of baseline parameters to predict the subsequent development of MS. These parameters were not performed serially to assess their correlation with clinical diagnosis. QUALITY ASSESSMENT: Patients evaluated using Poser criteria regardless of results on initial tests?: No – symptomatic recurrence did not require objective examination abnormalities Follow up > 80%?: Yes – 86%

Evidence Table 1a. Diagnostic reliability of McDonald criteria (continued)

Study	Study Design	Patients	Clinical Presentation	Additional Data Used for Diagnosis	Results	Comments/Quality Scoring
Tintoré, Rovira, Río, et al., 2003	Cohort study; data collected prospectively, McDonald criteria applied retrospectively Duration of follow up: Mean, 39 ± 17.2 mo; range, 12-77 mo; all patients were followed up for at least 1 yr (inclusion criterion), 122 for at least 2 yr, and 86 for at least 3 yr Location: Barcelona, Spain	Total no. at start: 139 Dropouts: 17 by 2 yr; 53 by 3 yr Completed: 139 were followed up for at least 1 yr (inclusion criterion), 122 for at least 2 yr, and 86 for at least 3 yr Age: Mean, 30; range, 13-49	Clinically isolated syndrome suggestive of CNS demyelination involving the optic nerve (41.5%), brainstem (24.5%), spinal cord (28%), or combinations of the above (6%), and not attributable to other diseases; age < 50 yr Analysis included only patients with clinical and MRI examinations within 3 mo of onset of symptoms and clinical follow up of at least 12 mo	Baseline MRIs completed within 3 mo of onset of symptoms 1) MRI – standard MRI techniques used after the first demyelinating event and 12 mo later 2) CSF – the presence of oligoclonal bands was assessed after the first demyelinating event	1) At 1 yr, 15 patients (11%) had a second clinical attack and therefore fulfilled the requirement for dissemination in time and space necessary for clinically definite MS according to the Poser criteria. Of these 15 patients, 10 also fulfilled the radiologic conditions of dissemination in time and space. 2) Fifty-one patients (37%) fulfilled MRI requirements for dissemination in time and space and therefore were considered to have MS according to the McDonald criteria. Ten of these 51 patients (20%) had a second clinical event during the first year of follow up. In total, 56 of 139 patients (40%) fulfilled the McDonald criteria for MS either by MRI or clinically. 3) The McDonald criteria showed a sensitivity of 74%, specificity of 85%, PPV of 80%, NPV of 80%, and accuracy of 80% in predicting conversion to clinically definite MS: Clinically definite MS at 3 yr + - McDonald criteria at 1 yr + 28 7 - 10 41 4) In the first year the Poser criteria allowed the diagnosis of clinically definite MS in 11% compared with 37% with the McDonald criteria.	This article precisely and specifically evaluates Question 1a. QUALITY ASSESSMENT: Patients evaluated using Poser criteria regardless of results on initial tests?: Yes Follow up > 80%?: Yes – 100% (first yr)

Evidence Table 1b. Inter-rater reliability of diagnosis with McDonald and Poser criteria

Study	Study Design	Patients & Physicians	Patients' Clinical Presentation	Diagnostic Criteria and Data Available	Results	Comments/Quality Scoring
Ford, Johnson, and Rigby, 1996	Cross-sectional diagnostic test study (retrospective) Single-center Setting: General neurology outpatient clinic Location: Leeds, UK	*Patients:* N = 85 Age: Mean, 46; range, 23-74 *Physicians:* N = 2 (both neurologists)	Patients had been diagnosed according to Poser criteria as having clinically definite MS, laboratory-supported definite MS, clinically probable MS, laboratory-supported probable MS, or suspected MS, or as "unable to classify"; all were outpatients at study clinic	1) Diagnostic criteria used: Poser 2) Data available for diagnosis: Diagnoses made entirely on basis of data contained in case records of patients; precise data contained in these unclear	Overall, there was substantial agreement between the two observers in classifying multiple sclerosis according to the Poser criteria (κ = 0.65, 95% CI = 0.52 to 0.78). There was poor agreement in the historical data used to classify the cases (κ = 0.30, 95% CI = 0.03 to 0.57).	This study was a retrospective review of case records and therefore the evaluators lacked the ability to examine patients themselves and therefore variation in clinical judgment occurred. The authors note that "retrospective analysis may also underestimate the extent of variation between observers." This study specifically utilized Poser criteria for diagnosis. The authors note that possible sources of observed disagreement likely include lack of adequate documentation contained in medical records. QUALITY ASSESSMENT: Evaluating physicians blinded to one another's diagnosis?: Yes Did study sample include an appropriate spectrum of patients (not just "difficult" cases)?: Yes
Zipoli, Portaccio, Siracusa, et al., 2003	Cross-sectional diagnostic test study Single-center Setting: University department of neurology Location: Florence, Italy	*Patients:* N = 44 Age (mean $\pm$ SD): 31 $\pm$ 7.5 *Physicians:* N = 4 neurologists	All cases consecutively admitted for diagnostic assessment at study site between Sep 2001 and June 2002 and prospectively followed up for $\geq$ 6 mo; data collected via chart review Patients' (preexisting) diagnoses as follows: 41 MS (15 relapsing-remitting,	1) Diagnostic criteria used: Poser McDonald 2) Data available for diagnosis: Family and patient clinical history Complete neurological exam Lab tests (blood counts, etc.) Occurrence of new or worsening symptoms Brain MRI Spinal cord MRI (when appropriate) CSF examination Evoked potentials	Poser criteria: Diagnosis of MS: κ = 0.57 Dissemination in time: κ = 0.69 Dissemination is space: κ = 0.46 Diagnosis of clinically definite MS: κ = 0.39 Diagnosis of clinically probable MS: κ = 0.37 McDonald criteria: Diagnosis of MS (all categories): κ = 0.52 Diagnosis of MS: κ = 0.52 Diagnosis of possible MS: κ = 0.49 Diagnosed not MS: κ = 0.64	This study specifically addressed the inter-rater reliability of the Poser and McDonald criterion. It thus provides data directly answering Question 1b. The primary difficulty in the McDonald criteria appeared to be decreased agreement in MRI interpretation – specifically in those patients with high lesion loads. The authors commented that this study utilized neurologist evaluators not neuroradiologists and previous studies have correlated level or radiographic training with agreement in interpretation. Judging dissemination in time was of particular difficulty in those patients with clinically isolated symptoms. The authors suggested that neuroradiologists be encouraged to interpret scans in MS patients with the

Evidence Table 1b. Inter-rater reliability of diagnosis with McDonald and Poser criteria (continued)

Study	Study Design	Patients & Physicians	Patients' Clinical Presentation	Diagnostic Criteria and Data Available	Results	Comments/Quality Scoring
			2 secondary progressive, 5 primary progressive, 19 presenting with first clinical attack) 1 cerebral autosomal dominant arteriopathy with subcortical infarcts and leuko-encephalopathy 1 migraine with aura 1 Leber's hereditary optic neuropathy	"Other examinations performed for the differential diagnosis"		McDonald MRI criteria in mind – providing specific information regarding lesion location and timing. QUALITY ASSESSMENT: Evaluating physicians blinded to one another's diagnosis?: Yes Did study sample include an appropriate spectrum of patients (not just "difficult" cases)?: Yes

Evidence Table 2. Predictors of physical and mental impairments at 12 months

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Possible Predictors Considered	Results	Comments/Quality Scoring
Chapman, Sylantiev, Nisipeanu, et al., 1999	Inclusion: Clinically definite MS; relapsing-remitting course Exclusion: None	Prospective, population-based, cohort study Duration of follow up: Follow up conducted every 3 mo for a period of 2 yr	Total no. at start: 47 *APOE* ε4: N = 9 heterozygous for *APOE* ε4 allele N = 1 homozygous for *APOE* ε4 allele N = 37 without allele Completed: N = 8 *APOE* ε4 N = 33 Non-*APOE* ε4 Dropouts: N = 2 *APOE* ε4 N = 4 Non-*APOE* ε4 Age (mean): *APOE* ε4: 34.0 ± 1.4 Non-*APOE* ε4: 36.0 ± 2.3 years Baseline measures of physical and mental functioning: *APOE* ε4: EDSS Mean: 3.10 ± 0.45 EDSS Range: 1.5-6.0 Exacerbation rate, per year: 1.05 ± 0.05 Non-*APOE* ε4: EDSS Mean: 2.62 ± 0.25 EDSS Range: 0-6.0 Exacerbation rate, per year: 1.12 ± 0.06	Presence of *APOE* ε4 allele	1) Significant interaction of genotype with change in disability over 2-yr time period (P = 0.02): *APOE* ε4: Mean EDSS deteriorated to 4.00 ± 0.63 Non-*APOE* ε4: Mean EDSS stable at 2.74 ± 0.31 2) No significant difference (P > 0.35) for the three possible predictors: a. Duration of illness at entry: *APOE* ε4: 48 ± 12 mo Non-*APOE* ε4: 57 ± 10 mo b. Exacerbation rate over previous 2 yr: *APOE* ε4: 1.05 ± 0.05 per yr Non-*APOE* ε4: 1.12 ± 0.06 per yr c. EDSS score: *APOE* ε4: 3.10 ± 0.45 Non-*APOE* ε4: 2.62 ± 0.25 3) Exacerbation characteristics: Mean EDSS before peak: *APOE* ε4: 3.67 ± 1.30 Non-*APOE* ε4: 2.00 ± 0.54 Mean EDSS at peak: *APOE* ε4: 4.67 ± 1.30 Non-*APOE* ε4: 3.37 ± 0.44 Mean EDSS at resolution of exacerbation: *APOE* ε4: 4.50 ± 1.26 Non-*APOE* ε4: 2.04 ± 0.52 Borderline significant interaction (P = 0.049, 1-tailed) between groups for EDSS scores at peak and at resolution, indicating impaired recovery in *APOE* ε4 carriers	For all missing data, the last observation was carried forward in the statistical analyses. Information about the number of observations that were carried forward was not provided. QUALITY ASSESSMENT: Study described as "population-based"?: No Sample of patients assembled at a *common* point in the course of their disease?: Yes Sample of patients assembled at an *early* point in the course of their disease?: Yes Follow up > 80%?: Yes Outcomes assessed using a widely used scale?: Yes Outcomes assessed in a blind fashion?: Unclear If subgroups with different prognoses identified: a) was there adjustment for important prognostic factors? No b) was there independent validation?: NA

Evidence Table 2. Predictors of physical and mental impairments at 12 months (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Possible Predictors Considered	Results	Comments/Quality Scoring
Cottrell, Kremen-chutzky, Rice, et al., 1999a **and** **Cottrell, Kremen-chutzky, Rice, et al., 1999b**	Inclusion: Primary progressive MS Exclusion: None specified	Prospective, population-based, cohort study Duration of follow up: Original cohort followed up for mean of 23 yr; follow-up time for 2nd cohort NR	Total no. at start: Original cohort, 216; 2nd cohort, 165 Dropouts: NR Completed: NR Age: Mean age at onset, 38.5 in original cohort, 38.9 in 2nd cohort Baseline measures of physical and mental functioning: Mean DSS score at presentation (4) reported for 2nd cohort only	DSS at time 0 – evaluated in relation to 3 different groups of patients: a) Original cohort; b) Simulated group of patients at DSS 3, 4, or 5 who had progressed one level in the last yr and had reached DSS 3 by 5 yr; c) Simulated group of patients at DSS 4, 5, or 6 who had progressed one level in the last year and had reached DSS 4 by 10 yr Prognostic factors considered: a) Sex b) Age of onset c) System involved at onset d) Number of systems e) Rate of early disability	Probability of progression to next DSS level within 1 year (original cohort, n = 216): DSS Level / Probability / Median / N entering 1 / 0.87 / 0.6 yr / 190 2 / 0.26 / 1.9 yr / 182 3 / 0.31 / 1.8 yr / 179 4 / 0.40 / 1.3 yr / 171 5 / 0.33 / 1.6 yr / 163 6 / 0.04 / 4.0 yr / 174 7 / 0.10 / 3.9 yr / 131 8 / 0.02 / 11.5 yr / 125 9 / 0.08 / 7.2 yr / 48 Multiple regression (accelerated failure time) analysis of prognostic factors for DSS 8: Factor / Regression Coefficient / SE / P-value / Effect Tested Sex / 0.037 / 0.078 / 0.63 / M vs. F Age at onset / -0.001 / 0.004 / 0.15 / Linear Years to DSS 3 / 0.067 / 0.011 / 0.0001 / Linear No. of systems / -0.457 / 0.19 / 0.01 / 3 vs. 1 No. of systems / -0.09 / 0.08 / 0.27 / 2 vs. 1 Origin of case / -0.08 / 0.1 / 0.41 / Middlesex vs. Non-Middlesex	QUALITY ASSESSMENT: Study described as “population-based”?: Yes Sample of patients assembled at a *common* point in the course of their disease?: Yes Sample of patients assembled at an *early* point in the course of their disease?: Yes Follow up > 80%?: NR Outcomes assessed using a widely used scale?: No Outcomes assessed in a blind fashion?: Unclear If subgroups with different prognoses identified: a) was there adjustment for important prognostic factors? Yes b) was there independent validation?: No

Evidence Table 2. Predictors of physical and mental impairments at 12 months (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Possible Predictors Considered	Results	Comments/Quality Scoring
Fuhr, Borggrefe-Chappuis, Schindler, et al., 2001	Inclusion: Clinically definite MS; relapsing-remitting or secondary progressive course; EDSS score ≥ 2 and ≤ 6.5; MRI during last 12 mo consistent with MS diagnosis; MRI during 2 wk before entry showing at least one gadolinium-enhancing lesion Exclusion: Chronic steroid or immunosuppressive drug treatment during past 6 mo; acute steroid treatment for a relapse during past 4 wk	Prospective case series Duration of follow up: 2 yr	Total no. at start: 30 25 relapsing-remitting 5 secondary progressive Completed: 30 Dropouts: 0 Age: Median 37.5 (range, 26-50) Sex: Male: 6 (20%) Female: 24 (80%) Baseline measures of physical and mental functioning: Median EDSS at entry: 4.65 (range, 2-6.5) Mean disease duration at entry: 9.2 years (range, 1.5-22 years)	Combined motor evoked potentials (MEPs) and visual evoked potentials (VEPs), sum of Z-transformed latencies at baseline	<table><tr><td></td><td></td><td colspan="2">Δ EDSS 0 to 24 mo</td></tr><tr><td rowspan="3">Sum of Z-transformed latencies</td><td></td><td>> 0</td><td>≤ 0</td></tr><tr><td>> 0</td><td>9</td><td>3</td></tr><tr><td>≤ 0</td><td>8</td><td>7</td></tr></table> Sensitivity = 9/17 (53%) Specificity = 7/10 (70%) PPV = 9/11 (82%) NPV = 7/15 (47%) Prevalence = 12/27 (44%) Median EDSS at entry: 4.65 (range, 2-6.5) Median EDSS at end of study: 5.1 (range, 2-9)	Table in "Results" column, as well as predictive value information, calculated by abstractor using data from Figure 2.0 for sum of Z-transformed latencies at T_0 QUALITY ASSESSMENT: Study described as "population-based"?: No Sample of patients assembled at a *common* point in the course of their disease?: Unclear Sample of patients assembled at an *early* point in the course of their disease?: Unclear Follow up > 80%?: Yes Outcomes assessed using a widely used scale?: Yes Outcomes assessed in a blind fashion?: No If subgroups with different prognoses identified: a) was there adjustment for important prognostic factors? NA b) was there independent validation?: NA
Goodkin, Hertsgaard, and Rudick, 1989	Inclusion: Definite or probable MS Exclusion: None specified	Prospective, clinic-based, cohort study Duration of follow up: 1-5 yr (mean 2.6 yr)	Total no. at start: 425 336 definite MS 89 probable MS Completed: 254 definite MS Dropouts: 82 definite MS 89 probable MS Age: No mean reported	Disease type (determined from patient history and neurological records) Disease types: S = stable RRS = relapsing remitting stable RRP = relapsing remitting progressive CP = chronic	Change in EDSS score at 2 yr (mean ± SD) (P = 0.1296): S = 0.108 ± 1.275 RRS = 0.098 ± 1.693 RRP = 0.717 ± 2.340 CP = 0.689 ± 1.301 No significant difference was found among the various disease types for changes in EDSS over the 2-yr time period No significant difference in exacerbation rates by disease type	QUALITY ASSESSMENT: Study described as "population-based"?: No Sample of patients assembled at a *common* point in the course of their disease?: Yes Sample of patients assembled at an *early* point in the course of their disease?: Yes Follow up > 80%?: Yes Outcomes assessed using a widely used scale?: Yes Outcomes assessed in a blind fashion?: Unclear

Evidence Table 2. Predictors of physical and mental impairments at 12 months (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Possible Predictors Considered	Results	Comments/Quality Scoring
				progressive		If subgroups with different prognoses identified: a) was there adjustment for important prognostic factors? NA b) was there independent validation?: NA
			Baseline measures of physical and mental functioning: EDSS at entry (mean ± SD) (P < 0.0001): S = 4.054 ± 6.025 RRS = 2.646 ± 3.878 RRP = 3.760 ± 2.770 CP = 5.844 ± 3.163 Disease type at entry (N): S = 80 RRS = 155 RRP = 48 CP = 142			
Koziol, Wagner, Sobel, et al., 2001	Inclusion: MS; relapsing-remitting disease course Exclusion: Not evaluable at 12 mo	Prospective, population-based, RCT Duration of follow up: Examinations performed every month for 12 mo	Total no. at start: 50 N = 24 placebo N = 26 Cladribine Completed: 50 Dropouts: 0 Age (mean): Placebo: 40.1 yr (range 31-52) Cladribine: 44.0 yr (range 31-52) Baseline measures of physical and mental functioning: EDSS: Placebo: Mean = 3.8 Range = 2.5-6.5 Cladribine: Mean = 3.9 Range = 2-6.5	1) Presence of enhancing lesions on MRI 2) Occurrence of new enhancing lesions on MRI 3) Occurrence of new hypointense lesions (“black holes”) on MRI	1) Enhancing lesions in 3 consecutive monthly MRI images immediately preceding exacerbation: PPV = 0.21 (0.121-0.306) NPV = 0.89 (0.859-0.923) Sensitivity = 0.36 (0.220-0.508) Specificity = 0.85 (0.778-0.903) Prevalence = 0.69 2) New enhancing lesions in 3 consecutive monthly MRI images immediately preceding exacerbation: PPV = 0.23 (0.124-0.357) NPV = 0.89 (0.857-0.920) Sensitivity = 0.31 (0.180-0.459) Specificity = 0.89 (0.841-0.929) Prevalence = 0.64 3) New black holes in 3 consecutive monthly MRI images immediately preceding exacerbation: PPV = 0.20 (0.041-0.426) NPV = 0.89 (0.855-0.916) Sensitivity = 0.19 (0.085-0.321) Specificity = 0.94 (0.911-0.959)	Prevalence not provided; calculated using equation: Prevalence = SN/(SN + PPV (1-SP)) QUALITY ASSESSMENT: Study described as “population-based”?: Yes Sample of patients assembled at a *common* point in the course of their disease?: Unclear Sample of patients assembled at an *early* point in the course of their disease?: Unclear Follow up > 80%?: Yes Outcomes assessed using a widely used scale?: Yes Outcomes assessed in a blind fashion?: Unclear If subgroups with different prognoses identified: a) was there adjustment for important prognostic factors? NA b) was there independent validation?: NA

Evidence Table 2. Predictors of physical and mental impairments at 12 months (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Possible Predictors Considered	Results	Comments/Quality Scoring
			SNRS: Placebo: Mean = 75.8 Range = 54-98 Cladribine: Mean = 76.1 Range = 41-93		Prevalence = 0.42 4) Conclusion – presence of possible predictors 1, 2 and/or 3 (MRI imaging-derived markers) are not useful in predicting exacerbations within 6 mo, but absence of predictors is associated with fewer relapses	
Nortvedt, Riise, Myhr, et al., 2000	Inclusion: Clinical or laboratory-supported definite relapsing-remitting MS; EDSS ≤ 5.5; ≥ 2 relapses during 2 yr preceding enrollment; stable disease at inclusion Exclusion: Age < 18 or > 50; pregnant or lactating women; interferon treatment; immunosuppressive treatment during the previous year; steroid treatment during the month before inclusion; chronic progressive course; liver or renal disease; other serious concomitant disease	Prospective, not population-based, based on subjects in a double-blind RCT Duration of follow up: 12 mo	Total no. at start: 97 Completed: 91 Dropouts: 6 lost to follow-up before 12 mo Age: Mean: 34 Range: 21-48 Baseline measures of physical and mental functioning: Mean EDSS: 2.9 (range 0-5.5) Mean disease duration: 6.9 years Baseline QOL ratings (n): Poor = 5 Fair = 33 Good = 43 Very good = 9 Excellent = 1	Quality of life as reported by SF-36 Health Survey	Mean change in EDSS over 12 mo: Increase of 0.19 (range: -1 to 2.5) Baseline EDSS score was not correlated to change in EDSS score (P = 0.65) Initial QOL — Increased EDSS over 12 mo Poor/Fair — 16/38 (42%) Good/Very Good/ Excellent — 12/53 (23%) Relative risk = 1.9 (CI, 1.0 to 3.5) The risk of experiencing a worsening EDSS score was 1.9 (95% CI, 1.0 to 3.5) for those who evaluated their health as poor or fair compared to good, very good, or excellent. No other measure in the SF-36 was predictive of EDSS worsening, after adjusting for multiple comparisons.	QUALITY ASSESSMENT: Study described as "population-based"?: No Sample of patients assembled at a *common* point in the course of their disease?: Yes Sample of patients assembled at an *early* point in the course of their disease?: No Follow up > 80%?: Yes Outcomes assessed using a widely used scale?: Yes Outcomes assessed in a blind fashion?: No If subgroups with different prognoses identified: a) was there adjustment for important prognostic factors? No b) was there independent validation?: NA

Evidence Table 2. Predictors of physical and mental impairments at 12 months (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Possible Predictors Considered	Results	Comments/Quality Scoring
Rovaris, Comi, Ladkani, et al., 2003	Inclusion: Age 18-50; clinically definite MS for at least 1 yr; relapsing-remitting disease course; EDSS 0.0-5.0; ≥ 1 documented relapse in preceding 2 yr; ≥ 1 contrast-enhancing lesion on screening brain MRI images; clinically relapse-free and without steroid treatment in the 30 days before study Exclusion: None specified	Cohort derived from subjects in a RCT Duration of follow up: 9 mo	Total no. at start: 239 (119 received 20 mg glatiramer acetate [GA]; 120 received placebo) Placebo group: Completed: 113 Dropouts: 7 Age: 34.0 ± 7.5 years GA group: Completed: 112 Dropouts: 7 Age: 34.1 ± 7.4 years Baseline measures of physical and mental functioning: Disease duration (mean ± SD): Placebo: 7.9 ± 5.5 yr GA: 8.3 ± 5.5 yr Prior 2-yr relapse rate (mean ± SD): Placebo: 2.5 ± 1.4 GA: 2.8 ± 1.8 EDSS score (mean ± SD): Placebo: 2.4 ± 1.2 GA: 2.3 ± 1.1 No. of enhancing lesions (mean ± SD): Placebo: 4.4 ± 7.1 GA: 4.2 ± 4.8	Overall burden (volume) of T2-hyperintense at baseline (T2BLV) or T1-hypointense (T1BLV) lesions	Spearman rank correlation coefficients between measure and EDSS Score (p value): All Patients (n = 239) Measure Baseline Change T2BLV 0.28 (< 0.001) 0.16 (0.02) T1BLV 0.19 (0.003) 0.18 (0.006) Multivariate regression reported to show that number of relapses during the study period was correlated with the number of relapses in the 2 yr before randomization (p = 0.005); when number of contrast-enhancing lesions at baseline was added, it was significant (p < 0.001).	Details of multivariate modeling, including validation, not provided QUALITY ASSESSMENT: Study described as "population-based"?: No Sample of patients assembled at a *common* point in the course of their disease?: No Sample of patients assembled at an *early* point in the course of their disease?: No Follow up > 80%?: Yes Outcomes assessed using a widely used scale?: Yes Outcomes assessed in a blind fashion?: Unclear If subgroups with different prognoses identified: a) was there adjustment for important prognostic factors? Yes b) was there independent validation?: No

Evidence Table 2. Predictors of physical and mental impairments at 12 months (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Possible Predictors Considered	Results	Comments/Quality Scoring
Runmarker, Andersson, Odén, et al., 1994	Inclusion: Definite or probable MS; relapsing-remitting course; acute onset Exclusion: Progressive course from onset; lack of sufficient patient data	Prospective, population-based, cohort study Duration of follow up: 25 yr	Total no. at start: 308 255 with definite or probable disease 200 with sufficient data for analysis and non-progressive disease at onset Completed: 200 Dropouts (from original cohort): 4 lost to follow up 63 died before end of 25-yr follow up Age (at onset): < 19: 25 20-29: 71 30-39: 65 40-49: 32 ≥ 50: 7 Baseline measures of physical and mental functioning: NR	1) Age at onset (Age) 2) Sex (1 = female) 3) Degree of remission after relapse (Remis, 1 = incomplete) 4) Mono- or polyregional symptoms (Region, 1 = polyregional) 5) Type of affected nerve fibers (1 = afferent with origin inside CNS, 2 = efferent or mixed) (Type 1 or Type 2) 6) Number of affected neurological systems (# Sys) 7) Time since onset (Time since onset)	(Probability of event = EXP(Σ coeff x value) Model 1 – analysis from onset, start of progressive disease as endpoint (n = 200): Factor / Coeff / SE / Risk Ratio Constant -4.550 0.5446 Age 0.04748 0.01611 1.049 Sex 0.8388 0.6150 2.314 Remis 0.2659 0.2028 1.305 Type 1 0.1639 0.3886 1.178 Type 2 0.4954 0.2822 1.641 Region 0.07666 0.3971 1.080 (Age) x (Sex) -0.04222 0.01895 0.959 (Remis) x (Region) 1.046 0.5329 2.846 Model 2 – analysis from onset, DSS 6 as endpoint: Factor / Coeff / SE / Risk Ratio Constant -4.917 0.4323 Age 0.02498 0.009119 1.025 Type 1 0.6290 0.4145 1.876 Type 2 0.7872 0.3327 2.197 Region 0.7978 0.2639 2.221 Model 3 – analysis from end of 5th calendar year, start of progressive disease as endpoint (n = 151): Factor / Coeff / SE / Risk Ratio Constant -2.921 0.4767 Sex -0.07462 0.2891 0.928 # Sys -0.8975 0.4228 0.408 Remis 0.6295 0.4108 1.877 Type 1 0.3800 0.5765 1.462 Type 2 -0.08682 0.4639 0.917 (# Sys) x (Remis) 0.3330 0.1284 1.395 (# Sys) x (Type 1) 0.8177 0.4592 2.265 (# Sys) x 0.8991 0.4277 2.457	QUALITY ASSESSMENT: Study described as "population-based"?: Yes Sample of patients assembled at a *common* point in the course of their disease?: Yes Sample of patients assembled at an *early* point in the course of their disease?: Yes Follow up > 80%?: Yes Outcomes assessed using a widely used scale?: Yes Outcomes assessed in a blind fashion?: Unclear If subgroups with different prognoses identified: a) was there adjustment for important prognostic factors? Yes b) was there independent validation?: Yes

Evidence Table 2. Predictors of physical and mental impairments at 12 months (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Possible Predictors Considered	Results	Comments/Quality Scoring
					(Type 2) (Sex) x (Remis) -0.9739 0.4610 0.378 Model 4 – analysis from end of 5th calendar year after onset, DSS 6 as endpoint: Factor Coeff SE Risk Ratio Constant -4.258 0.4007 # Sys -0.05465 0.09212 0.947 Remis -0.3798 0.3717 0.684 Type 1 1.004 0.4760 2.729 Type 2 0.6038 0.3927 1.829 Region 0.7181 0.4292 2.051 (# Sys) x (Remis) 0.4114 0.1324 1.509 Model 5 – model for the relationship between age at onset, current age, and the risk of start of progressive course: Factor Coeff SE Risk Ratio Constant -7.572 1.211 Time since onset 0.3569 0.08758 1.429 Age at onset 0.1631 0.05984 1.177 (Time since onset)^2 -0.007357 0.002389 0.993 (Age at onset)^2 -0.001447 0.0007719 0.999 Remis 0.3588 0.1774 1.432 (Time since onset) x (Age at onset) -0.006126 0.001816 0.994	
Stevenson, Leary, Losseff, et al., 1998	Inclusion: Patients recruited from previous cohort – patients had clinically definite MS; control subjects – healthy (non-MS)	Prospective, not population-based, case series Duration of follow up: 1 yr	Total no. at start: 41 (28 patients, 13 controls) Patient disease types: 12 primary progressive (PPMS);	Baseline cross-sectional area of spinal cord	Change in cord size, patients vs. controls: Mean change in cord area, mm^2 (%): Controls: -0.77 (-0.92) Patients: -2.26 (-3.71) p = 0.05 (% change, p = 0.03) Patient subgroups: Number of patients with definite change in	QUALITY ASSESSMENT: Study described as “population-based”?: No Sample of patients assembled at a *common* point in the course of their disease?: No Sample of patients assembled at an *early* point in the course of their

Evidence Table 2. Predictors of physical and mental impairments at 12 months (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Possible Predictors Considered	Results	Comments/Quality Scoring
	Exclusion: None specified		6 secondary progressive (SPMS); 6 relapsing-remitting (RRMS); 4 benign (BMS) Completed: 41 Dropouts: 0 Age: Control: 46.3 (range 30-59); Patients: 45.1 (range 27-65) Baseline measures of physical and mental functioning: Mean disease duration in years (range): PPMS: 10.9 (4-22) SPMS: 19.3 (17-24) RRMS: 5.6 (2-9) BMS: 17.3 (13-22) Median EDSS (range): PPMS: 5.75 (3.0-8.5) SPMS: 7.25 (6.0-8.0) RRMS: 3.25 (1.5-6.5) BMS: 2.25 (2.0-3.0) Mean cord size (mm^2): PPMS: 71.98 SPMS: 57.03 RRMS: 83.97 BMS: 71.35 Control: 80.95		EDSS: PPMS: 2/12 SPMS: 2/6 RRMS: 1/6 BMS: 3/4 Mean change in cord area, mm^2 (%): PPMS: -3.52 (-5.2), $p \leq 0.001$ SPMS: -0.26 (-0.7), p = NS RRMS: -2.98 (-3.8), $p \leq 0.001$ BMS: -0.41 (-0.8), p = NS Compared with 20 patients without definite increase in EDSS over 12 months, the 8 patients with definite increase in EDSS had similar cord area at baseline (p = 0.69) and similar change in cord area during the year (p = 0.51).	disease?: No Follow up > 80%?: Yes Outcomes assessed using a widely used scale?: Yes Outcomes assessed in a blind fashion?: Unclear If subgroups with different prognoses identified: a) was there adjustment for important prognostic factors? No b) was there independent validation?: No

Evidence Table 2. Predictors of physical and mental impairments at 12 months (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Possible Predictors Considered	Results	Comments/Quality Scoring
Trotter, Clifford, McInnis, et al., 1989	Inclusion: Definite MS (chronic progressive or stable); age 20-50 Exclusion: Chronic progressive MS with an increase over the prior year of > 8 points on MRD or > 3 points on EDSS	Prospective, not population-based, case series Duration of follow up: 18 mo	Total no. at start: 42 30 chronic progressive MS (CPMS; 15 untreated [placebo] patients); 10 stable MS patients; 12 normal control subjects Completed: 37 Dropouts: 5 from CPMS placebo group Age, mean ± SD (range): Total CPMS patients: 41.3 ± 8.9 (22-57); Untreated CPMS patients (subset): 40.4 ± 10.2 (22-57); Stable MS patients: 36.2 ± 13.1 (26-60); Normal controls: 36.2 ± 10.4 (26-58) Baseline measures of physical and mental functioning: EDSS: Untreated CPMS (n = 9): 5.7 ± 1.2 (3.0-7.0); Stable MS (n = 10): 5.9 ± 0.9 (3.5-6.5)	1) Concanavalin A suppressor assay 2) Mitogen stimulation 3) Phenotyping of peripheral blood mononuclear cells 4) Interleukin-2 levels	IL-2 baseline vs. Δ EDSS over 18 months R = 0.66 P = 0.01 Illustrative 2 x 2 table (derived from Figure 5; retrospectively selected cutpoint of 40 U/mL) Sensitivity = 67% Specificity = 100% PPV = 100% NPV = 75% Prevalence 50% No other measures correlated with prognosis	Multiple comparisons, not addressed. A priori cutpoints for test results not provided. Results not provided for normal controls separate from non-progressing MS patients. Only 12 patients with IL-2 and 18-mo EDSS reported of the original patient series. QUALITY ASSESSMENT: Study described as "population-based"?: No Sample of patients assembled at a *common* point in the course of their disease?: Nor Sample of patients assembled at an *early* point in the course of their disease?: No Follow up > 80%?: Yes Outcomes assessed using a widely used scale?: Yes Outcomes assessed in a blind fashion?: Unclear If subgroups with different prognoses identified: a) was there adjustment for important prognostic factors? NA b) was there independent validation?: NA

		Δ EDSS over 18 mo	
		≥ 1	< 1
IL-2 (U/mL)	> 40	4	0
	≤ 40	2	6

Evidence Table 2. Predictors of physical and mental impairments at 12 months (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Possible Predictors Considered	Results	Comments/Quality Scoring
Villar, Masjuan, González-Porqué, et al., 2002	Inclusion: MS diagnosis, Exclusion:	Prospective case series Duration of follow up (months): Overall: Mean: 21.6 ± 2.28 Range: 6-36 Group 1 (intrathecal IgM synthesis [ITMS]) (mean): 18.00 ± 2.83 Group 2 (no ITMS) (mean): 24.67 ± 3.29 (between-group difference NS) Lumbar puncture to determine presence/ absence of ITMS performed within 6 mo of clinical onset (mean 1.14 ± 0.33 mo)	Total no. at start: 22 21 relapsing-remitting 1 primary progressive Group 1: 10 Group 2: 12 Completed: 22 Dropouts: 0 Age: Group 1: 27.91 ± 2.86 Group 2: 29.00 ± 2.91 EDSS: Group 1: 1.05 ± 0.27 Group 2: 1.17 ± 0.24 Mo. since onset: Group 1: 1.53 ± 0.65 Group 2: 0.83 ± 0.25 Albumin index: Group 1: 5.42 ± 0.81 Group 2: 4.40 ± 0.49 IgG quotient: Group 1: 4.23 ± 0.63 Group 2: 4.32 ± 0.64 IgM index: Group 1: 0.248 ± 0.059 Group 2: 0.063 ± 0.016 P = 0.003 Cells: Group 1: 6.00 ± 3.48 Group 2: 8.75 ± 3.24	Presence of ITMS	Mean EDSS score at end of follow-up period: Group 1: 1.70 ± 0.23 Group 2: 0.79 ± 0.22 P = 0.02 Probability of progression of at least 1 unit in the EDSS after at least 1 yr of evolution (n = 18; those who made it to at least 1 yr of follow-up): Group 1: 50% Group 2: No increase in EDSS shown P = 0.01 Mean number of relapses during year 1: Group 1: 1.86 ± 0.46 Group 2: 0.2 ± 0.13 P = 0.0068 Probability of remaining without interferon-β treatment: Group 1: 0% after 20 months Group 2: 45.7% at end of study P = 0.0001	QUALITY ASSESSMENT: Study described as "population-based"?: Yes/No Sample of patients assembled at a *common* point in the course of their disease?: Yes Sample of patients assembled at an *early* point in the course of their disease?: No Follow up > 80%?: Yes Outcomes assessed using a widely used scale?: Yes Outcomes assessed in a blind fashion?: Yes If subgroups with different prognoses identified: a) was there adjustment for important prognostic factors? NA b) was there independent validation?: NA

Evidence Table 3a. Disease-modifying therapies and long-term improvement

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Achiron, Gabbay, Gilad, et al., 1998	Inclusion: Clinically definite relapsing remitting MS of > 1 yr duration; average yearly exacerbation rate 0.5-3 in 2 yr preceding study; EDSS score 0-6.0; age 18-60 Exclusion: Secondary progression disease course; serum immunoglobulin deficiency; long-term steroid or cytotoxic treatment 12 mo prior to study; major psychiatric disorder; major cognitive impairment	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: 2 yr Provider specialty: Neurologists Location: Tel Hashomer, Israel	No. of patients randomized: 40 Dropouts: 2 Completed: 38 Age (mean ± SE): IV IgG: 35.4 ± 2.1 Placebo: 33.8 ± 2.4 Baseline EDSS (mean ± SE): IV IgG: 2.90 ± 0.43 Placebo: 2.82 ± 0.37 Baseline relapse rate (mean ± SE per yr in 2 yr preceding study): IV IgG: 1.85 ± 0.26 Placebo: 1.55 ± 0.17	1) IV immunoglobulin (IV IgG); loading dose of 0.4g/kg/body weight per day for 5 consecutive days, followed by booster doses of 0.4 g/kg/body weight once daily every 2 mo for 2 yr (n = 20) 2) Placebo (n = 20)	1) Physical functioning: Definition of "improvement": 1.0-point change in EDSS compared with baseline Proportion of patients with "improvement": In the IV IgG group 23.5% of patients improved vs. 10.8% in the placebo group Other (non-improvement) outcomes: No significant change in mean EDSS in treatment arm 2) Relapse frequency: Definition of "relapse": The rapid appearance, reappearance, or worsening of one or more neurological abnormalities, persisting at least 48 hr, after a relatively stable or improving neurological state of at least 30 days. A relapse was confirmed only when the patient's symptoms were accompanied by objective changes on neurological examination by a blinded neurologist. Definition of "improvement": Not specified on a per patient basis Proportion of patients with "improvement": Not specified Other (non-improvement) outcomes: a) Yearly exacerbation rates IV IgG / Placebo / P-value Baseline 1.85 / 1.55 / 0.34 Year 1 0.75 / 1.8 / 0.0002 Year 2 0.42 / 1.42 / 0.0009 2-yr total 0.59 / 1.61 / 0.0006	This article demonstrates that a larger proportion of patients demonstrated improvement in EDSS when treated with IV IgG compared with placebo. The definition of improvement was a 1.0-point improvement on EDSS. There are no data delineating how many patients may have improved greater than 1.0 point. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? No

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					b) Exacerbation-free patients: IV IgG / Placebo / P-value Year 1: 8 / 1 / 0.001 Year 2: 12 / 3 / 0.001 Total study: 6 / 0 / 0.001 c) Median time to first exacerbation (days): IV IgG / Placebo / P-value 233 / 82 / 0.003	
Bastianello, Pozzilli, D'Andrea, et al., 1994	Inclusion: Definite diagnosis of MS; relapsing-remitting disease course (≥ 2 relapses in 24 mo prior to study entry); disease duration 1-10 yr; EDSS 2.0-5.0; age 18-45; selected to undergo serial MRI scans (subgroup of total study population) Exclusion: HIV-positive; previous cardiovascular disease; left ventricular ejection fraction < 50% by echocardiography; renal, liver, and/or respiratory dysfunction; diabetes; malignancy; psychiatric illness; pregnancy or no contraception; use of immunosuppressant drugs or steroids in previous 3 mo	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: 1 yr (preliminary results from planned 2-yr trial) Provider specialty: Neurologists Location: 7 sites in Italy	No. of patients randomized: 25 (subgroup of total study population selected to undergo serial MRI scans) Dropouts: 0 Completed: 25 Age (mean ± SD): MTX: 29.9 ± 5.2 Placebo: 28.5 ± 6.5 Baseline EDSS (mean ± SD): MTX: 3.7 ± 0.7 Placebo: 3.5 ± 1.0 Baseline relapse rate (mean in previous 2 yr ± SD): MTX: 2.8 ± 1.2 Placebo: 3.3 ± 1.2	1) Mitoxantrone (MTX) 8 mg/m^2 by 30-min IV infusion every month for 1 yr (n = 13) 2) Placebo (n = 12)	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: No statistical difference was observed in mean EDSS change at 1 yr (p = 0.18) 2) Relapse frequency: Definition of "relapse": The appearance of new symptom or worsening of an old one, attributable to MS and lasting at least 24 hours in the absence of fever Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: MTX / Placebo / P value MER: 0.54 / 1.67 / 0.014 PWE: 5(38%) / 10(83%) / 0.02 MER = Mean exacerbation rate PWE = Number (%) of patients with exacerbations	This trial reports initial findings demonstrating a benefit of mitoxantrone in reducing mean exacerbation rates, but does not provide quantitative information regarding absolute improvement of specific patients over baseline status. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Bornstein, Miller, Slagle, et al., 1987	Inclusion: Definite MS; relapsing-remitting form of MS; ≥ 2 well-demarcated and well-documented relapses in previous 2 yr; EDSS ≤ 6; emotionally stable; age 20-35 Exclusion: None specified	RCT (parallel-group, double-blind, single-center, matched-pairs design) Duration of study treatment/follow up: 2 yr Provider specialty: Neurologists Location: 1 site in Bronx, NY	No. of patients randomized: 50 Dropouts: 7 dropped out before 2 yr, but 5 of these were included in analysis Completed: 43 completed trial; 48 included in analysis Age (mean): Cop 1: 30.0 Placebo: 31.0 Baseline EDSS (mean): Cop 1: 2.9 Placebo: 3.2 Baseline relapse rate (mean over 2 yr): Cop 1: 3.8 Placebo: 3.9	1) Glatiramer acetate = Copolymer 1 (Cop 1) by SC injection, 20 mg self-injected daily for 2 yr (n = 25) 2) Placebo (n = 25)	1) Physical functioning: Definition of "improvement": Reduction in EDSS by 1, 2, or 3 points over 2 yr Proportion of patients with "improvement": Placebo / Cop 1 1.0 point: 8.7% / 20.0% 2.0 points: 0 / 12.0% 3.0 points: 4.4% / 0 2) Relapse frequency: Definition of "relapse": The rapid onset of new symptoms or a worsening of preexisting symptoms that persisted for 48 hours or more, when accompanied by observed objective changes on the neurological examination involving an increase of a atl east one grade in the score for one of the eight functional groups or the Kurtzke Scale Definition of "improvement": Decrease in 2-yr relapse rate in comparison with individual baseline relapse rate Proportion of patients with "improvement": Placebo – 12 of 23 patients experienced a decrease in relapse rate over the 2yr period Cop 1 – 24 of 25 patients experienced a decrease in relapse rate over the 2-yr treatment period Other (non-improvement) outcomes: Exacerbation-free patients: Placebo – 26% Cop 1 – 56% P = 0.036	This early study of the efficacy of Copolymer 1 in the treatment of relapsing-remitting MS demonstrated benefits of treatment in the reduction of relapse rates and improved disability status. Data are presented regarding the number of patients demonstrating improvement on EDSS. Although significant efforts were made to maintain blinding, the physician evaluator correctly identified 70% of those taking placebo and 78% of those taking Cop 1. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Bornstein, Miller, Slagle, et al., 1991	Inclusion: Definite diagnosis of MS by Poser criteria; evidence of a chronic-progressive course for ≥ 18 mo; ≤ 2 exacerbations in previous 24 mo; EDSS score 2.0-6.5; emotionally stable and able to participate in clinical trial; age 20-60 During a 6- to 15-mo pre-trial observation period, patients required to demonstrate progression in one of following ways: worsening of 2 grades in a functional system; worsening of 1 grade in 2 unrelated functional systems; worsening of 2 units on the Ambulation Index; or worsening of 1 grade on the EDSS. Must not have progressed beyond 6.5 on EDSS or have had > 1 exacerbation during pre-trial observation period. Exclusion: None specified	RCT (parallel-group, double-blind, two-center) Duration of study treatment/follow up: 2 yr or until confirmed progression (whichever first) Provider specialty: Neurologists Location: Bronx, NY; and Houston, TX	No. of patients randomized: 106 Dropouts: 20 Completed: 86 Age (mean): Cop 1: 41.6 Placebo: 42.3 Baseline EDSS: Mean: Cop 1: 5.7 Placebo: 5.5 Cop 1 Plac < 5: 22% 27% 5-5.5: 8% 15% 6-6.5: 71% 58% Baseline relapse rate: NR	1) Copolymer 1 (Cop 1) by SC injection; 15 mg self-injected twice per day for 2 yr (n = 51) 2) Placebo (n = 55)	1) Physical functioning: Definition of “improvement”: Not defined Proportion of patients with “improvement”: Cop 1: 19.6% improved 37.3% remained stable 41.1% worsened Placebo: 14.5% improved 34.6% remained stable 50.9% worsened Other (non-improvement) outcomes: The primary endpoint, confirmed progression of 1.0 or 1.5 units (depending on baseline disability) on the Kurtzke Disability Status Scale, was not statistically different in the two groups 2) Relapse frequency: Definition of “relapse”: Not defined Definition of “improvement”: Not assessed Proportion of patients with “improvement”: Not delineated	This study provides no significant information regarding improvement of patients on this therapy. QUALITY ASSESSMENT: Described as “randomized”? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as “double-blind”? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
British and Dutch Multiple Sclerosis Azathio-prine Trial Group, 1988	Inclusion: Clinically definite MS (≥ 2 episodes and 2 clinical lesions or 2 episodes and 1 subclinical lesion [revealed by VEP or CT]); or laboratory confirmed MS (≥ 2 anatomically separate episodes, 1 clinical lesion, and oligoclonal bands or increased IgG in the CSF); or currently progressive MS (2 separate lesions [of which 1 might be subclinical], oligoclonal bands, or increased IgG in the CSF, and progres-sion for at least 6 mo); patients with relapsing-remitting disease had to have been in a remittent phase for ≥ 1 mo and have had ≥ 1 relapses in the previous year; EDSS ≤ 6 (ambulant); age 15-50; not on other immunomodulatory drugs or hyperbaric oxygen treatment Exclusion: Concomitant systemic disease; mental deficit that precluded understanding and	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: 3 yr Provider specialty: Neurologists Location: 20 sites in the UK and The Netherlands	No. of patients randomized: 354 (199 [56%] clinically definite, 37 [10%] laboratory confirmed; 51 [14%] progressive from onset; 67 [19%] progressive after remission) Lost to follow up (cumulative totals): 20 at 1 yr, 24 at 2 yr, 22 at 3 yr, 153 at 4 yr Discontinued treatment (cumulative totals): 48 at 1 yr, 64 at 2 yr, 75 at 3 yr Completed: 279 completed treatment, 332 followed up through 3 yr Age (mean ± SD): Azathioprine: 39 ± 8.6 Placebo: 38 ± 8.3 Baseline EDSS (mean ± SD): Azathioprine: 3.69 ± 1.50 Placebo: 3.66 ± 1.62 Baseline relapse	1) Azathioprine PO 2.5 mg/kg (to the nearest 25 mg) daily (n = 174) 2) Placebo (n = 180)	1) Physical functioning: Definition of “improvement”: Not defined Proportion of patients with “improvement”: Not delineated Other (non-improvement) outcomes: The only statistically significant result was a reduction in the deterioration of the Ambulation Index in the azathioprine group compared with the placebo group after 3 yr	The treatment effect in this study was marginal, and no data are reported that delineate improvement of any patient with respect to baseline status. QUALITY ASSESSMENT: Described as “randomized”? Yes Method of randomization clearly described? No Concealment of allocation? Yes Described as “double-blind”? Yes Patients blinded? Yes/No/Unclear Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	cooperation		rate (months since last relapse): Az Plac 1-6: 43% 45% 7-12: 20% 18% > 12: 37% 37%			
Canadian Cooperative Multiple Sclerosis Study Group, 1991	Inclusion: Clinically definite or laboratory-supported definite MS in a progressive phase (deterioration of at least 1 point on EDSS over preceding 12 mo); EDSS 4.0-6.5; age ≥ 15 Exclusion: Previous treatment with cyclophosphamide, cyclosporin, antilymphocyte globulin, or interferon; treatment with azathioprine or plasma exchange in preceding yr or corticosteroids in preceding mo; illnesses that might be adversely affected by study treatments; substantial cognitive impairment; unwillingness to use contraception during trial and for 2 yr after; weekly venous access difficult	RCT (parallel-group, not double-blinded, multicenter) Duration of study treatment/follow up: Duration of treatment variable (see at right, under "Interventions"); patients followed up for at least 12 mo; mean follow up, 30.4 mo Provider specialty: Neurologists Location: 9 sites in Canada	No. of patients randomized: 168 (81 relapsing-progressive, 86 chronic-progressive, 1 unkown) Dropouts: 2 (died) Completed: 166 Age (mean at disease onset ± SD): Cyclophosphamide IV: 31.9 ± 10.3 Plasma exchange: 29.9 ± 7.9 Placebo: 32.1 ± 9.7 Baseline EDSS (mean ± SD): Cyclophosphamide IV: 5.79 ± 0.61 Plasma exchange: 5.66 ± 0.72 Placebo: 5.79 ± 0.64 Baseline relapse rate: NR	1) Cyclophosphamide IV + prednisone PO (n = 55). Cyclophos-phamide 1g given intravenously on alternate days until WBC count fell below 4.5 x 10^9/L or until total dose of 9 g reached. Prednisone 40 mg given orally for 10 days, then reduced by 10 mg on alternate days and discontinued on day 16. 2) Plasma exchange + cyclophosphamide PO + prednisone PO (n = 57). Plasma exchange of one plasma volume (40 mL/kg) done weekly for 20 wk with either intermittent (5 sites) or continuous (4 sites) flow-type centrifuges. Replacement = 5% serum albumin. Oral cyclophosphamide 1.5-2.0 mg/kg given daily for 22 wk; dose adjusted to achieve target WBC of 4.0-5.0 x 10^9/L. Oral prednisone 20 mg given every other day	1) Physical functioning: Definition of "improvement": 1.0-point improvement on EDSS sustained for 6 mo Proportion of patients with "improvement": No statistically significant difference among the treatment arms Number of patients improved: Cycl PEX Placebo 1 yr 3 (6%) 4 (8%) 1 (2%) 2 yr 2 (6%) 1 (3%) 0 3 yr 2 (4%) 1 (2%) 1 (2%) Other (non-improvement) outcomes: No statistically significant difference between treatment arms in any outcome measure	This study provides data specifically addressing the number of patients who improved with regard to EDSS, but the results show no statistically significant benefit of the treatments studied. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? No (treating providers) Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
				and tapered over 22 wk. 3) Placebo (placebo oral cyclophospha-mide and prednisone for 22 wk + sham plasma exchange for 20 wk) (n = 56)		
Cohen, Cutter, Fischer, et al., 2002	Inclusion: Clinically definite secondary progressive MS, with or without recent relapses; disease progression over previous 1 yr; cranial MRI demonstrating lesions consistent with MS; EDSS 3.5-6.5; age 18-60 Exclusion: Primary progressive disease course; inability to complete MS Functional Composite at baseline; prior treatment with interferon-β	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: 2 yr Provider specialty: Neurologists Location: 42 sites in US, Europe, and Canada	No. of patients randomized: 436 Dropouts: 115; of these, 63 had complete 2-yr follow up Completed: 321 completed treatment; 384 followed up for 2 yr Age (mean ± SD): IFNβ-1a: 47.2 ± 8.2 Placebo: 47.9 ± 7.7 Baseline EDSS (mean ± SD): IFNβ-1a: 5.2 ± 1.1 Placebo: 5.2 ± 1.1 Baseline relapse rate (mean ± SD, prior 3 yr): IFNβ-1a: 1.5 ± 2.1 Placebo: 1.3 ± 2.1	1) Interferon β-1a (IFNβ-1a) 60 µg weekly by IM injection for 2 yr (n = 217); half dose (30 µg) given for first four doses to minimize adverse events 2) Placebo for 2 yr (n = 219)	1) Physical functioning: Definition of "improvement": Not defined for individual patients Proportion of patients with "improvement": Improvement based on EDSS – baseline to 24 months Placebo – 7.3% IFNβ-1a – 7.5% No statistically significant difference Other (non-improvement) outcomes: 24-month MSFC data-median: Placebo IFNβ-1a P value MSFC -0.161 -0.362 0.033 9HPT -0.290 -0.202 0.024 Timed 25-ft walk – no statistical difference PASAT – no statistical difference 2) Relapse frequency: Definition of "relapse": New or recurrent neurological symptoms, not associated with fever or infection, lasting at least 48 hours and accompanied by objective change on the examining neurologist's examination at an unscheduled visit corresponding to the reported symptoms Definition of "improvement": Not delineated on individual patients Proportion of patients with "improvement":	This study examined the benefit of IFNβ-1a in secondary progressive MS utilizing assessments of EDSS, MSFC, and MSQLI and demonstrated beneficial effects on MSFC and MSQLI. This was the first use of the MSFC in a large-scale MS trial. The beneficial effects of treatment observed on MSFC were primarily driven by improvements in upper extremity function. The report focuses on between-group differences and provides few data on individual patient improvement. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					Not delineated Other (non-improvement) outcomes: Annual relapse rate: Placebo – 0.30 IFNβ-1a – 0.20 P = 0.008 Relapse-free patients – intention to treat: Placebo – 63% IFNβ-1a – 74% P=0.023 3) Quality of life: The MS Quality of Life Inventory (MSQLI) was administered to English-speaking subjects at baseline, 12 months, and 24 months Definition of "improvement": Not defined Proportion of patients with "improvement": NR Other (non-improvement) outcomes: Significant benefit favoring IFNβ-1a treatment was observed on 8 of 11 subscales of the MSQLI, with a favorable trend on the remaining three scales. The IFNβ-1a group improved from baseline to month 24 on 10 of 11 subscales (all except Bladder Control Scale). In contrast, the placebo group worsened from baseline to month 24 on 10 of 11 subscales, the Modified Fatigue Impact Scale being the only subscale showing improvement. Data not shown (reference made to www.neurology.org web site).	

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Currier, Haerer, and Meydrech, 1993	Inclusion: Definite MS; a worsening in function or an exacerbation in the previous yr; understanding and willingness to cooperate Exclusion: History or evidence of renal or hepatic disease; gross obesity; diabetes	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: Initially 1 yr; changed during trial to 18 mo Provider specialty: Neurologist Location: Jackson, MS	No. of patients randomized: 45 (20 "exacerbating remitting" and 24 "chronic" MS [latter includes 18 "exacerbating progressive," 3 "chronic progres-sive," and 3 "spinal patients"]) Dropouts: 9 Completed: 36 Age (median, reported only by MS type): Exacerbating remitting: 39.5 Chronic: 46.8 Baseline EDSS: NR Baseline relapse rate (total number of exacerbations in 12 mo preceding trial; reported only for patients with "exacerbating remitting" MS): Methotrexate: 9 in 9 patients Placebo: 12 in 11 patients	1) Methotrexate PO; 2.5 mg every 12 hr for 3 consecutive doses once per wk (7.5 mg/ wk) for 18 mo (n = 22) 2) Placebo (n = 22)	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: 2) Relapse frequency: Definition of "relapse": 1.0-point EDSS worsening (unsustained) Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: No statistically significant difference in treatment groups except for a difference in the mean number of exacerbations p = 0.05 – data presented in graphical form only	This study provides no data regarding individual patient improvement on therapy. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
De Castro, Cartoni, Millefiorini, et al., 1995	Inclusion: Definite diagnosis of MS according to Poser criteria; relapsing-remitting disease course; ≥ 2 relapses in 24 mo prior to study entry; disease duration 1-10 yr; EDSS 2.0-5.0; age 18-45 Exclusion: HIV-positive; heart, renal, lung, or liver disease; psychiatric disease; pregnancy or lactation; known allergy to cortico-steroids; other neurological disease; use of corticosteroids during previous 3 mo; use of levamisol, isoprinosin, or plasmapheresis during previous 3 mo; treatment with interferon; immunosuppressive therapy during previous 12 mo	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: 1 yr Provider specialty: NR (presumably neurologists and cardiologists) Location: 1 site in Italy	No. of patients randomized: 20 Dropouts: NR (implied 0) Completed: NR (implied 20) Age (mean ± SD): MTX: 31 ± 5 Placebo: 30 ± 4 Baseline EDSS (mean ± SD): MTX: 3.77 ± 0.72 Placebo: 3.33 ± 0.75 Baseline relapse rate (mean in previous 2 yr ± SD): MTX: 2.82 ± 0.98 Placebo: 3.00 ± 1.94	1) Mitoxantrone (MTX) 8 mg/m^2 by 30-min IV infusion every month for 1 yr (n = 13) 2) Placebo (n = 12)	1) Physical functioning: Definition of “improvement”: Not defined Proportion of patients with “improvement”: Not delineated Other (non-improvement) outcomes: No statistically significant difference between treatment arms with respect to changes in EDSS 2) Relapse frequency: Definition of “relapse”: Not defined Definition of “improvement”: Not defined Proportion of patients with “improvement”: Not delineated Other (non-improvement) outcomes: Difference in relapse rate favored treatment with mitoxantrone p = 0.005	This study demonstrated a statistically significant reduction in mean relapse rate in the treatment arm but did not include data regarding the clinical improvement of individual patients. QUALITY ASSESSMENT: Described as “randomized”? Yes Method of randomization clearly described? No Concealment of allocation? Yes Described as “double-blind”? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? No

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
European Study Group on Interferon beta-1b in Secondary Progressive MS, 1998	Inclusion: Clinically or laboratory supported definite diagnosis of secondary progressive MS; EDSS 3.0-6.5; ≥ 2 relapses or ≥ 1.0-point increase in EDSS in previous 2 yr; age 18-55 Exclusion: None specified	RCT (parallel-group, double-blind, multicenter) Mean duration of treatment/follow up: Treatment scheduled to last 36 mo, with 3-mo follow up; article reports results of prospectively planned interim analysis of all patients in study for ≥ 2 yr; mean follow up time 901 days for IFNβ-1b and 892 days for placebo Provider specialty: NR (presumably neurologists) Location: 32 sites in Europe	No. of patients randomized: 718 Lost to follow up: 57 Withdrew from treatment, but had complete follow up: 130 Completed treatment and follow up: 531 Age (mean ± SD): IFNβ-1b: 41.1 ± 7.2 Placebo: 40.9 ± 7.2 Baseline EDSS (mean ± SD): IFNβ-1b: 5.1 ± 1.1 Placebo: 5.2 ± 1.1 Baseline relapse rate (% of patients without relapse in 2 yr preceding study): IFNβ-1b: 31.9% Placebo: 28.2%	1) Interferon β-1b (IFNβ-1b) by SC injection; initial dose 0.5 mL (4 MIU) every other day, increased after 2 wk to 1.0 mL (8 MIU) every other day for up to 3 yr (n = 360) 2) Placebo (n = 358)	1) Physical functioning: Primary endpoint was time to confirmed progression in disability defined as a 1.0-point increase on EDSS sustained for at least 3 months, or a 0.5-point increase if the baseline EDSS was 6.0 or 6.5 Results: Significant difference in time to confirmed progression of disability in favor of IFNβ1-b (p = 0.0008) On average IFNβ1-b delayed confirmed progression by 9-12 months in this patient population Confirmed EDSS progression: Placebo: 46.7% IFNβ1-b: 38.9% p = 0.0048 2) Relapse frequency: Definition of "relapse": Not defined Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: a) Mean annual relapse rate: Placebo / IFN β-1b / p Overall 0.64 / 0.44 / 0.0002 Year 1 0.82 / 0.57 / 0.0095 Year 2 0.47 / 0.35 / 0.0201 Year 3 0.35 / 0.24 / 0.1624 b) Proportion of patients with moderate to severe relapse: Placebo: n = 190 (53.1%) IFNβ1-b: n = 157 (43.6%) p = 0.008	This article demonstrates the efficacy of IFNβ-1b over placebo in reducing the rate of progression and in reducing the relapse rate. It does not provide data regarding improvement of individual patients over their baseline functional status. See also the entry for Kappos, Polman, Pozzilli, et al., 2001, below. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Fazekas, Deisen-hammer, Strasser-Fuchs, et al., 1997a **and** **Fazekas, Deisen-hammer, Strasser-Fuchs, et al., 1997b** **and** **Strasser-Fuchs, Fazekas, Deisen-hammer, et al., 2000**	Inclusion: Clinically definite diagnosis of relapsing-remitting MS; EDSS score 1.0-6.0; ≥ 2 clearly identified and documented relapses during previous 2 yr; age 15-64; first manifestation of MS at age 10-59 Exclusion: Immuno-suppressive or immunomodulatory therapy in previous 3 mo; corticosteroids in previous 2 wk; primary or secondary progressive MS; benign course of disease as indicated by a deterioration rate (EDSS score divided by duration of disease in years) < 0.25	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: 2 yr Provider specialty: Neurologists Location: 13 sites in Austria	No. of patients randomized: 150 Lost to follow up: 2 (before start of treatment) Stopped treatment: 28 Completed treatment: 120 Age (mean [95% CI]): IV IgG: 36.7 (34.3-39.1) Placebo: 37.3 (35.0-39.6) Baseline EDSS (mean [95% CI]): IV IgG: 3.3 (3.0-3.6) Placebo: 3.3 (2.9-3.7) Baseline relapse rate (mean per yr [95% CI]): IV IgG: 1.3 (1.1-1.5) Placebo: 1.4 (1.2-1.6)	1) IV immunoglobulin (IV IgG); 0.15-0.20 g/kg body weight once per month for 2 yr (n = 75) 2) Placebo (n = 73)	1) Physical functioning: Definition of "improvement": 1.0-point decrease in EDSS by the end of the study Proportion of patients with "improvement": IV IgG – 31% of patients improved Placebo – 14% of patients improved Other (non-improvement) outcomes: Between-group differences in the absolute change on the EDSS score and in the proportion of patients stable or worsened 2) Relapse frequency: Definition of "relapse": The appearance or reappearance of one or more neurological abnormalities that persisted for at least 24 hours and had been preceded by a stable or improving neurological state of at least 30 days. A relapse was confirmed only if the patient's symptoms were accompanied by objective changes of at least one grade in the scored for one of the eight functional groups on the EDSS. Definition of "improvement": Not delineated Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: IV IgG / Placebo / P Relapse-free Patients: 53% / 36% / 0.03 Mean Annual Relapse Rate Year 1: 0.49 / 1.30 / 0.011 Year 2: 0.42 / 0.83 / 0.006 3) Quality of life: Incapacity Status Scale and the Environmental Status Scale	These studies demonstrate benefit from treatment with IV IgG over placebo with regards to progression of EDSS. Moreover, the study documents an increased proportion of patients who demonstrated improvement on EDSS over the 2-yr trial. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					Definition of "improvement": Not defined prospectively Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: The mean change of rating scores of 15 of 16 items was more favorable following IV IgG treatment. The total mean change of ratings over all ISS items was significantly in favor of IV IgG-treated patients (P = 0.01) Similarly, IV IgG-treated patients noted improvement in 4 of 7items of the ESS compared to no item rated as improved by placebo patients.	
Ghezzi, Di Falco, Locatelli, et al., 1989	Inclusion: Definite MS Exclusion: Disease duration < 1 yr; EDSS > 7; concomitant diseases contraindicating immunosuppression	RCT (parallel-group, open-label, single-center) Duration of study treatment/follow up: 18 mo Provider specialty: NR (presumably neurologists) Location: 1 site in Gallarate, Italy	No. of patients randomized: 185 (74 relapsing, 111 relapsing-progressive) Dropouts: 50 Completed: 135 Age (mean at onset [with range], completers only): Relapsing (R)-azathioprine: 26 (15-42) R-control: 26 (18-42) Relapsing-progressive (RP)-azathioprine: 29 (12-44) RP-placebo: 31 (16-47) Baseline EDSS (mean [with range],	1) Azathioprine PO 2.5 mg/kg per day for 18 mo (n = 69) 2) No azathioprine (n = 66)	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": Relapsing patients who improved: Azathioprine – 5 of 32 Controls – 0 of 22 P > 0.10 Relapsing-progressive patients: Azathioprine – 2 of 37 Controls – 3 of 44 p > 0.10 Other (non-improvement) outcomes: No statistical difference between the treatment arms with respect to EDSS 2) Relapse frequency: Definition of "relapse": Not defined Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated	This unblended trial of azathioprine in MS did not find statistically significant differences in any outcome measures. Data are presented that delineate individual patient improvement. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? No Patients blinded? No Investigators blinded? Unclear Outcome assessors blinded? Unclear No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
			completers only): R-azathioprine: 2.1 (1-5) R-control: 2.2 (1-5) RP-azathioprine: 3.8 1-6.5) RP-placebo: 3.7 (1-7) Baseline relapse rate (mean [with range], completers only, time frame not specified): mean at onset [with range], completers only): R-azathioprine: 1.2 (0.2-4) R-control: 1.1 (0.2-3) RP-azathioprine: 0.6 (0.1-3.3) RP-placebo: 0.4 (0.1-2.5)		Other (non-improvement) outcomes: No statistically significant difference in treatment arms	
Goodkin, Bailly, Teetzen, et al., 1991	Inclusion: Clinically definite or laboratory-supported definite MS; seen at study clinic from 1983 to 1989; relapsing-remitting disease course (≥ 2 exacerbations in previous 18 mo); no exacerbation in previous 1 mo; EDSS 2.0-6.5; AI 1.0-6.0; age 18-65 Exclusion: Chronic	RCT (parallel-group, double-blind [patients and examining physician, not treating physician], single-center) Duration of study treatment/follow up: 2 yr Provider specialty: Neurologists	No. of patients randomized: 59 randomized, 54 began treatment No. followed for 2 yr: 52 No. treated per protocol for 2 yr: 43 Age (mean ± SD at onset; n = 54 starting treatment): Azathioprine: 29.4	1) Azathioprine PO; initial dose 50 mg 3 times per day, adjusted to target dose of 3 mg/kg, with increases made in increments of 25 mg per day no more than once per month; WBC maintained at 3500-4000/µL (n = 29) 2) Placebo (n = 25)	1) Physical functioning: Definitions of "improvement": Score reflects combined results of change lasting more than 2 mo in any of following: ≥ 1.0-point on EDSS for patients with baseline EDSS ≤ 5.0, *or* ≥ 0.5-point on EDSS for patients with baseline EDSS ≥ 5.5, *or* ≥ 1.0 point on AI, *or* ≥ 20% deterioration from baseline in 9HPT or BBT Proportion of patients with "improvement": Placebo = 20% Azathioprine = 22.2%	This study demonstrates a modest benefit of azathioprine in reducing mean exacerbation rates and provides specific data regarding the proportion of patients who improve on therapy with regard to EDSS and other functional measures. The proportion of patients who improved was, however, not statistically different among the treatment groups. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	progressive disease (worsening in functional status measurements over 6 mo without exacerbation); use of corticosteroids in previous 1 mo; use of immunosuppressant medication in previous 1 yr; pregnant; unwilling to practice birth control; systemic illness of medical condition that precluded safe administration of study drugs	Location: 1 site in Fargo, ND	± 8.5 Placebo: 30.0 ± 6.8 Baseline EDSS (mean ± SD; n = 54 starting treatment): Azathioprine: 3.18 ± 1.19 Placebo: 3.72 ± 1.60 Baseline relapse rate (mean ± SD in previous 18 mo; no = 54 starting treatment): Azathioprine: 2.34 ± 0.55 Placebo: 2.32 ± 0.63		Other (non-improvement) outcomes: Difference in mean change in EDSS 2) Relapse frequency: Definition of "relapse": Objective worsening in the EDSS of ≥ 0.5 points, Ambulation Index (AI) of ≥ 1.0 points, or ≥ 20% deterioration from baseline performance on the nine-hole peg test (9HPT) or box-and-block test (BBT) in patients who were stable or improving within the last month Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Mean on-trial exacerbation rates for each group: AZA / Placebo / P Year 1: 0.74 / 1.17 / 0.16 Year 2: 0.30 / 0.79 / 0.05 Total 2 year: 1.04 / 1.88 / 0.08	Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes
Goodkin, Rudick, VanderBrug Medendorp, et al., 1995	Inclusion: Clinically definite chronic progressive MS; progressive neurological impairment during period of ≥ 6 mo prior to start of study; no exacerbation for previous 8 mo; ≤ 1 exacerbation in previous 2 yr; disease duration > 1 yr; EDSS 3.0-6.5; AI 2.0-6.0; no cortico-steroids during previous 1 mo or	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: 2 yr Provider specialty: Neurologists Location: 1 site in Cleveland, OH	No. of patients randomized: 60 (18 primary progressive, 42 secondary progressive) Dropouts: 9 Completed: 51 Age (mean ± SD): METH: 43 ± 9.3 Placebo: 46 ± 8.8 Baseline EDSS (mean):	1) Methotrexate (METH), one 7.5-mg oral tablet per week for 2 yr (n = 31) 2) Placebo (n = 29)	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: The primary outcome measure was time to treatment failure on a composite measure of physical functioning that utilized EDSS, Ambulation Index, Box and Block Test and 9-Hole Peg Test for 2 mo or more. Treatment failure was pre-defined on the basis of specific levels of deterioration on any of these scales. There was a significant relationship between	This study evaluated therapy with low-dose oral methotrexate (6.5 mg) weekly in patients with chronic progressive MS and found significant benefit on a composite measure of physical functioning. The most prominent benefit observed was in upper extremity function. The study did not evaluate individual patient improvement and provided no data specifically addressing the proportion of patients improved. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	immunosuppressant medication for previous 1 yr; no prior lymphoid irradiation; willing to use contraception; age 21-60 Exclusion: Pregnancy; systemic illness or medical condition that precluded safe administration of study drugs; clinically evident cognitive impairment		METH: 5.5 Placebo: 5.3 Baseline relapse rate: NR		sustained progression and treatment group favoring the METH treatment: METH = 51.6%, Placebo = 82.8% (p = 0.011). This treatment effect was strongest for the 9HPT and was seen to a lesser extent (p = NS) for the BBT and EDSS.	Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes
Hartung, Gonsette, König, et al., 2002	Inclusion: Worsening relapsing-remitting MS (stepwise progression of disability between relapses) or secondary progressive MS; EDSS 3.0-6.0; worsening of ≥ 1 point on EDSS in previous 18 mo; no relapse in previous 8 wk; no treatment with glucocorticosteroids in previous 8 wk; no previous treatment with mitoxantrone, interferons, glatiramer acetate, cytotoxic drugs, or total-body lymphoid irradiation; left ventricular ejection fraction > 50%; WBC,	RCT (parallel-group, double-blind [patients and assessors, not treating physicians], multicenter) Duration of study treatment/follow up: Treatment lasted 2 yr; patients followed for total of 3 yr Provider specialty: Neurologists Location: 17 sites in Belgium, Germany, Hungary, and Poland	No. of patients randomized: 194 randomized; 188 included in baseline measures (94 worsening relapsing-remitting, 94 secondary progressive) Dropouts: 56 Completed: 138 assessed at 3 yr Age (mean ± SD): MTX 12 mg: 39.94 ± 6.85 MTX 5 mg: 39.92 ± 8.06 Placebo: 40.02 ± 7.88 Baseline EDSS (mean ± SD):	1) Mitoxantrone (MTX) 12 mg/m^2 by slow IV infusion every 3 months for 2 yr; dose could be reduced in response to adverse events, infection, or low WBC or platelet count (n = 63) 2) Mitoxantrone (MTX) 5 mg/m^2 by slow IV infusion every 3 months for 2 yr; dose could be reduced in response to adverse events (n = 66) 3) Placebo (n = 65)	1) Physical functioning: EDSS, Ambulation Index, and standard neurological status scores were established at each scheduled and unscheduled visit Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Mean and median EDSS change, Ambulation Index change, SNS change 2) Relapse frequency: Definition of "relapse": Severe relapse defined as the occurrence of new symptoms lasting for longer than 48 hours with a change in functional system score of more than 2 points, or a deterioration of at least 1 point in at least one of the four following systems: pyramidal, brainstem, cerebellar, or visual Definition of "improvement": Not defined	This study evaluated therapy with mitoxantrone (12 mg/m^2) IV every 3 months in the treatment of worsening relapsing-remitting MS and secondary progressive MS. Investigators found statistically significant differences in the treatment groups on the following outcome measures: multivariate analysis of outcome, change in EDSS, change in Ambulation Index, adjusted total number of treated relapses, time to first treated relapse, and change in standardized neurological status. The 5-mg/m^2 dose arm demonstrated less convincing benefits. This study did not provide data regarding improvement in individual patients. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	neutrophil, and platelet counts in normal ranges; age 18-55 Exclusion: None specified		MTX 12 mg: 4.45 ± 1.05 MTX 5 mg: 4.64 ± 1.01 Placebo: 4.69 ± 0.97 Baseline relapse rate (mean ± SD in previous 1 yr): MTX 12 mg: 1.27 ± 1.12 MTX 5 mg: 1.42 ± 1.26 Placebo: 1.31 ± 1.14		Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Number of treated relapses per patient (median, with range): Placebo: 1 (0-5) MTX 12 mg: 0 (0-2) p = 0.0002	Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes
Hauser, Dawson, Lehrich, et al., 1983	Inclusion: Clinically definite MS; severe progressive disease, with worsening in previous 9 mo (defined as a decrease of ≥ 1 points on functional status or disability scales, either continuous decline or continuous decline with superimposed exacerbations); no corticosteroid therapy in previous month; no immunosuppressive therapy in previous yr Exclusion: Medical illnesses incompatible with safe administration of study medications	RCT (parallel-group, not double-blinded, two-center) Duration of study treatment/follow up: Treatment duration variable (see at right, under "Interventions"; patients followed for total of 1 yr Provider specialty: NR (presumably neurologists) Location: 2 sites in Boston, MA	No. of patients randomized: 58 Dropouts: 0 Completed: 58 Age (mean ± SE): ACTH: 35.2 ± 1.5 CYCLO + ACTH: 32.9 ± 1.8 PEX + CYCLO + ACTH: 36.3 ± 1.7 Baseline EDSS (mean ± SE): ACTH: 5.6 ± 0.2 CYCLO + ACTH: 5.8 ± 0.2 PEX + CYCLO + ACTH: 5.6 ± 0.2 Baseline relapse rate: NR	1) Adrenocorticotropic hormone (ACTH) (n = 20). Initially given intravenously daily over 8-hr period, with doses as follows: 25 units on days 1-3, 20 units on days 4-6, 15 units on days 7-9, 10 units on days 10-12, and 5 units on days 13-15. IM injections then given on days 16-18 (40 units each) and days 19-21 (20 units each), after which treatment discontinued. 2) High-dose cyclophosphamide (CYCLO) + ACTH (n = 20). CYCLO administered intravenously daily for 10-14 days at dosage of 400-500 mg	1) Physical functioning: Definition of "improvement": Decrease of one or more points on either the Ambulation Index or the Disability-Status Scale, as compared with the score at the time of entry Proportion of patients with "improvement": ACTH alone – 5% ACTH + CYCLO – 40% ACTH, PEX and oral CYCLO – 20% Other (non-improvement) outcomes: Physician's clinical assessment of stabilized neurological status 2) Relapse frequency: Definition of "relapse": Not defined Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated	This study provides evidence that intensive immunosuppressive therapy, (particularly IV ACTH combined with high-dose IV cyclophosphamide) significantly reduces progressive MS in the population of patients who have severe, progressive MS. The study specifically demonstrates that the proportion of patients who experience clinical improvement on EDSS and Ambulation Index is increased with this therapy. The authors appropriately state that this is not a standard therapy and do not recommend the routine use of this regimen in patients with MS. "Its use should be restricted to experimental treatment programs or to carefully selected patients with rapid or unremitting progressive disease who have not responded to conventional regimens." This recommendation is based on the recognition that long-term studies have yet to be published and that there exists the potential for

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
				per day in 4 divided doses (total dose 80-100 mg/kg body weight). Discontinued when WBC count fell to approximately 4000/mm^3. Large volumes of fluids administered orally and by IV to prevent bladder toxicity. ACTH given as above, beginning on same day as CYCLO. 3) Plasma exchange (PEX) + low-dose CYCLO + ACTH (n = 18). PEX performed by means of continuous-glow exchange; approximately 1-1.5 plasma volumes removed per exchange and replaced with 5% serum albumin. 4-5 exchanges given over a 2-wk period. CYCLO given at low dose (2 mg/kg/day) for 8 wk (dose decreased if WBC count fell below 4000/mm^3). ACTH as above. All 3 treatments started together.		significant long-term toxicities. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? No Described as "double-blind"? No Patients blinded? No Investigators blinded? No Outcome assessors blinded? No No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
IFNB Multiple Sclerosis Study Group, 1993 **and** **IFNB Study Group and the University of British Columbia MS/MRI Analysis Group, 1995** **and** **IFNB Study Group and the University of British Columbia MS/MRI Analysis Group, 1996** **and** **Pliskin, Hamer, Goldstein, et al., 1996**	Inclusion: Clinically definite or laboratory-supported definite MS for > 1 yr; EDSS ≤ 5.5; ≥ 2 acute exacerbations in previous 2 yr; clinically stable for at least 30 days before entry; no ACTH or prednisone during 30 days prior to entry; age 18-50 Exclusion: Prior treatment with azathioprine or cyclophosphamide	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: Original study period 2 yr; later extended; median time on study was 48.0 mo for the IFNβ-1b 8 MIU group, 45.0 mo for the IFNβ-1b 1.6 MIU group, and 46.0 mo for the placebo group Provider specialty: Neurologists Location: 4 sites in Canada and 7 in US	No. of patients randomized: 372 Dropouts: Sixty-five patients discontinued treatment during the first 2 yr (23 placebo, 18 in the 1.6 MIU, and 24 in the 8 MIU groups) 154 (over entire study period) Completed: 307 through 2 yr; 218 through end of study Age (mean ± SE): IFNβ-1b 8 MIU: 35.2 ± 0.6 IFNβ-1b 1.6 MIU: 35.3 ± 0.7 Placebo: 36.0 ± 0.6 Baseline EDSS (mean ± SE): IFNβ-1b 8 MIU: 3.0 ± 0.1 IFNβ-1b 1.6 MIU: 2.9 ± 0.1 Placebo: 2.8 ± 0.1 Baseline relapse rate (mean in past 2 yr ± SE): IFNβ-1b 8 MIU: 3.4 ± 0.2 IFNβ-1b 1.6 MIU: 3.3 ± 0.1	1) Recombinant interferon β-1b (IFNβ-1b), 8 MIU self-administered by SC injection every other day for duration of study (n = 124) 2) Recombinant IFNβ-1b, 1.6 MIU self-administered by SC injection every other day for duration of study (n = 125) 3) Placebo (n = 123)	1) Physical functioning: A secondary endpoint, progression in disability, was defined as a persistent increase of one or more EDSS points confirmed on two consecutive evaluations separated by at least 3 months Results: Median time to progression (yr) Placebo – 4.18 1.6 MIU – 3.49 8 MIU – 4.79 Time to progression (placebo vs. 8 MIU) P = 0.096 2) Relapse frequency: Definition of "relapse": Appearance of a new symptom or worsening of an old symptom, attributable to MS; accompanied by an appropriate new neurological abnormality; lasting at least 24 hours in the absence of fever; and preceded by stability or improvement for at least 30 days Annual relapse rate: Year 1 Placebo – 1.44 1.6 MIU – 1.22 8 MIU – 0.96 Placebo vs. 8 MIU: p < 0.001 Year 2 Placebo – 1.18 1.6 MIU – 1.04 8 MIU – 0.85 Placebo vs. 8 MIU: p ≤ 0.03 Year 3 Placebo – 0.92 1.6 MIU – 0.80 8 MIU – 0.66 Placebo vs. 8 MIU: p = 0.084 Year 4 Placebo – 0.88 1.6 MIU – 0.68 8 MIU – 0.67 Placebo vs. 8 MIU: p = 0.166 Year 5 Placebo – 0.81 1.6 MIU – 0.66	These articles demonstrate the efficacy of IFNβ-1b over placebo in reducing exacerbation rates and limiting MRI disease activity, but contain no data to demonstrate the absolute improvement of any patient over baseline status. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
			Placebo: 3.6 ± 0.1		8 MIU – 0.57 Placebo vs. 8 MIU: p = 0.393 3) Cognitive functioning: Immediate and delayed recall memory and visual reproduction subtests of the Wechsler Memory Scale, forms 1 and 2, attention/mental speed (Trailmaking Test part B; Stroop Color-Word Test), dominant and nondominant morot function (Purdue Pegboard), and Beck Depression Inventory were administered to patients in all groups during the course of the study. No baseline measurements were made. Results: A significant main effect for time ($F = 15.75$ [2, 27], $p < 0.001$) and an interaction effect between treatment condition and time of testing ($F = 4.15$ [2, 27], $p < 0.03$) were found for WMS VR-Delayed Recall. Follow-up pairwise comparisons indicated an improvement in delayed visual reproduction between the second and fourth years of treatment in the high-dose group (WMS VR-Delayed Recall; $p < 0.003$). The placebo and low-dose groups did not change significantly. No other neuropsychological parameters demonstrated a significant difference between the groups during the study.	
Jacobs, Cookfair, Rudick, et al., 1996 **and** **Rudick, Goodkin, Jacobs, et al., 1997** **and**	Inclusion: Definite MS for ≥ 1 yr; EDSS 1.0-3.5; relapsing disease course, with ≥ 2 documented exacerbations in previous 3 yr and no exacerbations for at least past 2 mo; age 18-55 Exclusion: Prior	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: Variable (enrollment date varied, but end-of-study date same for all patients)	No. of patients randomized: 301 Dropouts: Not completely clear; 23 early withdrawals, variable treatment durations Completed: 287 followed up through 1 yr; 172	1) Interferon β-1a (IFNβ-1a) 6 million units by IM injection weekly for up to 3 yr (n = 158) 2) Placebo for up to 3 yr (n = 143)	1) Physical functioning: Definition of "improvement": ≥ 0.5- or 1.0-point improvement on EDSS Proportion of patients with "improvement": Placebo IFNβ-1a Improved Unsustained ≥ 1.0 10 (11.5%) 16 (19.3%) 0.5 10 (11.5%) 13 (15.7%) Improved	The study described in these reports demonstrates significant improvement with regard to progression of disability as measured by EDSS, reduction in relapse rates, and improvement in various neuropsychological test parameters in patients treated with IFNβ-1a compared with placebo. Most of the data presented compare treatment groups rather than presenting data on individual patient improvement. Some data are delineated with regard to the number of patients with improved

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Fischer, Priore, Jacobs, et al., 2000 **and** **Jacobs, Rudick, and Simon, 2000** **and** **Rudick, Fisher, Lee, et al., 2000**	immunosuppressant or interferon therapy; adrenocorticotropic hormone or corticosteroid treatment in previous 2 mo; pregnancy or nursing; unwilling to practice contraception; chronic progressive MS; any disease other than MS compromising organ function	Provider specialty: Neurologists Location: 4 sites in US	through 2 yr; 31 through 3 yr Age (mean ± SE): IFNβ-1a: 36.7 ± 0.57 Placebo: 36.9 ± 0.64 Baseline EDSS (mean ± SE): IFNβ-1a: 2.4 ± 0.06 Placebo: 2.3 ± 0.07 Baseline relapse rate (mean ± SE, time frame not specified): IFNβ-1a: 1.2 ± 0.05 Placebo: 1.2 ± 0.05		Sustained ≥ 1.0 5 (8.9%) 10 (18.2%) 0.5 9 (16.1%) 14 (25.5%) Other (non-improvement) outcomes: Time to sustained progression of disability, the primary outcome measure, was significantly greater in IFNβ-1a-treated patients than in placebo-treated patients (p = 0.02) 2) Relapse frequency: Definition of "relapse": Appearance of new neurological symptoms or worsening of preexisting neurological symptoms lasting at least 48 hours in a patient who had been neurologically stable or improving for the previous 30 days accompanied by objective change on neurological examination (worsening of 0.5 point on the EDSS or a worsening by ≥ 1.0 point on the pyramidal, cerebellar, brainstem, or visual functional system scores) Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Annual relapse rates: Placebo IFNβ-1a P value All patients 0.82 0.67 0.04 104 week patient subset 0.90 0.61 0.002 3) Cognitive functioning: The Comprehensive NP Battery is a broad-spectrum battery comprising measures from the core battery recommended by the National MS Society Cognitive Function Study Group as well as additional measures covering cognitive domains of theoretical	EDSS scores of 0.5 or 1.0 points. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					interest Definition of "improvement": Not defined for individual patients Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Relapsing MS patients treated with IFNβ-1a for 2 yr performed significantly better than placebo patients on a composite of information processing and learning/recent memory measures (set A from the Comprehensive NP Battery). A similar trend was observed on a composite measure of visuospatial abilities and executive functions (set B) but not on the set C composite (verbal abilities and attention span).	
Johnson, Brooks, Cohen, et al., 1995 **and** **Weinstein, Schwid, Schiffer, et al., 1999** **and** **Liu, Blumhardt, and the Copolymer 1 Multiple Sclerosis Study Group, 2000** **and**	Inclusion: Clinically definite or laboratory-supported MS; relapsing-remitting course; ambulatory, with EDSS 0-5.0; ≥ 2 clearly documented relapses in 2 yr prior to entry; onset of first relapse ≥ 1 yr before randomization; neurological stability and freedom from corticosteroid therapy for ≥ 30 days prior to entry; age 18-45 Exclusion: Previous Copolymer 1 therapy; previous immuno-suppressive therapy with cyctotoxic chemotherapy or	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: 2 yr Provider specialty: Neurologists Location: 11 sites in the US	No. of patients randomized: 251 Dropouts: 36 Completed: 215 Age (mean ± SD): Cop 1: 34.6 ± 6.0 Placebo: 34.3 ± 6.5 Baseline EDSS (mean ± SD): Cop 1: 2.8 ± 1.2 Placebo: 2.4 ± 1.3 Baseline relapse rate (mean ± SD for prior 2 yr): Cop 1: 2.9 ± 1.3 Placebo: 2.9 ± 1.1	1) Glatiramer acetate = Copolymer 1 (Cop 1) by SC injection; 20 mg self-injected daily for 2 yr (n = 125) 2) Placebo (n = 126)	1) Physical functioning: Definition of "improvement": ≥ 1.0-point EDSS reduction Proportion of patients with "improvement": Original 2-yr trial: Cop 1 – 24.8% Placebo – 15.2% Extension study: Cop 1 – 27.2% Placebo – 12.0% Other (non-improvement) outcomes: Mean change in EDSS, Ambulation Index, proportion of progression-free patients, area under curve analyses of EDSS progression 2) Relapse frequency: Definition of "relapse": Appearance or reappearance of one or more neurological	This study demonstrated the benefit of Copolymer 1 therapy in reduction of relapse rates and in proportion of patients who improved by ≥ 1.0 points on EDSS. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Johnson, Brooks, Cohen, et al., 1998	lymphoid irradiation; need for aspirin or chronic NSAIDs during trial; [other generic exclusions]				abnormalities persisting for at least 48 hours and immediately preceded by a relatively stable or improving neurological state of at least 30 days. A relapse was confirmed only when a patient's symptoms were accompanied by objective changes on the neurological examination consistent with an increase of at least a half a step on the EDSS, two points on one of the seven functional systems, or one point on two or more of the functional systems. Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Relapse rate: Cop 1 Placebo P-value Relapse rate 24 months 1.19 1.68 0.007 Annual relapse rate 0.59 0.84 Relapse free 33.6% 27.0% 0.098 Extension Relapse rate 1.34 1.98 0.002 Extension Annual relapse rate 0.58 0.81 3) Cognitive functioning: Brief Repeatable Battery of Neuropsychological Tests – consisting of 5 tests including measures of sustained attention and concentration (Paced Auditory Serial Addition Test and Symbol Digit Modalities Test), verbal learning and delayed recall (Buschke Selective Reminder Test), visuospatial learning and delayed recall (10/36 Spatial Recall Test), and semantic retrieval (Word	

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					List Generation Test) Definition of "improvement": Not defined Proportion of patients with "improvement": Mean neuropsychologic test scores were improved at 12 and 24 months compared with baseline for placebo and glatiramer groups. No differences were detected between the treatment groups for any of the neuropsychologic test results. Other (non-improvement) outcomes:	
Kappos, Polman, Pozzilli, et al., 2001 **and** **Freeman, Thompson, Fitzpatrick, et al., 2001**	Inclusion: Clinically or laboratory supported definite diagnosis of secondary progressive MS; EDSS 3.0-6.5; ≥ 2 relapses or ≥ 1.0-point increase in EDSS in previous 2 yr; age 18-55 Exclusion: None specified	RCT (parallel-group, double-blind, multicenter) Mean duration of treatment/follow up: Treatment lasted up to 36 mo; article reports results at study termination; mean follow-up time 1068 ± 176 days for IFNβ-1b and 1054 ± 199 days for placebo Provider specialty: NR (presumably neurologists) Location: 32 sites in Europe	No. of patients randomized: 718 Lost to follow up: 88 Withdrew from treatment: 132 Completed treatment and follow up: 498 Age (mean ± SD): IFNβ-1b: 41.1 ± 7.2 Placebo: 40.9 ± 7.2 Baseline EDSS (mean ± SD): IFNβ-1b: 5.1 ± 1.1 Placebo: 5.2 ± 1.1 Baseline relapse rate (% of patients without relapse in 2 yr preceding study):	1) Interferon β-1b (IFNβ-1b) by SC injection; initial dose 0.5 mL (4 MIU) every other day, increased after 2 wk to 1.0 mL (8 MIU) every other day for up to 3 yr (n = 360) 2) Placebo (n = 358)	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Time to confirmed progression in EDSS favored IFNβ-1b, p = 0.007 Percent of patients progression-free Placebo – 46.1% IFNβ-1b – 54.7% P = 0.031 2) Relapse frequency: Definition of "relapse": Previously defined Definition of "improvement": Not defined Proportion of patients with "improvement": Not assessed Other (non-improvement) outcomes: Percent of patients relapse-free: Placebo – 36.3% IFNβ-1b – 42.5% P = 0.083	These studies examined further analyses and quality-of-life parameters from the previously published trial conducted by the European Study Group in Interferon-β1b in Secondary-Progressive MS, 1998, above. Significant improvements in EDSS, relapse rate, and quality-of-life parameters were demonstrated. This study provides data on individual patient improvement only with regard to relapse rates. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
			IFNβ-1b: 31.9% Placebo: 28.2%		Percent of patients relapse-free or decrease in relapse rate: Placebo – 45.0% IFNβ-1b – 53.1% P = 0.031 3) Quality of life: The SIP is a generic self-report questionnaire of health-related quality of life, which examines the individual's perception of the impact of the disease process on behavior in everyday life. The total score ranges from 0 (best) to 100 (worst). The GEMS scale was developed specifically for this study and provides a global evaluation of the neurologist's perception of change in terms of disease status and disability. The scale provides 7 points ranging from "very much better" to "very much worse." No published information is available determining its measurement properties. Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: The difference in total SIP score for the two groups shows a non-statistically significant trend in favor of IFNβ-1b. The SIP physical dimension score demonstrates a statistically significant benefit in favor of IFNβ-1b therapy at 6 and 12 months. A significant treatment effect of IFNβ-1b was demonstrated in the psychosocial dimension scores at 18 months but not at the end of the study.	

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Khatri, McQuillen, Harrington, et al., 1985	Inclusion: Clinically definite MS; chronic progressive disease course (continuous worsening on serial neurological exams during previous 12 mo); patient insured, and insurance company would pay for plasma exchange Exclusion: None specified	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: 18 mo Provider specialty: Neurologists Location: 1 site in Milwaukee, WI	No. of patients randomized: 59 Dropouts: 4 Completed: 55 Age (mean, completers): Genuine: 37.8 Sham: 42.2 Baseline EDSS (mean, completers): Genuine: 6.6 Sham: 6.3 Baseline relapse rate: NR	1) Plasma exchange (n = 30); during each exchange, plasma volume equivalent to 5% of patient's body weight exchanged for 5% albumin solution and normal saline in equal ratios; exchanges performed once per week for 20 wk 2) Sham plasma exchange (patient's plasma returned after it had been separated) (n = 29); exchanges performed once per week for 20 wk Patients in both groups also received: a) Oral cyclophospha-mide (1.5 mg/kg per day, rounded to nearest 50 mg); b) prednisone (1 mg/kg every other day, gradually decreasing doses after 15th wk); and c) pooled human immune serum globulin (40 ml in 4 divided IM injections over 2 days after each exchange)	1) Physical functioning: Two scoring scales were used in measuring clinical change, the Kurtzke DSS and the Canter Scale, which measures changes in activities of daily living Definition of "improvement": ≥ 1-point improvement on DSS Proportion of patients with "improvement": At 5 mo, 14 plasmapheresis patients improved and 8 sham pheresis patients improved with details as follows: 5-mo evaluation: PP: 3 or more points: 5; 2 points: 5; 1 point: 4 Sham: 3 or more points: 0; 2 points: 4; 1 point: 4 11-mo evaluation: PP: 3 or more points: 3; 2 points: 4; 1 point: 4 Sham: 3 or more points: 0; 2 points: 1; 1 point: 4 Other (non-improvement) outcomes: Not delineated 2) Relapse frequency: Definition of "relapse": Not defined Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Not delineated 3) Cognitive functioning: Standard	This study evaluated plasmapheresis in the treatment of chronic progressive MS. The results suggest a benefit to plasmapheresis with regard to EDSS measured at 5 and 11 months. Observations suggest some improvement in cognitive function, although the details are not delineated. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					neurological examination Definition of "improvement": Not defined Proportion of patients with "improvement": 4 patients with cognitive deficits improved in these functions at the 15th PP treatment, but this did not occur in similar patients in the sham group	
Leary, Miller, Stevenson, et al., 2003	Inclusion: Primary progressive MS (progressive history without relapse or remission, ≥ 2 typical lesions on MRI brain or spinal cod, and oligoclonal bands in the CSF not present in parallel serum or abnormal visual evoked potentials); disease duration ≥ 2 yr; EDSS 2.0-7.0; age 18-60 Exclusion: Interferon, immunosuppressant, or chronic steroid therapy in previous 3 mo; pregnancy or lactation; seizure in previous 3 mo; history of severe depression	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: 2 yr Provider specialty: NR (presumably neurologists) Location: 1 site in London, UK	No. of patients randomized: 50 Dropouts: 7 withdrew from treatment; all but 1 of these followed up for 2 yr Completed: 43 completed treatment; 49 followed up for 2 yr Age (mean [with range]): IFNβ-1a 60: 47 (25-59) IFNβ-1a 30: 46.5 (29-58) Placebo: 43 (30-59) Baseline EDSS (median [with range]): IFNβ-1a 60: 5.5 (2.0-6.5) IFNβ-1a 30: 5.5 (3.5-7.0) Placebo: 4.5 (2.0-7.0) Baseline relapse	1) Interferon β-1a (IFNβ-1a) 60 µg weekly by IM injection for 2 yr (n = 15) 2) IFNβ-1a 30 µg weekly by IM injection for 2 yr (n = 15) 3) Placebo for 2 yr (n = 20)	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Primary endpoint was time to sustained progression in disability, and there was no statistically significant difference among the treatment arms	This study examined the efficacy of IFNβ-1a in the treatment of primary progressive MS with a primary endpoint of time to sustained progression and found no statistically significant treatment effect. No data are reported regarding individual patient improvement. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
			rate: NA			
Milanese, La Mantia, Salmaggi, et al., 1988	Inclusion: Clinically definite MS by Schumacher's criteria; relapsing-remitting (with ≥ 2 relapses in previous 3 yr) or progressive (with continuous worsening of neurological status over previous 1 yr) disease course Exclusion: Conditions which did not permit regular examination or which hampered patient's reliability (e.g., DSS > 7 or psychic disturbances); contraindications to immunosuppressive treatment; previous use of immuno-suppressive therapy; pregnancy	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: 1 yr (see "Comments") Provider specialty: Neurologists Location: 1 site in Milan, Italy	No. of patients randomized: 23 included in 1-yr analysis reported here (13 relapsing-remitting, 10 progressive) Dropouts: 0 (though 2 dropped out after 1 yr; see "Comments") Completed: 23 Age (mean): AZA-relapsing: 33.1 Placebo-relapsing: 34.1 AZA-progressive: 38.1 Placebo-progressive: 42.4 Baseline EDSS (mean): AZA-relapsing: 2.17 Placebo-relapsing: 2.43 AZA-progressive: 5.00 Placebo-progressive: 3.86 Baseline relapse rate (mean per yr): AZA-relapsing: 1.144 Placebo-relapsing: 0.890	1) Azathioprine (AZA) PO 2-2.5 mg/kg per day for 1 yr (n = 9) 2) Placebo for 1 yr (n = 14)	1) Physical functioning: Definition of "improvement": Not delineated Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: No statistically significant difference at 1 yr 2) Relapse frequency: Definition of "relapse": Schumacher criteria Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Relapse rate – Progressive MS: Pre- Final AZA 0.5 0.42 Placebo 0.32 0.42 Relapse rate – Relapsing-remitting MS: Pre- Final AZA 1.14 0.98 Placebo 0.89 0.92 No statistically significant differences in relapse rates	This study evaluated the efficacy of azathioprine in patients with relapsing-remitting and progressive MS. No statistically significant differences were detected in the first year of this 3-year trial. At the time of publication 17 of 38 patients had withdrawn from the study resulting in significant questions regarding the utility of 3-year data. No information is provided regarding individual patient improvement. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
			AZA-progressive: 0.500 Placebo-progressive: 0.318			
Millefiorini, Gasperini, Pozzilli, et al., 1997	Inclusion: Clinically definite or laboratory-supported relapsing-remitting MS; disease duration 1-10 yr; EDSS 2-5; at least 2 exacerbations in previous 2 yr; age 18-45 Exclusion: HIV-positive; previous cardiovascular disease; left ventricular ejection fraction < 50%; renal, liver, and/or respiratory dysfunction; diabetes; malignancy; psychiatric illness; pregnancy; women not using contraception; use of steroids in previous 3 mo; previous immunosuppressant therapy	RCT (parallel-group, double-blind [patients and assessors, not treating physicians], multicenter) Duration of study treatment/follow up: Treatment lasted 1 yr; patients followed for total of 2 yr Provider specialty: Neurologists Location: 8 sites in Italy	No. of patients randomized: 51 (all relapsing-remitting) Dropouts: 9 Completed: 42 completed all assessments (including MRIs) Age (mean ± SD): MTX: 30.9 ± 6.0 Placebo: 28.7 ± 6.5 Baseline EDSS (mean ± SD): MTX: 3.6 ± 0.9 Placebo: 3.5 ± 1.2 Baseline relapse rate (mean ± SD in previous 2 yr): MTX: 2.8 ± 1.2 Placebo: 2.8 ± 1.1	1) Mitoxantrone (MTX), 30-min IV infusion (8 mg/m^2) ever month for 1 yr (n = 27) 2) Placebo (n = 24)	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: % of patients who progressed by 1.0 point on EDSS – found statistically significant benefit of mitoxantrone at 2 yr 2) Relapse frequency: Definition of "relapse": Appearance of a new symptom or worsening of an old symptom, attributable to MS, accompanied by a documented new neurological abnormality, lasting more than 48 hours and preceded by stability or improvement for at least 30 days Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Number of exacerbation (mean ± SD): MTX: 0.89 ± 2.1 Placebo: 2.62 ± 1.9 p = 0.0002 Exacerbation-free patients: MTX: 17 (63%) Placebo: 5 (21%) p = 0.006	This study examined the efficacy of mitoxantrone in patients with relapsing-remitting MS and found statistically significant benefit of mitoxantrone with regard to EDSS progression and relapse rate reduction. No data are presented with regard to individual patient improvement. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? No – appears that there were none

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Multiple Sclerosis Study Group, 1990	Inclusion: Clinically definite MS for ≥ 1 yr; EDSS 3.0-7.0; age 18-55; chronic and progressive clinical deterioration of ≥ 1 grade, but not > 3 grades, on EDSS in previous 12 mo, with some decline in last 6 mo; no acute relapse in previous 3 mo; no immunosuppressive drugs in previous 3 mo; no unproven therapies for MS (e.g., hyperbaric oxygen, gangliosides, snake venom [!]) in previous 1 mo; no prior treatment with cyclophosphamide or radiation; no uncontrolled hypertension (SBP > 170 mmHg or DBP > 110 mmHg), malignancy, recent myocardial infarction, chronic pulmonary disease, active infection, hepatic or renal dysfunction, or other neurological disorders; not using medications known to interfere with study drugs Exclusion: Known sensitivity or adverse reactions to immunosuppressive	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: 2 yr Provider specialty: Neurologists Location: 12 sites in US	No. of patients randomized: 547 Dropouts: 120 (cyclosporine) + 87 (placebo) = 207 Completed: 340 Age (mean ± SD): Cyclosporine: 40.5 ± 7.7 Placebo: 40.6 ± 8.2 Baseline EDSS (mean ± SD): Cyclosporine: 5.4 ± 1.2 Placebo: 5.4 ± 1.2 Baseline relapse rate: NR	1) Cyclosporine PO (liquid suspension); initial dose of 6 mg/kg diluted in milk or orange juice and taken each morning with breakfast; dose adjusted to achieve whole-blood cyclosporine trough level of 400-600 ng/mL, later reduced to 300-500 ng/mL; maximum dose permitted was 10 mg/kg/day (n = 273) 2) Placebo (n = 274)	1) Physical functioning: Extensive evaluations performed including EDSS, incapacity status scales, functional system scores of the Multiple Sclerosis Minimal Record of Disability, standardized neurological examination, quantitative examination of neurological functional, Ambulation Index, physical examination, and clinical evaluation Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Mean change in EDSS – found benefit of cyclosporine therapy with p = 0.006 in patients completing study, and p = 0.002 in all patients. 2) Relapse frequency: Definition of "relapse": Not defined Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes:	This study evaluated cyclosporine therapy in chronic progressive MS patients. The study is complicated by a high dropout rate, but appears to demonstrate statistically significant benefit as measured by a reduction in progression in EDSS. This study does not present data on individual patient improvement. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes – a total of 37.3% of all patients withdrew by the end of the study, necessitating some modifications to the primary outcome assessments. These modifications were made prior to data analysis. 56% of patients randomized to receive cyclosporine completed 24 months of continuous therapy, whereas 68% of those randomized to placebo successfully completed the trial (p=0.003)

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	drug; severe dementia; paraplegia or gait ataxia sufficient to prevent walking; severe upper extremity ataxia preventing independent feeding or dressing					
Nose-worthy, O'Brien, Petterson, et al., 2001	Inclusion: One or more episodes of demyelinating optic neuritis occurring in the setting of clinically definite or laboratory-supported definite MS or in the presence of cranial MRI changes consistent with MS; first episode of optic neuritis between ages of 18 and 45; age < 50 at enrollment; fixed, apparently irreversible loss of visual acuity in at least one eye that met following criteria: a) visual acuity worse than 20/40 for a period of at least 6 mo and unchanged on at least 2 exams separated by at least 1 mo; b) optic disc pallor as detected by study neuro-ophthalmologist; c) abnormal visual field measured on Humphrey Field	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: Treatment lasted 12 wk + 5 days; patients followed for total of 12 mo Provider specialty: Ophthalmologists and neurologists Location: 1 site in Rochester, MN	No. of patients randomized: 55 (42 relapsing-remitting, 13 secondary progressive) Dropouts: 2 (both between 6 and 12 mo) Completed: 53 Age (mean ± SD): IV IgG: 38.0 ± 7.2 Placebo: 39.2 ± 6.7 Baseline EDSS (mean ± SD, excluding visual functional status scores): IV IgG: 3.6 ± 2.5 Placebo: 3.0 ± 2.5 Baseline relapse rate: NR	1) IV immunoglobulin (IV IgG) 0.4 g/kg daily for 5 days, then once per month for 3 months (total of 8 infusions) (n = 27) 2) Placebo (n = 28)	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Several measures of visual function were assessed, as well as EDSS. No measures demonstrated statistically significant benefit from therapy. 2) Relapse frequency: Definition of "relapse": Not defined Definition of "improvement": Not assessed Proportion of patients with "improvement": Not assessed Other (non-improvement) outcomes:	This study evaluated the efficacy of IV IgG in the treatment of optic neuritis in patients with MS. The study was terminated early due to negative results. No data are presented that demonstrate individual patient improvement. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	Analyzer with a mean deviation ≤ -4.00 and a pattern of defect consistent with optic neuritis; no adrenocorticotropic hormone or corticosteroids in previous 2 mo Exclusion: Primary progressive MS; nondemyelinating cause for visual loss; preexisting ocular abnormalities; serious intercurrent medical illness; concomitant use of experimental drug for MS or other disease; serum creatinine > 1.5 times normal; pregnancy or unwillingness to use contraception; known antibody deficiency syndrome; need for IV IgG administration					
Patti, L'Episcopo, Cataldi, et al., 1999	Inclusion: Definite MS; disease course relapsing-remitting (with ≥ 2 documented relapses in previous 2 yr and EDSS ≤ 3.5) or secondary progressive (with deterioration of ≥ 1.0 point on the EDSS over previous 2 yr and EDSS ≤ 7.0); emotionally stable;	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: 2 yr Provider specialty: Neurologists	No. of patients randomized: 98 (58 relapsing-remitting, 40 secondary progressive) Dropouts: 0 Completed: 98 Age (mean): Relapsing-	1) Natural interferon-β (nIFNβ) 6 MIU by IM injection three times per wk for 2 yr (n = 49) 2) Placebo for 2 yr (n = 49)	1) Physical functioning: Definition of "improvement": Decrease of 0.5 or 1.0 in EDSS Proportion of patients with "improvement": Relapsing-remitting patients: Placebo – 1 of 29 patients (3.4%) improved nIFNβ – 15 of 29 patients (52%) improved P = 0.002 Secondary progressive patients: Placebo – 1 of 20 patients (5%) improved nIFNβ – 8 of 20 patients (40%) improved	This study examined treatment effect of nIFNβ in relapsing-remitting and secondary-progressive MS. Statistically significant differences were found in the treatment group with regard to proportion of patients improving by 0.5 or 1.0 points on EDSS and in the proportion of patients relapse-free. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	negative for HIV, HbsAg, and Borreliosis; free of other immune or neurological diseases; clinically stable for ≥ 30 days; no ACTH or corticosteroids in previous 30 days; age 18-45 Exclusion: Pregnancy; prior treatment with azathioprine or cyclophosphamide (in previous 1 yr)	Location: 1 site in Catania, Italy	remitting (RR) patients: 36.6 Secondary progressive (SP) patients: 36.9 Baseline EDSS (mean): RR-nIFNβ: 3.06 RR-placebo: 3.1 SP-nIFNβ: 5.8 SP-placebo: 6.0 Baseline relapse rate (mean over previous 2 yr): RR-nIFNβ: 1.8 RR-placebo: 1.9 SP-nIFNβ: 0.4 SP-placebo: 0.6		P = 0.006 2) Relapse frequency: Definition of "relapse": Rapid onset of new symptoms or a worsening of preexisting symptoms persisting for 48 hours or more and were accompanied by objective changes on the neurologic examination – an increase of at least one grade in the score for at least one of the functional groups of EDSS Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: The probability of remaining exacerbation-free was significantly higher in the nIFNβ-treated group (presented in graphical form; p < 0.001)	Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes
Patzold, Hecker, and Pockling-ton, 1982	Inclusion: Confirmed MS; resident in district of study site Exclusion: None specified	RCT (parallel-group, open-label, single-center) Duration of study treatment/follow up: 2 yr Provider specialty: Neurologists Location: 1 site in Hanover, Germany	No. of patients randomized: 142 Dropouts: 27 before completing 1 yr; 17 more before completing 2 yr Completed: 115 completed 1 yr (53 intermittent, 52 intermittent-progressive, 10 progressive); 98 completed 2 yr (47 intermittent, 43 intermittent-progressive, 8 progressive)	1) Azathioprine PO, daily dose of 2 mg/kg for 2 yr (n = 74) 2) No azathioprine (n = 68)	1) Physical functioning (EDSS *not* assessed): Definition of "improvement": Not defined Proportion of patients with "improvement": Not assessed Other (non-improvement) outcomes: Patients were evaluated clinically and the severity of disease was calculated by means of an objective weighting scale corresponding to the data recorded by the examiner. In the untreated group on average MS deteriorated three times as rapidly as in the treated group. 2) Relapse frequency:	This study examined the efficacy of azathioprine in the treatment of MS. This trial suffers from two major design issues – lack of blinding, and lack of validated treatment outcome measures. The significance of the findings is unclear. This study does not provide data regarding individual patient improvement. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? No Described as "double-blind"? No Patients blinded? No Investigators blinded? No Outcome assessors blinded? No No. of withdrawals in each group stated?

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
			Age: NR Baseline EDSS: NR Baseline relapse rate: NR		Definition of "relapse": Definite worsening of condition lasting for 24 hr or more, or the occurrence or recurrence of symptoms and signs after a period of 4 wk in which these had either disappeared or improved Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: No. of relapses: Azathioprine: 2.4 ± 2.0 Control: 1.9 ± 1.3	Yes
PRISMS Study Group and the University of British Columbia MS/MRI Analysis Group, 1998 **and** **Liu and Blumhardt, 1999** **and** **Liu and Blumhardt, 2002** **and** **Patten and Metz, 2001**	Inclusion: Clinically definite or laboratory-supported definite MS of at least 1 yr duration; relapsing-remitting MS with ≥ 2 relapses in preceding 2 yr and EDSS score 0-5.0; adult Exclusion: Any previous systemic treatment with interferons, lymphoid irradiation, or cyclophosphamide; other immuno-modulatory or immunosuppressive treatment in previous 12 mo	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: 2 yr Provider specialty: Neurologists Location: 22 sites in Canada, Australia, and 7 European countries	No. of patients randomized: 560 Lost to follow up: 27 Withdrew from treatment: 31 Followed up to 2 yr: 533 Completed treatment to 2 yr: 502 Age (median with IQR): IFNβ-1a 44 µg: 35.6 (28.4-41.0) IFNβ-1a 22 µg: 34.8 (29.3-39.8) Placebo: 34.6 (28.8-40.4) Baseline EDSS (mean ± SD):	1) Interferon β-1a (IFNβ-1a) by SC injection, 44 µg (12 MIU), 3 times weekly (n = 184) 2) IFNβ-1a by SC injection, 22 µg (6 MIU), 3 times weekly (n = 189) 3) Placebo (n = 187)	1) Physical functioning: Definition of "improvement": In the categorical disability trend analysis sustained improvement was defined as a decrease of at least 1.0 EDSS point confirmed at 3 months and sustained until the end of the study Proportion of patients with "improvement": Not stated – in the categorical disability trend analysis data were not reported on the number of patients with sustained improvement. 31% of treated patients and 20% of placebo patients attained stable course. Other (non-improvement) outcomes: 22-mcg dose and 44-mcg dose patients both had mean reduction in EDSS compared with placebo of 0.25 2-yr change in EDSS: Mean / AUC Placebo +0.48 / +0.48 22-mcg dose +0.23 / +0.05 44-mcg dose +0.24 / +0.06	This study provides significant data regarding the benefit of treatment over placebo with regard to relapse rate and EDSS outcome measures. These data are reported as group improvement and no data are provided on individual patient improvement from baseline status. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
			IFNβ-1a 44 µg: 2.5 ± 1.3 IFNβ-1a 22 µg: 2.5 ± 1.2 Placebo: 2.4 ± 1.2 Baseline relapse rate (mean relapses in previous 2 yr [± SD]: IFNβ-1a 44 µg: 3.0 ± 1.1 IFNβ-1a 22 µg: 3.0 ± 1.1 Placebo: 3.0 ± 1.3		2) Relapse frequency (primary outcome measure): Definition of "relapse": As defined by Schumacher criteria, required the appearance of a new symptom or worsening of an old symptom over at least 24 hr that could be attributed to MS activity and was preceded by stability or improvement for at least 30 days Definition of "improvement": Proportion of patients with "improvement": - Not stated Other (non-improvement) outcomes: Relapses per patient: Placebo – 2.56 22 mcg dose – 1.82 44 mcg dose – 1.73 % reduction in relapses vs. placebo: 22 mcg dose – 29 44 mcg dose – 32 % relapse free over 1 year: Placebo – 22 22 mcg dose – 37 44 mcg dose – 45 % relapse free over 2 years: Placebo – 16 22 mcg dose – 27 44 mcg dose – 32 Moderate or severe relapses - % with no relapses: Placebo – 42 22 mcg dose – 61 44 mcg dose – 62 % with no admissions for MS:	

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					Placebo – 75 22 mcg dose – 77 44 mcg dose - 82 3) Cognitive functioning [describe scale/ instrument used]: Definition of "improvement": Not assessed Proportion of patients with "improvement": Not assessed 5) Quality of life: Center for Epidemiological Studies Depression Rating Scale was used to assess whether treatment with IFNβ-1a was associated with depression Other (non-improvement) outcomes: Proportion of patients exceeding cut-point did not vary significantly across treatment groups	
Rice, Filippi, and Comi, 2000	Inclusion: Clinically definite or laboratory-supported MS according to Schumacher or Poser criteria; chronic progressive disease course (slow progression of signs and symptoms over preceding 12 mo); EDSS 3.0-6.5; serum creatinine < 1.5 mg/dL and creatinine clearance ≥ 80% of age-adjusted normal; aspartate and alanine transaminase and alkaline phosphatase levels < twice the normal upper limit;	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: 12 mo Provider specialty: NR (presumably neurologists) Location: 6 sites in Canada and the US	No. of patients randomized: 159 (111 secondary progressive, 48 primary progressive) Dropouts: 4 Completed: 155 Age (mean): High-dose: 43.8 Low-dose: 44.6 Placebo: 44.2 Baseline EDSS (mean): High-dose: 5.6 Low-dose: 5.6 Placebo: 5.6	1) Cladribine by SC injection, 6 monthly courses of 0.07 mg/kg/day for 5 consecutive days (total dose 2.1 mg/kg), followed by 2 monthly courses of placebo (n = 52) 2) Cladribine by SC injection, 2 monthly courses of 0.07 mg/kg/day for 5 consecutive days (total dose 0.7 mg/kg), followed by 6 monthly courses of placebo (n = 53) 3) Placebo, 8 monthly courses (n = 54)	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Primary outcome measure was mean change in EDSS – no statistical difference in treatment groups observed 2) Relapse frequency: Definition of "relapse": Not assessed Definition of "improvement": Not delineated Proportion of patients with "improvement": Not assessed	This study evaluated two different doses of cladribine and found no statistically significant difference in clinical outcomes. No data are provided regarding individual patient improvement. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? No – 97% of all patients completed the study

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	neutrophil count > 1600/µL; platelet count > 130,000/µL; clinically normal ECG and chest X-ray; age 21-60 Exclusion: Significant history of medical disease in previous 2 yr; use of corticosteroids or other immunosup-pressants in previous 3 mo; total lymphoid irradiation; persistent leukopenia or thrombocytopenia after treatment with immunosuppressive agents; alcohol or drug abuse or attempted suicide in previous 1 yr; malignancy in previous 5 yr; pregnancy or nursing; HIV+; use of experimental drug or device in last 60 days; previous participation in cladribine trial		Baseline relapse rate: NR			
Romine, Sipe, Koziol, et al., 1999	Inclusion: Clinically definite relapsing-remitting MS for at least 1 yr; ≥ 2 relapses in previous 2 yr; EDSS ≤ 6.5 Exclusion: Treatment with immunosup-	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: Treatment lasted 8 mo; patients followed	No. of patients randomized: 52 Dropouts: 2 before 12 mo, plus 6 more before 18 mo Completed: 50 to 12 mo, 44 to 18 mo	1) Cladribine by SC injection; 5 consecu-tive daily injections of 0.07 mg/kg/day given monthly for 6 mo for total cumulative dose of 2.1 mg/kg; during remaining 2 mo of 8-mo treatment period, placebo given unless	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": Not assessed Other (non-improvement) outcomes: No significant differences between the two groups with regard to EDSS or SNRS scores over the 18-mo period	This study evaluated the efficacy of cladribine compared with placebo in patients with relapsing-remitting MS. No statistical difference was found with regard to EDSS scores. A modest benefit was found in favor of cladribine with regard to relapse rate and severity. The data were not evaluated with regard to clinical improvement of individual patients.

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	pressive drugs in previous 3 mo; serum creatinine > 1.5 mg/dL; serum glutamic-oxaloacetic transaminase/serum glutamic-pyruvic transaminase or alkaline phosphatase elevated to twice the upper limit of normal; neutrophil counts of < 1600/µL or platelet counts < 130,000/µL; previous total lymphoid irradiation or extensive myelosuppressive chemotherapy	for total of 18 mo Provider specialty: Neurologists Location: 1 site in La Jolla, CA	Age (mean, with range): Cladribine: 43.4 (30-52) Placebo: 39.8 (31-52) Baseline EDSS (mean, with range): Cladribine: 3.9 (2.0-6.5) Placebo: 3.8 (2.0-6.5) Baseline relapse rate (number in previous 1 yr): Cladribine: 1: 5 (19%) 2: 16 (59%) 3-4: 6 (22%) Placebo: 1: 13 (52%) 2: 5 (20%) 3-4: 7 (28%)	investigators had had to substitute placebo for a monthly dose earlier due to blood count inadequacy, in which case active drug could be given during mo 7 or 8 (n = 27) 2) Placebo (n = 25)	2) Relapse frequency: Definition of "relapse": Appearance of new symptoms or worsening of an existing symptom, attributable to MS and accompanied by objective worsening of neurological findings and must have been preceded by disease stability or improvement lasting for at least 30 days, and the worsening must have lasted at least 24 hours and occur in the absence of fever Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Relapse rate: Cladribine – 0.77 (95% CI, 0.37 to 1.41) Placebo – 1.67 (95% CI, 1.02 to 2.57)	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes
Schwartz, Coulthard-Morris, Cole, et al., 1997	Inclusion: Relapsing-remitting MS Exclusion: None specified	RCT (see under "Comments") Duration of study treatment/follow up: 1 yr Provider specialty: NR Location: NR; patients had applied to lottery to gain access to experimental drug	No. of patients randomized: NR Dropouts: NR Completed: 79 Age (mean): IFNβ-1b: 43.9 Control: 43.3 Baseline EDSS: NR Baseline relapse rate: NR	1) Recombinant interferon β-1b (IFNβ-1b); dose, route of administration, and treatment regimen not described (n = 34) 2) Usual care (n = 45)	1) Physical functioning: Not assessed 2) Relapse frequency: Not assessed 3) Cognitive functioning: Multiple scales used as below Definition of "improvement": Improvement was defined as population mean change Proportion of patients with "improvement": Not assessed Other (non-improvement) outcomes: Wechsler Memory Scale delayed visual recall demonstrated improvement in the	As recognized by the authors, the small sample size may have precluded the finding of statistical significance on some of the other measures of cognitive function Study design was retrospective, taking advantage of random allocation of IFNβ-1b in a treatment lottery; however, control condition was not standardized, and follow-up data were collected by survey and thus were subject to respondent bias QUALITY ASSESSMENT: Described as "randomized"? No

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					high-dose group compared with placebo ($p < 0.003$). Other measures failed to reach statistical significance. Individual patient data and percentage of patients improving not reported.	Method of randomization clearly described? No Concealment of allocation? No Described as "double-blind"? No Patients blinded? No Investigators blinded? No Outcome assessors blinded? No No. of withdrawals in each group stated? Yes
Sipe, Romine, Koziol, et al., 1994	Inclusion: Clinically definite or laboratory-supported definite chronic progressive MS for more than 2 yr Exclusion: Serum creatinine ≥ 132 µmol/L or creatinine clearance < 80% of age-adjusted normal; serum transaminases or hepatic alkaline phosphatase more than twice the upper limit of normal; neutrophil count < 1600 µL or platelet count < 130,000/µL; inadequate birth control; plans to father a child during study; treatment with corticosteroids or other immunosup-pressive medications in previous 6 mo; decreased marrow reserve as manifested by leukopenia or thrombocytopenia for > 6 wk after	RCT (designed as 2-yr crossover trial, but analyzed as parallel-group trial after 1 yr; double-blind [examining physicians and patients, *not* treating physicians], single-center, matched-pair design) Duration of study treatment/follow up: 1 yr Provider specialty: Neurologists Location: 1 site in La Jolla, CA	No. of patients randomized: 51 (49 initially entered + 2 replacements for dropouts) Dropouts: 3 cladribine patients (2 of whom were replaced), 1 placebo patient (included in analyses) Completed: 47 (48 analyzed) Age (mean, with range): Cladribine: 43.0 (28-53) Placebo: 42.7 (21-54) Baseline EDSS (mean ± SE): Cladribine: 4.7 ± 0.3 Placebo: 4.6 ± 0.3 Baseline relapse rate: NR	Central venous access device surgically implanted in all patients for study drug administration 1) Cladribine administered by continuous 7-day IV infusion at the rate of 0.1 mg/kg daily; total of 4 monthly courses given (n = 24) 2) Placebo infusion (n = 24)	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Paired differences in the two groups were significant in favor of cladribine: EDSS: Cladribine 4.4 ± 2.0; Placebo 5.6 ± 1.5; P-value $p < 0.01$ SNRS: Cladribine 74.8 ± 10.3; Placebo 62.6 ± 11.3; P-value $p < 0.001$ 2) Relapse frequency: Definition of "relapse": Not defined Definition of "improvement": Not defined Proportion of patients with "improvement": Not assessed Other (non-improvement) outcomes: None	This study examined the effect of cladribine therapy in patients with progressive MS and found a statistically significant benefit to cladribine therapy with regard to group differences in progression as measured by EDSS and SNRS. No data are presented with regard to improvement of individual patients. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	conclusion of immunosuppressive treatment					
SPECTRIMS Study Group, 2001	Inclusion: Clinically definite secondary progressive MS (defined as progressive deterioration of disability for ≥ 6 mo, with increase of ≥ 1 EDSS point over the last 2 yr [or 0.5 point between EDSS 6.0 and 6.5], with or without superimposed exacerbations, following an initial relapsing-remitting course); EDSS 3.0-6.5; pyramidal functional score ≥ 2; age 18-55 Exclusion: Immunosuppressive or immunomodulatory treatments during previous 3-12 mo (depending on drug); corticosteroid use or disease exacerbation in previous 8 wk; severe concurrent illness; pregnancy or lactation; unwilling-ness to use contraception	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: 3 yr Provider specialty: Neurologists Location: 22 sites in Europe, Canada, and Australia	No. of patients randomized: 618 Dropouts: 112 withdrew from treatment; 65 of these were followed up for 3 yr Completed: 506 completed treatment; 571 were followed up for 3 yr Age (mean ± SD): IFNβ-1a 44: 42.6 ± 7.3 IFNβ-1a 22: 43.1 ± 7.2 Placebo: 42.7 ± 6.8 Baseline EDSS (mean ± SD): IFNβ-1a 44: 5.3 ± 1.1 IFNβ-1a 22: 5.5 ± 1.1 Placebo: 5.4 ± 1.1 Baseline relapse rate (mean ± SD in previous 2 yr): IFNβ-1a 44: 0.9 ± 1.3 IFNβ-1a 22: 0.9 ± 1.4 Placebo: 0.9 ± 1.2	1) Interferon β-1a (IFNβ-1a) 44 µg by SC injection three times weekly for 3 yr (n = 204) 2) IFNβ-1a 22 µg by SC injection three times weekly for 3 yr (n = 209) 3) Placebo (n = 205)	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: The primary outcome, time to sustained progression, revealed no statistically significant difference among treatment arms. 2) Relapse frequency: Definition of "relapse": Appearance of a new symptom or worsening of an old symptom attributable to MS, accompanied by an appropriate new neurologic abnormality or focal neurologic dysfunction lasting at least 24 hours in the absence of fever and preceded by stability or improvement for at least 30 days Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Mean annual relapse rate: IFN 22 mcg Placebo IFN 44 mcg 0.50 0.71 0.50 p < 0.001 p < 0.001	This study examined the benefit of IFNβ-1a in the treatment of secondary progressive MS. There was no significant treatment effect on the primary outcome measure of time to confirmed progression. Significant benefits were demonstrated with regard to relapse rates. No data on improvement with regard to individual patients. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
van de Wyngaert, Beguin, D'Hooghe, et al., 2001	Inclusion: Definite clinical diagnosis of MS by Poser criteria; relapsing, secondary progressive disease course; at least partial recovery from last relapse at least 1 mo before study entry; EDSS 3.0-6.0; worsening of EDSS by 1 point in previous 12 mo; effective birth control; normal isotopic cardiac ventriculography and routine blood analysis at entry; age 18-50 Exclusion: Remittent disease course, primary progressive disease, or secondary progressive disease without relapses; major illness other than MS or immuno-suppressive drugs other than corticosteroids in previous 3 yr	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: Treatment lasted 32 mo; patients followed up for an additional 4 mo Provider specialty: Neurologists Location: 1 site in Belgium	No. of patients randomized: 49 Dropouts: 25 Completed: 24 Age (mean ± SD): MTX: 38.3 ± 6.9 MP: 39.2 ± 7.8 Baseline EDSS (mean, with range): MTX: 5.1 (3.0-6.0) MP: 5.0 (3.0-6.0) Baseline relapse rate (mean in previous 12 mo ± SD): MTX: 2.3 ± 1.0 MP: 2.2 ± 1.2	1) Mitoxantrone (MTX) 12 mg/m^2 initially given intravenously over one hour once per month for 3 mo; then given once every 3 mo, 10 times, until month 32; each treatment preceded by IV administration of 3 vials of alizapride (anti-emetic) (n = 28) 2) Methylprednisolone (MP) 1 g initially given intravenously over one hour between 8 and 10 a.m. once per month for 3 mo; then given once every 3 mo, 10 times, until month 32 (n = 21)	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": 35% of patients receiving MTX improved clinically compared with 22% receiving placebo – difference not statistically significant Other (non-improvement) outcomes: 2) Relapse frequency: Definition of "relapse": Not defined Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Mean number of relapses/patient/year was significantly lower in the MTX group after 2 and 3 years of treatment (p = 0.016 and 0.029, respectively)	This study examined the effectiveness of cladribine in relapsing, secondary progressive MS. The study demonstrated a non-significant trend in favor of cladribine with regard to the number of patients who improved. The precise definition of improvement was not given. The small sample size may have contributed to the lack of statistical significance. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Unclear Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease-modifying therapies and long-term improvement

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Achiron, Gabbay, Gilad, et al., 1998	Inclusion: Clinically definite relapsing remitting MS of > 1 yr duration; average yearly exacerbation rate 0.5-3 in 2 yr preceding study; EDSS score 0-6.0; age 18-60 Exclusion: Secondary progression disease course; serum immunoglobulin deficiency; long-term steroid or cytotoxic treatment 12 mo prior to study; major psychiatric disorder; major cognitive impairment	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: 2 yr Provider specialty: Neurologists Location: Tel Hashomer, Israel	No. of patients randomized: 40 Dropouts: 2 Completed: 38 Age (mean ± SE): IV IgG: 35.4 ± 2.1 Placebo: 33.8 ± 2.4 Baseline EDSS (mean ± SE): IV IgG: 2.90 ± 0.43 Placebo: 2.82 ± 0.37 Baseline relapse rate (mean ± SE per yr in 2 yr preceding study): IV IgG: 1.85 ± 0.26 Placebo: 1.55 ± 0.17	1) IV immunoglobulin (IV IgG); loading dose of 0.4g/kg/body weight per day for 5 consecutive days, followed by booster doses of 0.4 g/kg/body weight once daily every 2 mo for 2 yr (n = 20) 2) Placebo (n = 20)	1) Physical functioning: Definition of "improvement": 1.0-point change in EDSS compared with baseline Proportion of patients with "improvement": In the IV IgG group 23.5% of patients improved vs. 10.8% in the placebo group Other (non-improvement) outcomes: No significant change in mean EDSS in treatment arm 2) Relapse frequency: Definition of "relapse": The rapid appearance, reappearance, or worsening of one or more neurological abnormalities, persisting at least 48 hr, after a relatively stable or improving neurological state of at least 30 days. A relapse was confirmed only when the patient's symptoms were accompanied by objective changes on neurological examination by a blinded neurologist. Definition of "improvement": Not specified on a per patient basis Proportion of patients with "improvement": Not specified Other (non-improvement) outcomes: a) Yearly exacerbation rates IV IgG / Placebo / P-value Baseline 1.85 / 1.55 / 0.34 Year 1 0.75 / 1.8 / 0.0002 Year 2 0.42 / 1.42 / 0.0009 2-yr total 0.59 / 1.61 / 0.0006	This article demonstrates that a larger proportion of patients demonstrated improvement in EDSS when treated with IV IgG compared with placebo. The definition of improvement was a 1.0-point improvement on EDSS. There are no data delineating how many patients may have improved greater than 1.0 point. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? No

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					b) Exacerbation-free patients: IV IgG / Placebo / P-value Year 1: 8 / 1 / 0.001 Year 2: 12 / 3 / 0.001 Total study: 6 / 0 / 0.001 c) Median time to first exacerbation (days): IV IgG / Placebo / P-value 233 / 82 / 0.003	
Bastianello, Pozzilli, D'Andrea, et al., 1994	Inclusion: Definite diagnosis of MS; relapsing-remitting disease course (≥ 2 relapses in 24 mo prior to study entry); disease duration 1-10 yr; EDSS 2.0-5.0; age 18-45; selected to undergo serial MRI scans (subgroup of total study population) Exclusion: HIV-positive; previous cardiovascular disease; left ventricular ejection fraction < 50% by echocardiography; renal, liver, and/or respiratory dysfunction; diabetes; malignancy; psychiatric illness; pregnancy or no contraception; use of immunosuppressant drugs or steroids in previous 3 mo	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: 1 yr (preliminary results from planned 2-yr trial) Provider specialty: Neurologists Location: 7 sites in Italy	No. of patients randomized: 25 (subgroup of total study population selected to undergo serial MRI scans) Dropouts: 0 Completed: 25 Age (mean ± SD): MTX: 29.9 ± 5.2 Placebo: 28.5 ± 6.5 Baseline EDSS (mean ± SD): MTX: 3.7 ± 0.7 Placebo: 3.5 ± 1.0 Baseline relapse rate (mean in previous 2 yr ± SD): MTX: 2.8 ± 1.2 Placebo: 3.3 ± 1.2	1) Mitoxantrone (MTX) 8 mg/m^2 by 30-min IV infusion every month for 1 yr (n = 13) 2) Placebo (n = 12)	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: No statistical difference was observed in mean EDSS change at 1 yr (p = 0.18) 2) Relapse frequency: Definition of "relapse": The appearance of new symptom or worsening of an old one, attributable to MS and lasting at least 24 hours in the absence of fever Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: MTX / Placebo / P value MER: 0.54 / 1.67 / 0.014 PWE: 5(38%) / 10(83%) / 0.02 MER = Mean exacerbation rate PWE = Number (%) of patients with exacerbations	This trial reports initial findings demonstrating a benefit of mitoxantrone in reducing mean exacerbation rates, but does not provide quantitative information regarding absolute improvement of specific patients over baseline status. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Bornstein, Miller, Slagle, et al., 1987	Inclusion: Definite MS; relapsing-remitting form of MS; ≥ 2 well-demarcated and well-documented relapses in previous 2 yr; EDSS ≤ 6; emotionally stable; age 20-35 Exclusion: None specified	RCT (parallel-group, double-blind, single-center, matched-pairs design) Duration of study treatment/follow up: 2 yr Provider specialty: Neurologists Location: 1 site in Bronx, NY	No. of patients randomized: 50 Dropouts: 7 dropped out before 2 yr, but 5 of these were included in analysis Completed: 43 completed trial; 48 included in analysis Age (mean): Cop 1: 30.0 Placebo: 31.0 Baseline EDSS (mean): Cop 1: 2.9 Placebo: 3.2 Baseline relapse rate (mean over 2 yr): Cop 1: 3.8 Placebo: 3.9	1) Glatiramer acetate = Copolymer 1 (Cop 1) by SC injection, 20 mg self-injected daily for 2 yr (n = 25) 2) Placebo (n = 25)	1) Physical functioning: Definition of "improvement": Reduction in EDSS by 1, 2, or 3 points over 2 yr Proportion of patients with "improvement": Placebo / Cop 1 1.0 point: 8.7% / 20.0% 2.0 points: 0 / 12.0% 3.0 points: 4.4% / 0 2) Relapse frequency: Definition of "relapse": The rapid onset of new symptoms or a worsening of preexisting symptoms that persisted for 48 hours or more, when accompanied by observed objective changes on the neurological examination involving an increase of a atl east one grade in the score for one of the eight functional groups or the Kurtzke Scale Definition of "improvement": Decrease in 2-yr relapse rate in comparison with individual baseline relapse rate Proportion of patients with "improvement": Placebo – 12 of 23 patients experienced a decrease in relapse rate over the 2yr period Cop 1 – 24 of 25 patients experienced a decrease in relapse rate over the 2-yr treatment period Other (non-improvement) outcomes: Exacerbation-free patients: Placebo – 26% Cop 1 – 56% P = 0.036	This early study of the efficacy of Copolymer 1 in the treatment of relapsing-remitting MS demonstrated benefits of treatment in the reduction of relapse rates and improved disability status. Data are presented regarding the number of patients demonstrating improvement on EDSS. Although significant efforts were made to maintain blinding, the physician evaluator correctly identified 70% of those taking placebo and 78% of those taking Cop 1. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Bornstein, Miller, Slagle, et al., 1991	Inclusion: Definite diagnosis of MS by Poser criteria; evidence of a chronic-progressive course for ≥ 18 mo; ≤ 2 exacerbations in previous 24 mo; EDSS score 2.0-6.5; emotionally stable and able to participate in clinical trial; age 20-60 During a 6- to 15-mo pre-trial observation period, patients required to demonstrate progression in one of following ways: worsening of 2 grades in a functional system; worsening of 1 grade in 2 unrelated functional systems; worsening of 2 units on the Ambulation Index; or worsening of 1 grade on the EDSS. Must not have progressed beyond 6.5 on EDSS or have had > 1 exacerbation during pre-trial observation period. Exclusion: None specified	RCT (parallel-group, double-blind, two-center) Duration of study treatment/follow up: 2 yr or until confirmed progression (whichever first) Provider specialty: Neurologists Location: Bronx, NY; and Houston, TX	No. of patients randomized: 106 Dropouts: 20 Completed: 86 Age (mean): Cop 1: 41.6 Placebo: 42.3 Baseline EDSS: Mean: Cop 1: 5.7 Placebo: 5.5 Cop 1 Plac < 5: 22% 27% 5-5.5: 8% 15% 6-6.5: 71% 58% Baseline relapse rate: NR	1) Copolymer 1 (Cop 1) by SC injection; 15 mg self-injected twice per day for 2 yr (n = 51) 2) Placebo (n = 55)	1) Physical functioning: Definition of “improvement”: Not defined Proportion of patients with “improvement”: Cop 1: 19.6% improved 37.3% remained stable 41.1% worsened Placebo: 14.5% improved 34.6% remained stable 50.9% worsened Other (non-improvement) outcomes: The primary endpoint, confirmed progression of 1.0 or 1.5 units (depending on baseline disability) on the Kurtzke Disability Status Scale, was not statistically different in the two groups 2) Relapse frequency: Definition of “relapse”: Not defined Definition of “improvement”: Not assessed Proportion of patients with “improvement”: Not delineated	This study provides no significant information regarding improvement of patients on this therapy. QUALITY ASSESSMENT: Described as “randomized”? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as “double-blind”? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
British and Dutch Multiple Sclerosis Azathio-prine Trial Group, 1988	Inclusion: Clinically definite MS (≥ 2 episodes and 2 clinical lesions or 2 episodes and 1 subclinical lesion [revealed by VEP or CT]); or laboratory confirmed MS (≥ 2 anatomically separate episodes, 1 clinical lesion, and oligoclonal bands or increased IgG in the CSF); or currently progressive MS (2 separate lesions [of which 1 might be subclinical], oligoclonal bands, or increased IgG in the CSF, and progres-sion for at least 6 mo); patients with relapsing-remitting disease had to have been in a remittent phase for ≥ 1 mo and have had ≥ 1 relapses in the previous year; EDSS ≤ 6 (ambulant); age 15-50; not on other immunomodulatory drugs or hyperbaric oxygen treatment Exclusion: Concomitant systemic disease; mental deficit that precluded understanding and	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: 3 yr Provider specialty: Neurologists Location: 20 sites in the UK and The Netherlands	No. of patients randomized: 354 (199 [56%] clinically definite, 37 [10%] laboratory confirmed; 51 [14%] progressive from onset; 67 [19%] progressive after remission) Lost to follow up (cumulative totals): 20 at 1 yr, 24 at 2 yr, 22 at 3 yr, 153 at 4 yr Discontinued treatment (cumulative totals): 48 at 1 yr, 64 at 2 yr, 75 at 3 yr Completed: 279 completed treatment, 332 followed up through 3 yr Age (mean ± SD): Azathioprine: 39 ± 8.6 Placebo: 38 ± 8.3 Baseline EDSS (mean ± SD): Azathioprine: 3.69 ± 1.50 Placebo: 3.66 ± 1.62 Baseline relapse	1) Azathioprine PO 2.5 mg/kg (to the nearest 25 mg) daily (n = 174) 2) Placebo (n = 180)	1) Physical functioning: Definition of “improvement”: Not defined Proportion of patients with “improvement”: Not delineated Other (non-improvement) outcomes: The only statistically significant result was a reduction in the deterioration of the Ambulation Index in the azathioprine group compared with the placebo group after 3 yr	The treatment effect in this study was marginal, and no data are reported that delineate improvement of any patient with respect to baseline status. QUALITY ASSESSMENT: Described as “randomized”? Yes Method of randomization clearly described? No Concealment of allocation? Yes Described as “double-blind”? Yes Patients blinded? Yes/No/Unclear Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	cooperation		rate (months since last relapse): Az Plac 1-6: 43% 45% 7-12: 20% 18% > 12: 37% 37%			
Canadian Cooperative Multiple Sclerosis Study Group, 1991	Inclusion: Clinically definite or laboratory-supported definite MS in a progressive phase (deterioration of at least 1 point on EDSS over preceding 12 mo); EDSS 4.0-6.5; age ≥ 15 Exclusion: Previous treatment with cyclophosphamide, cyclosporin, antilymphocyte globulin, or interferon; treatment with azathioprine or plasma exchange in preceding yr or corticosteroids in preceding mo; illnesses that might be adversely affected by study treatments; substantial cognitive impairment; unwillingness to use contraception during trial and for 2 yr after; weekly venous access difficult	RCT (parallel-group, not double-blinded, multicenter) Duration of study treatment/follow up: Duration of treatment variable (see at right, under "Interventions"); patients followed up for at least 12 mo; mean follow up, 30.4 mo Provider specialty: Neurologists Location: 9 sites in Canada	No. of patients randomized: 168 (81 relapsing-progressive, 86 chronic-progressive, 1 unkown) Dropouts: 2 (died) Completed: 166 Age (mean at disease onset ± SD): Cyclophosphamide IV: 31.9 ± 10.3 Plasma exchange: 29.9 ± 7.9 Placebo: 32.1 ± 9.7 Baseline EDSS (mean ± SD): Cyclophosphamide IV: 5.79 ± 0.61 Plasma exchange: 5.66 ± 0.72 Placebo: 5.79 ± 0.64 Baseline relapse rate: NR	1) Cyclophosphamide IV + prednisone PO (n = 55). Cyclophos-phamide 1g given intravenously on alternate days until WBC count fell below 4.5 x 10^9/L or until total dose of 9 g reached. Prednisone 40 mg given orally for 10 days, then reduced by 10 mg on alternate days and discontinued on day 16. 2) Plasma exchange + cyclophosphamide PO + prednisone PO (n = 57). Plasma exchange of one plasma volume (40 mL/kg) done weekly for 20 wk with either intermittent (5 sites) or continuous (4 sites) flow-type centrifuges. Replacement = 5% serum albumin. Oral cyclophosphamide 1.5-2.0 mg/kg given daily for 22 wk; dose adjusted to achieve target WBC of 4.0-5.0 x 10^9/L. Oral prednisone 20 mg given every other day	1) Physical functioning: Definition of "improvement": 1.0-point improvement on EDSS sustained for 6 mo Proportion of patients with "improvement": No statistically significant difference among the treatment arms Number of patients improved: Cycl PEX Placebo 1 yr 3 (6%) 4 (8%) 1 (2%) 2 yr 2 (6%) 1 (3%) 0 3 yr 2 (4%) 1 (2%) 1 (2%) Other (non-improvement) outcomes: No statistically significant difference between treatment arms in any outcome measure	This study provides data specifically addressing the number of patients who improved with regard to EDSS, but the results show no statistically significant benefit of the treatments studied. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? No (treating providers) Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
				and tapered over 22 wk. 3) Placebo (placebo oral cyclophospha-mide and prednisone for 22 wk + sham plasma exchange for 20 wk) (n = 56)		
Cohen, Cutter, Fischer, et al., 2002	Inclusion: Clinically definite secondary progressive MS, with or without recent relapses; disease progression over previous 1 yr; cranial MRI demonstrating lesions consistent with MS; EDSS 3.5-6.5; age 18-60 Exclusion: Primary progressive disease course; inability to complete MS Functional Composite at baseline; prior treatment with interferon-β	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: 2 yr Provider specialty: Neurologists Location: 42 sites in US, Europe, and Canada	No. of patients randomized: 436 Dropouts: 115; of these, 63 had complete 2-yr follow up Completed: 321 completed treatment; 384 followed up for 2 yr Age (mean ± SD): IFNβ-1a: 47.2 ± 8.2 Placebo: 47.9 ± 7.7 Baseline EDSS (mean ± SD): IFNβ-1a: 5.2 ± 1.1 Placebo: 5.2 ± 1.1 Baseline relapse rate (mean ± SD, prior 3 yr): IFNβ-1a: 1.5 ± 2.1 Placebo: 1.3 ± 2.1	1) Interferon β-1a (IFNβ-1a) 60 µg weekly by IM injection for 2 yr (n = 217); half dose (30 µg) given for first four doses to minimize adverse events 2) Placebo for 2 yr (n = 219)	1) Physical functioning: Definition of "improvement": Not defined for individual patients Proportion of patients with "improvement": Improvement based on EDSS – baseline to 24 months Placebo – 7.3% IFNβ-1a – 7.5% No statistically significant difference Other (non-improvement) outcomes: 24-month MSFC data-median: Placebo IFNβ-1a P value MSFC -0.161 -0.362 0.033 9HPT -0.290 -0.202 0.024 Timed 25-ft walk – no statistical difference PASAT – no statistical difference 2) Relapse frequency: Definition of "relapse": New or recurrent neurological symptoms, not associated with fever or infection, lasting at least 48 hours and accompanied by objective change on the examining neurologist's examination at an unscheduled visit corresponding to the reported symptoms Definition of "improvement": Not delineated on individual patients Proportion of patients with "improvement":	This study examined the benefit of IFNβ-1a in secondary progressive MS utilizing assessments of EDSS, MSFC, and MSQLI and demonstrated beneficial effects on MSFC and MSQLI. This was the first use of the MSFC in a large-scale MS trial. The beneficial effects of treatment observed on MSFC were primarily driven by improvements in upper extremity function. The report focuses on between-group differences and provides few data on individual patient improvement. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					Not delineated Other (non-improvement) outcomes: Annual relapse rate: Placebo – 0.30 IFNβ-1a – 0.20 P = 0.008 Relapse-free patients – intention to treat: Placebo – 63% IFNβ-1a – 74% P=0.023 3) Quality of life: The MS Quality of Life Inventory (MSQLI) was administered to English-speaking subjects at baseline, 12 months, and 24 months Definition of "improvement": Not defined Proportion of patients with "improvement": NR Other (non-improvement) outcomes: Significant benefit favoring IFNβ-1a treatment was observed on 8 of 11 subscales of the MSQLI, with a favorable trend on the remaining three scales. The IFNβ-1a group improved from baseline to month 24 on 10 of 11 subscales (all except Bladder Control Scale). In contrast, the placebo group worsened from baseline to month 24 on 10 of 11 subscales, the Modified Fatigue Impact Scale being the only subscale showing improvement. Data not shown (reference made to www.neurology.org web site).	

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Currier, Haerer, and Meydrech, 1993	Inclusion: Definite MS; a worsening in function or an exacerbation in the previous yr; understanding and willingness to cooperate Exclusion: History or evidence of renal or hepatic disease; gross obesity; diabetes	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: Initially 1 yr; changed during trial to 18 mo Provider specialty: Neurologist Location: Jackson, MS	No. of patients randomized: 45 (20 "exacerbating remitting" and 24 "chronic" MS [latter includes 18 "exacerbating progressive," 3 "chronic progres-sive," and 3 "spinal patients"]) Dropouts: 9 Completed: 36 Age (median, reported only by MS type): Exacerbating remitting: 39.5 Chronic: 46.8 Baseline EDSS: NR Baseline relapse rate (total number of exacerbations in 12 mo preceding trial; reported only for patients with "exacerbating remitting" MS): Methotrexate: 9 in 9 patients Placebo: 12 in 11 patients	1) Methotrexate PO; 2.5 mg every 12 hr for 3 consecutive doses once per wk (7.5 mg/ wk) for 18 mo (n = 22) 2) Placebo (n = 22)	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: 2) Relapse frequency: Definition of "relapse": 1.0-point EDSS worsening (unsustained) Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: No statistically significant difference in treatment groups except for a difference in the mean number of exacerbations p = 0.05 – data presented in graphical form only	This study provides no data regarding individual patient improvement on therapy. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
De Castro, Cartoni, Millefiorini, et al., 1995	Inclusion: Definite diagnosis of MS according to Poser criteria; relapsing-remitting disease course; ≥ 2 relapses in 24 mo prior to study entry; disease duration 1-10 yr; EDSS 2.0-5.0; age 18-45 Exclusion: HIV-positive; heart, renal, lung, or liver disease; psychiatric disease; pregnancy or lactation; known allergy to cortico-steroids; other neurological disease; use of corticosteroids during previous 3 mo; use of levamisol, isoprinosin, or plasmapheresis during previous 3 mo; treatment with interferon; immunosuppressive therapy during previous 12 mo	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: 1 yr Provider specialty: NR (presumably neurologists and cardiologists) Location: 1 site in Italy	No. of patients randomized: 20 Dropouts: NR (implied 0) Completed: NR (implied 20) Age (mean ± SD): MTX: 31 ± 5 Placebo: 30 ± 4 Baseline EDSS (mean ± SD): MTX: 3.77 ± 0.72 Placebo: 3.33 ± 0.75 Baseline relapse rate (mean in previous 2 yr ± SD): MTX: 2.82 ± 0.98 Placebo: 3.00 ± 1.94	1) Mitoxantrone (MTX) 8 mg/m^2 by 30-min IV infusion every month for 1 yr (n = 13) 2) Placebo (n = 12)	1) Physical functioning: Definition of “improvement”: Not defined Proportion of patients with “improvement”: Not delineated Other (non-improvement) outcomes: No statistically significant difference between treatment arms with respect to changes in EDSS 2) Relapse frequency: Definition of “relapse”: Not defined Definition of “improvement”: Not defined Proportion of patients with “improvement”: Not delineated Other (non-improvement) outcomes: Difference in relapse rate favored treatment with mitoxantrone p = 0.005	This study demonstrated a statistically significant reduction in mean relapse rate in the treatment arm but did not include data regarding the clinical improvement of individual patients. QUALITY ASSESSMENT: Described as “randomized”? Yes Method of randomization clearly described? No Concealment of allocation? Yes Described as “double-blind”? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? No

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
European Study Group on Interferon beta-1b in Secondary Progressive MS, 1998	Inclusion: Clinically or laboratory supported definite diagnosis of secondary progressive MS; EDSS 3.0-6.5; ≥ 2 relapses or ≥ 1.0-point increase in EDSS in previous 2 yr; age 18-55 Exclusion: None specified	RCT (parallel-group, double-blind, multicenter) Mean duration of treatment/follow up: Treatment scheduled to last 36 mo, with 3-mo follow up; article reports results of prospectively planned interim analysis of all patients in study for ≥ 2 yr; mean follow up time 901 days for IFNβ-1b and 892 days for placebo Provider specialty: NR (presumably neurologists) Location: 32 sites in Europe	No. of patients randomized: 718 Lost to follow up: 57 Withdrew from treatment, but had complete follow up: 130 Completed treatment and follow up: 531 Age (mean ± SD): IFNβ-1b: 41.1 ± 7.2 Placebo: 40.9 ± 7.2 Baseline EDSS (mean ± SD): IFNβ-1b: 5.1 ± 1.1 Placebo: 5.2 ± 1.1 Baseline relapse rate (% of patients without relapse in 2 yr preceding study): IFNβ-1b: 31.9% Placebo: 28.2%	1) Interferon β-1b (IFNβ-1b) by SC injection; initial dose 0.5 mL (4 MIU) every other day, increased after 2 wk to 1.0 mL (8 MIU) every other day for up to 3 yr (n = 360) 2) Placebo (n = 358)	1) Physical functioning: Primary endpoint was time to confirmed progression in disability defined as a 1.0-point increase on EDSS sustained for at least 3 months, or a 0.5-point increase if the baseline EDSS was 6.0 or 6.5 Results: Significant difference in time to confirmed progression of disability in favor of IFNβ1-b (p = 0.0008) On average IFNβ1-b delayed confirmed progression by 9-12 months in this patient population Confirmed EDSS progression: Placebo: 46.7% IFNβ1-b: 38.9% p = 0.0048 2) Relapse frequency: Definition of "relapse": Not defined Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: a) Mean annual relapse rate: Placebo / IFN β-1b / p Overall 0.64 / 0.44 / 0.0002 Year 1 0.82 / 0.57 / 0.0095 Year 2 0.47 / 0.35 / 0.0201 Year 3 0.35 / 0.24 / 0.1624 b) Proportion of patients with moderate to severe relapse: Placebo: n = 190 (53.1%) IFNβ1-b: n = 157 (43.6%) p = 0.008	This article demonstrates the efficacy of IFNβ-1b over placebo in reducing the rate of progression and in reducing the relapse rate. It does not provide data regarding improvement of individual patients over their baseline functional status. See also the entry for Kappos, Polman, Pozzilli, et al., 2001, below. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Fazekas, Deisen-hammer, Strasser-Fuchs, et al., 1997a **and** **Fazekas, Deisen-hammer, Strasser-Fuchs, et al., 1997b** **and** **Strasser-Fuchs, Fazekas, Deisen-hammer, et al., 2000**	Inclusion: Clinically definite diagnosis of relapsing-remitting MS; EDSS score 1.0-6.0; ≥ 2 clearly identified and documented relapses during previous 2 yr; age 15-64; first manifestation of MS at age 10-59 Exclusion: Immuno-suppressive or immunomodulatory therapy in previous 3 mo; corticosteroids in previous 2 wk; primary or secondary progressive MS; benign course of disease as indicated by a deterioration rate (EDSS score divided by duration of disease in years) < 0.25	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: 2 yr Provider specialty: Neurologists Location: 13 sites in Austria	No. of patients randomized: 150 Lost to follow up: 2 (before start of treatment) Stopped treatment: 28 Completed treatment: 120 Age (mean [95% CI]): IV IgG: 36.7 (34.3-39.1) Placebo: 37.3 (35.0-39.6) Baseline EDSS (mean [95% CI]): IV IgG: 3.3 (3.0-3.6) Placebo: 3.3 (2.9-3.7) Baseline relapse rate (mean per yr [95% CI]): IV IgG: 1.3 (1.1-1.5) Placebo: 1.4 (1.2-1.6)	1) IV immunoglobulin (IV IgG); 0.15-0.20 g/kg body weight once per month for 2 yr (n = 75) 2) Placebo (n = 73)	1) Physical functioning: Definition of "improvement": 1.0-point decrease in EDSS by the end of the study Proportion of patients with "improvement": IV IgG – 31% of patients improved Placebo – 14% of patients improved Other (non-improvement) outcomes: Between-group differences in the absolute change on the EDSS score and in the proportion of patients stable or worsened 2) Relapse frequency: Definition of "relapse": The appearance or reappearance of one or more neurological abnormalities that persisted for at least 24 hours and had been preceded by a stable or improving neurological state of at least 30 days. A relapse was confirmed only if the patient's symptoms were accompanied by objective changes of at least one grade in the scored for one of the eight functional groups on the EDSS. Definition of "improvement": Not delineated Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: IV IgG / Placebo / P Relapse-free Patients: 53% / 36% / 0.03 Mean Annual Relapse Rate Year 1: 0.49 / 1.30 / 0.011 Year 2: 0.42 / 0.83 / 0.006 3) Quality of life: Incapacity Status Scale and the Environmental Status Scale	These studies demonstrate benefit from treatment with IV IgG over placebo with regards to progression of EDSS. Moreover, the study documents an increased proportion of patients who demonstrated improvement on EDSS over the 2-yr trial. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					Definition of "improvement": Not defined prospectively Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: The mean change of rating scores of 15 of 16 items was more favorable following IV IgG treatment. The total mean change of ratings over all ISS items was significantly in favor of IV IgG-treated patients (P = 0.01) Similarly, IV IgG-treated patients noted improvement in 4 of 7items of the ESS compared to no item rated as improved by placebo patients.	
Ghezzi, Di Falco, Locatelli, et al., 1989	Inclusion: Definite MS Exclusion: Disease duration < 1 yr; EDSS > 7; concomitant diseases contraindicating immunosuppression	RCT (parallel-group, open-label, single-center) Duration of study treatment/follow up: 18 mo Provider specialty: NR (presumably neurologists) Location: 1 site in Gallarate, Italy	No. of patients randomized: 185 (74 relapsing, 111 relapsing-progressive) Dropouts: 50 Completed: 135 Age (mean at onset [with range], completers only): Relapsing (R)-azathioprine: 26 (15-42) R-control: 26 (18-42) Relapsing-progressive (RP)-azathioprine: 29 (12-44) RP-placebo: 31 (16-47) Baseline EDSS (mean [with range],	1) Azathioprine PO 2.5 mg/kg per day for 18 mo (n = 69) 2) No azathioprine (n = 66)	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": Relapsing patients who improved: Azathioprine – 5 of 32 Controls – 0 of 22 P > 0.10 Relapsing-progressive patients: Azathioprine – 2 of 37 Controls – 3 of 44 p > 0.10 Other (non-improvement) outcomes: No statistical difference between the treatment arms with respect to EDSS 2) Relapse frequency: Definition of "relapse": Not defined Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated	This unblended trial of azathioprine in MS did not find statistically significant differences in any outcome measures. Data are presented that delineate individual patient improvement. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? No Patients blinded? No Investigators blinded? Unclear Outcome assessors blinded? Unclear No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
			completers only): R-azathioprine: 2.1 (1-5) R-control: 2.2 (1-5) RP-azathioprine: 3.8 1-6.5) RP-placebo: 3.7 (1-7) Baseline relapse rate (mean [with range], completers only, time frame not specified): mean at onset [with range], completers only): R-azathioprine: 1.2 (0.2-4) R-control: 1.1 (0.2-3) RP-azathioprine: 0.6 (0.1-3.3) RP-placebo: 0.4 (0.1-2.5)		Other (non-improvement) outcomes: No statistically significant difference in treatment arms	
Goodkin, Bailly, Teetzen, et al., 1991	Inclusion: Clinically definite or laboratory-supported definite MS; seen at study clinic from 1983 to 1989; relapsing-remitting disease course (≥ 2 exacerbations in previous 18 mo); no exacerbation in previous 1 mo; EDSS 2.0-6.5; AI 1.0-6.0; age 18-65 Exclusion: Chronic	RCT (parallel-group, double-blind [patients and examining physician, not treating physician], single-center) Duration of study treatment/follow up: 2 yr Provider specialty: Neurologists	No. of patients randomized: 59 randomized, 54 began treatment No. followed for 2 yr: 52 No. treated per protocol for 2 yr: 43 Age (mean ± SD at onset; n = 54 starting treatment): Azathioprine: 29.4	1) Azathioprine PO; initial dose 50 mg 3 times per day, adjusted to target dose of 3 mg/kg, with increases made in increments of 25 mg per day no more than once per month; WBC maintained at 3500-4000/µL (n = 29) 2) Placebo (n = 25)	1) Physical functioning: Definitions of "improvement": Score reflects combined results of change lasting more than 2 mo in any of following: ≥ 1.0-point on EDSS for patients with baseline EDSS ≤ 5.0, *or* ≥ 0.5-point on EDSS for patients with baseline EDSS ≥ 5.5, *or* ≥ 1.0 point on AI, *or* ≥ 20% deterioration from baseline in 9HPT or BBT Proportion of patients with "improvement": Placebo = 20% Azathioprine = 22.2%	This study demonstrates a modest benefit of azathioprine in reducing mean exacerbation rates and provides specific data regarding the proportion of patients who improve on therapy with regard to EDSS and other functional measures. The proportion of patients who improved was, however, not statistically different among the treatment groups. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	progressive disease (worsening in functional status measurements over 6 mo without exacerbation); use of corticosteroids in previous 1 mo; use of immunosuppressant medication in previous 1 yr; pregnant; unwilling to practice birth control; systemic illness of medical condition that precluded safe administration of study drugs	Location: 1 site in Fargo, ND	± 8.5 Placebo: 30.0 ± 6.8 Baseline EDSS (mean ± SD; n = 54 starting treatment): Azathioprine: 3.18 ± 1.19 Placebo: 3.72 ± 1.60 Baseline relapse rate (mean ± SD in previous 18 mo; no = 54 starting treatment): Azathioprine: 2.34 ± 0.55 Placebo: 2.32 ± 0.63		Other (non-improvement) outcomes: Difference in mean change in EDSS 2) Relapse frequency: Definition of "relapse": Objective worsening in the EDSS of ≥ 0.5 points, Ambulation Index (AI) of ≥ 1.0 points, or ≥ 20% deterioration from baseline performance on the nine-hole peg test (9HPT) or box-and-block test (BBT) in patients who were stable or improving within the last month Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Mean on-trial exacerbation rates for each group: AZA / Placebo / P Year 1: 0.74 / 1.17 / 0.16 Year 2: 0.30 / 0.79 / 0.05 Total 2 year: 1.04 / 1.88 / 0.08	Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes
Goodkin, Rudick, VanderBrug Medendorp, et al., 1995	Inclusion: Clinically definite chronic progressive MS; progressive neurological impairment during period of ≥ 6 mo prior to start of study; no exacerbation for previous 8 mo; ≤ 1 exacerbation in previous 2 yr; disease duration > 1 yr; EDSS 3.0-6.5; AI 2.0-6.0; no cortico-steroids during previous 1 mo or	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: 2 yr Provider specialty: Neurologists Location: 1 site in Cleveland, OH	No. of patients randomized: 60 (18 primary progressive, 42 secondary progressive) Dropouts: 9 Completed: 51 Age (mean ± SD): METH: 43 ± 9.3 Placebo: 46 ± 8.8 Baseline EDSS (mean):	1) Methotrexate (METH), one 7.5-mg oral tablet per week for 2 yr (n = 31) 2) Placebo (n = 29)	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: The primary outcome measure was time to treatment failure on a composite measure of physical functioning that utilized EDSS, Ambulation Index, Box and Block Test and 9-Hole Peg Test for 2 mo or more. Treatment failure was pre-defined on the basis of specific levels of deterioration on any of these scales. There was a significant relationship between	This study evaluated therapy with low-dose oral methotrexate (6.5 mg) weekly in patients with chronic progressive MS and found significant benefit on a composite measure of physical functioning. The most prominent benefit observed was in upper extremity function. The study did not evaluate individual patient improvement and provided no data specifically addressing the proportion of patients improved. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	immunosuppressant medication for previous 1 yr; no prior lymphoid irradiation; willing to use contraception; age 21-60 Exclusion: Pregnancy; systemic illness or medical condition that precluded safe administration of study drugs; clinically evident cognitive impairment		METH: 5.5 Placebo: 5.3 Baseline relapse rate: NR		sustained progression and treatment group favoring the METH treatment: METH = 51.6%, Placebo = 82.8% (p = 0.011). This treatment effect was strongest for the 9HPT and was seen to a lesser extent (p = NS) for the BBT and EDSS.	Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes
Hartung, Gonsette, König, et al., 2002	Inclusion: Worsening relapsing-remitting MS (stepwise progression of disability between relapses) or secondary progressive MS; EDSS 3.0-6.0; worsening of ≥ 1 point on EDSS in previous 18 mo; no relapse in previous 8 wk; no treatment with glucocorticosteroids in previous 8 wk; no previous treatment with mitoxantrone, interferons, glatiramer acetate, cytotoxic drugs, or total-body lymphoid irradiation; left ventricular ejection fraction > 50%; WBC,	RCT (parallel-group, double-blind [patients and assessors, not treating physicians], multicenter) Duration of study treatment/follow up: Treatment lasted 2 yr; patients followed for total of 3 yr Provider specialty: Neurologists Location: 17 sites in Belgium, Germany, Hungary, and Poland	No. of patients randomized: 194 randomized; 188 included in baseline measures (94 worsening relapsing-remitting, 94 secondary progressive) Dropouts: 56 Completed: 138 assessed at 3 yr Age (mean ± SD): MTX 12 mg: 39.94 ± 6.85 MTX 5 mg: 39.92 ± 8.06 Placebo: 40.02 ± 7.88 Baseline EDSS (mean ± SD):	1) Mitoxantrone (MTX) 12 mg/m^2 by slow IV infusion every 3 months for 2 yr; dose could be reduced in response to adverse events, infection, or low WBC or platelet count (n = 63) 2) Mitoxantrone (MTX) 5 mg/m^2 by slow IV infusion every 3 months for 2 yr; dose could be reduced in response to adverse events (n = 66) 3) Placebo (n = 65)	1) Physical functioning: EDSS, Ambulation Index, and standard neurological status scores were established at each scheduled and unscheduled visit Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Mean and median EDSS change, Ambulation Index change, SNS change 2) Relapse frequency: Definition of "relapse": Severe relapse defined as the occurrence of new symptoms lasting for longer than 48 hours with a change in functional system score of more than 2 points, or a deterioration of at least 1 point in at least one of the four following systems: pyramidal, brainstem, cerebellar, or visual Definition of "improvement": Not defined	This study evaluated therapy with mitoxantrone (12 mg/m^2) IV every 3 months in the treatment of worsening relapsing-remitting MS and secondary progressive MS. Investigators found statistically significant differences in the treatment groups on the following outcome measures: multivariate analysis of outcome, change in EDSS, change in Ambulation Index, adjusted total number of treated relapses, time to first treated relapse, and change in standardized neurological status. The 5-mg/m^2 dose arm demonstrated less convincing benefits. This study did not provide data regarding improvement in individual patients. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	neutrophil, and platelet counts in normal ranges; age 18-55 Exclusion: None specified		MTX 12 mg: 4.45 ± 1.05 MTX 5 mg: 4.64 ± 1.01 Placebo: 4.69 ± 0.97 Baseline relapse rate (mean ± SD in previous 1 yr): MTX 12 mg: 1.27 ± 1.12 MTX 5 mg: 1.42 ± 1.26 Placebo: 1.31 ± 1.14		Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Number of treated relapses per patient (median, with range): Placebo: 1 (0-5) MTX 12 mg: 0 (0-2) p = 0.0002	Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes
Hauser, Dawson, Lehrich, et al., 1983	Inclusion: Clinically definite MS; severe progressive disease, with worsening in previous 9 mo (defined as a decrease of ≥ 1 points on functional status or disability scales, either continuous decline or continuous decline with superimposed exacerbations); no corticosteroid therapy in previous month; no immunosuppressive therapy in previous yr Exclusion: Medical illnesses incompatible with safe administration of study medications	RCT (parallel-group, not double-blinded, two-center) Duration of study treatment/follow up: Treatment duration variable (see at right, under "Interventions"; patients followed for total of 1 yr Provider specialty: NR (presumably neurologists) Location: 2 sites in Boston, MA	No. of patients randomized: 58 Dropouts: 0 Completed: 58 Age (mean ± SE): ACTH: 35.2 ± 1.5 CYCLO + ACTH: 32.9 ± 1.8 PEX + CYCLO + ACTH: 36.3 ± 1.7 Baseline EDSS (mean ± SE): ACTH: 5.6 ± 0.2 CYCLO + ACTH: 5.8 ± 0.2 PEX + CYCLO + ACTH: 5.6 ± 0.2 Baseline relapse rate: NR	1) Adrenocorticotropic hormone (ACTH) (n = 20). Initially given intravenously daily over 8-hr period, with doses as follows: 25 units on days 1-3, 20 units on days 4-6, 15 units on days 7-9, 10 units on days 10-12, and 5 units on days 13-15. IM injections then given on days 16-18 (40 units each) and days 19-21 (20 units each), after which treatment discontinued. 2) High-dose cyclophosphamide (CYCLO) + ACTH (n = 20). CYCLO administered intravenously daily for 10-14 days at dosage of 400-500 mg	1) Physical functioning: Definition of "improvement": Decrease of one or more points on either the Ambulation Index or the Disability-Status Scale, as compared with the score at the time of entry Proportion of patients with "improvement": ACTH alone – 5% ACTH + CYCLO – 40% ACTH, PEX and oral CYCLO – 20% Other (non-improvement) outcomes: Physician's clinical assessment of stabilized neurological status 2) Relapse frequency: Definition of "relapse": Not defined Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated	This study provides evidence that intensive immunosuppressive therapy, (particularly IV ACTH combined with high-dose IV cyclophosphamide) significantly reduces progressive MS in the population of patients who have severe, progressive MS. The study specifically demonstrates that the proportion of patients who experience clinical improvement on EDSS and Ambulation Index is increased with this therapy. The authors appropriately state that this is not a standard therapy and do not recommend the routine use of this regimen in patients with MS. "Its use should be restricted to experimental treatment programs or to carefully selected patients with rapid or unremitting progressive disease who have not responded to conventional regimens." This recommendation is based on the recognition that long-term studies have yet to be published and that there exists the potential for

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
				per day in 4 divided doses (total dose 80-100 mg/kg body weight). Discontinued when WBC count fell to approximately 4000/mm^3. Large volumes of fluids administered orally and by IV to prevent bladder toxicity. ACTH given as above, beginning on same day as CYCLO. 3) Plasma exchange (PEX) + low-dose CYCLO + ACTH (n = 18). PEX performed by means of continuous-glow exchange; approximately 1-1.5 plasma volumes removed per exchange and replaced with 5% serum albumin. 4-5 exchanges given over a 2-wk period. CYCLO given at low dose (2 mg/kg/day) for 8 wk (dose decreased if WBC count fell below 4000/mm^3). ACTH as above. All 3 treatments started together.		significant long-term toxicities. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? No Described as "double-blind"? No Patients blinded? No Investigators blinded? No Outcome assessors blinded? No No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
IFNB Multiple Sclerosis Study Group, 1993 **and** **IFNB Study Group and the University of British Columbia MS/MRI Analysis Group, 1995** **and** **IFNB Study Group and the University of British Columbia MS/MRI Analysis Group, 1996** **and** **Pliskin, Hamer, Goldstein, et al., 1996**	Inclusion: Clinically definite or laboratory-supported definite MS for > 1 yr; EDSS ≤ 5.5; ≥ 2 acute exacerbations in previous 2 yr; clinically stable for at least 30 days before entry; no ACTH or prednisone during 30 days prior to entry; age 18-50 Exclusion: Prior treatment with azathioprine or cyclophosphamide	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: Original study period 2 yr; later extended; median time on study was 48.0 mo for the IFNβ-1b 8 MIU group, 45.0 mo for the IFNβ-1b 1.6 MIU group, and 46.0 mo for the placebo group Provider specialty: Neurologists Location: 4 sites in Canada and 7 in US	No. of patients randomized: 372 Dropouts: Sixty-five patients discontinued treatment during the first 2 yr (23 placebo, 18 in the 1.6 MIU, and 24 in the 8 MIU groups) 154 (over entire study period) Completed: 307 through 2 yr; 218 through end of study Age (mean ± SE): IFNβ-1b 8 MIU: 35.2 ± 0.6 IFNβ-1b 1.6 MIU: 35.3 ± 0.7 Placebo: 36.0 ± 0.6 Baseline EDSS (mean ± SE): IFNβ-1b 8 MIU: 3.0 ± 0.1 IFNβ-1b 1.6 MIU: 2.9 ± 0.1 Placebo: 2.8 ± 0.1 Baseline relapse rate (mean in past 2 yr ± SE): IFNβ-1b 8 MIU: 3.4 ± 0.2 IFNβ-1b 1.6 MIU: 3.3 ± 0.1	1) Recombinant interferon β-1b (IFNβ-1b), 8 MIU self-administered by SC injection every other day for duration of study (n = 124) 2) Recombinant IFNβ-1b, 1.6 MIU self-administered by SC injection every other day for duration of study (n = 125) 3) Placebo (n = 123)	1) Physical functioning: A secondary endpoint, progression in disability, was defined as a persistent increase of one or more EDSS points confirmed on two consecutive evaluations separated by at least 3 months Results: Median time to progression (yr) Placebo – 4.18 1.6 MIU – 3.49 8 MIU – 4.79 Time to progression (placebo vs. 8 MIU) P = 0.096 2) Relapse frequency: Definition of "relapse": Appearance of a new symptom or worsening of an old symptom, attributable to MS; accompanied by an appropriate new neurological abnormality; lasting at least 24 hours in the absence of fever; and preceded by stability or improvement for at least 30 days Annual relapse rate: Year 1 Placebo – 1.44 1.6 MIU – 1.22 8 MIU – 0.96 Placebo vs. 8 MIU: p < 0.001 Year 2 Placebo – 1.18 1.6 MIU – 1.04 8 MIU – 0.85 Placebo vs. 8 MIU: p ≤ 0.03 Year 3 Placebo – 0.92 1.6 MIU – 0.80 8 MIU – 0.66 Placebo vs. 8 MIU: p = 0.084 Year 4 Placebo – 0.88 1.6 MIU – 0.68 8 MIU – 0.67 Placebo vs. 8 MIU: p = 0.166 Year 5 Placebo – 0.81 1.6 MIU – 0.66	These articles demonstrate the efficacy of IFNβ-1b over placebo in reducing exacerbation rates and limiting MRI disease activity, but contain no data to demonstrate the absolute improvement of any patient over baseline status. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
			Placebo: 3.6 ± 0.1		8 MIU – 0.57 Placebo vs. 8 MIU: p = 0.393 3) Cognitive functioning: Immediate and delayed recall memory and visual reproduction subtests of the Wechsler Memory Scale, forms 1 and 2, attention/mental speed (Trailmaking Test part B; Stroop Color-Word Test), dominant and nondominant morot function (Purdue Pegboard), and Beck Depression Inventory were administered to patients in all groups during the course of the study. No baseline measurements were made. Results: A significant main effect for time ($F = 15.75$ [2, 27], $p < 0.001$) and an interaction effect between treatment condition and time of testing ($F = 4.15$ [2, 27], $p < 0.03$) were found for WMS VR-Delayed Recall. Follow-up pairwise comparisons indicated an improvement in delayed visual reproduction between the second and fourth years of treatment in the high-dose group (WMS VR-Delayed Recall; $p < 0.003$). The placebo and low-dose groups did not change significantly. No other neuropsychological parameters demonstrated a significant difference between the groups during the study.	
Jacobs, Cookfair, Rudick, et al., 1996 **and** **Rudick, Goodkin, Jacobs, et al., 1997** **and**	Inclusion: Definite MS for ≥ 1 yr; EDSS 1.0-3.5; relapsing disease course, with ≥ 2 documented exacerbations in previous 3 yr and no exacerbations for at least past 2 mo; age 18-55 Exclusion: Prior	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: Variable (enrollment date varied, but end-of-study date same for all patients)	No. of patients randomized: 301 Dropouts: Not completely clear; 23 early withdrawals, variable treatment durations Completed: 287 followed up through 1 yr; 172	1) Interferon β-1a (IFNβ-1a) 6 million units by IM injection weekly for up to 3 yr (n = 158) 2) Placebo for up to 3 yr (n = 143)	1) Physical functioning: Definition of "improvement": ≥ 0.5- or 1.0-point improvement on EDSS Proportion of patients with "improvement": Placebo IFNβ-1a Improved Unsustained ≥ 1.0 10 (11.5%) 16 (19.3%) 0.5 10 (11.5%) 13 (15.7%) Improved	The study described in these reports demonstrates significant improvement with regard to progression of disability as measured by EDSS, reduction in relapse rates, and improvement in various neuropsychological test parameters in patients treated with IFNβ-1a compared with placebo. Most of the data presented compare treatment groups rather than presenting data on individual patient improvement. Some data are delineated with regard to the number of patients with improved

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Fischer, Priore, Jacobs, et al., 2000 **and** **Jacobs, Rudick, and Simon, 2000** **and** **Rudick, Fisher, Lee, et al., 2000**	immunosuppressant or interferon therapy; adrenocorticotropic hormone or corticosteroid treatment in previous 2 mo; pregnancy or nursing; unwilling to practice contraception; chronic progressive MS; any disease other than MS compromising organ function	Provider specialty: Neurologists Location: 4 sites in US	through 2 yr; 31 through 3 yr Age (mean ± SE): IFNβ-1a: 36.7 ± 0.57 Placebo: 36.9 ± 0.64 Baseline EDSS (mean ± SE): IFNβ-1a: 2.4 ± 0.06 Placebo: 2.3 ± 0.07 Baseline relapse rate (mean ± SE, time frame not specified): IFNβ-1a: 1.2 ± 0.05 Placebo: 1.2 ± 0.05		Sustained ≥ 1.0 5 (8.9%) 10 (18.2%) 0.5 9 (16.1%) 14 (25.5%) Other (non-improvement) outcomes: Time to sustained progression of disability, the primary outcome measure, was significantly greater in IFNβ-1a-treated patients than in placebo-treated patients (p = 0.02) 2) Relapse frequency: Definition of "relapse": Appearance of new neurological symptoms or worsening of preexisting neurological symptoms lasting at least 48 hours in a patient who had been neurologically stable or improving for the previous 30 days accompanied by objective change on neurological examination (worsening of 0.5 point on the EDSS or a worsening by ≥ 1.0 point on the pyramidal, cerebellar, brainstem, or visual functional system scores) Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Annual relapse rates: Placebo IFNβ-1a P value All patients 0.82 0.67 0.04 104 week patient subset 0.90 0.61 0.002 3) Cognitive functioning: The Comprehensive NP Battery is a broad-spectrum battery comprising measures from the core battery recommended by the National MS Society Cognitive Function Study Group as well as additional measures covering cognitive domains of theoretical	EDSS scores of 0.5 or 1.0 points. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					interest Definition of "improvement": Not defined for individual patients Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Relapsing MS patients treated with IFNβ-1a for 2 yr performed significantly better than placebo patients on a composite of information processing and learning/recent memory measures (set A from the Comprehensive NP Battery). A similar trend was observed on a composite measure of visuospatial abilities and executive functions (set B) but not on the set C composite (verbal abilities and attention span).	
Johnson, Brooks, Cohen, et al., 1995 **and** **Weinstein, Schwid, Schiffer, et al., 1999** **and** **Liu, Blumhardt, and the Copolymer 1 Multiple Sclerosis Study Group, 2000** **and**	Inclusion: Clinically definite or laboratory-supported MS; relapsing-remitting course; ambulatory, with EDSS 0-5.0; ≥ 2 clearly documented relapses in 2 yr prior to entry; onset of first relapse ≥ 1 yr before randomization; neurological stability and freedom from corticosteroid therapy for ≥ 30 days prior to entry; age 18-45 Exclusion: Previous Copolymer 1 therapy; previous immuno-suppressive therapy with cyctotoxic chemotherapy or	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: 2 yr Provider specialty: Neurologists Location: 11 sites in the US	No. of patients randomized: 251 Dropouts: 36 Completed: 215 Age (mean ± SD): Cop 1: 34.6 ± 6.0 Placebo: 34.3 ± 6.5 Baseline EDSS (mean ± SD): Cop 1: 2.8 ± 1.2 Placebo: 2.4 ± 1.3 Baseline relapse rate (mean ± SD for prior 2 yr): Cop 1: 2.9 ± 1.3 Placebo: 2.9 ± 1.1	1) Glatiramer acetate = Copolymer 1 (Cop 1) by SC injection; 20 mg self-injected daily for 2 yr (n = 125) 2) Placebo (n = 126)	1) Physical functioning: Definition of "improvement": ≥ 1.0-point EDSS reduction Proportion of patients with "improvement": Original 2-yr trial: Cop 1 – 24.8% Placebo – 15.2% Extension study: Cop 1 – 27.2% Placebo – 12.0% Other (non-improvement) outcomes: Mean change in EDSS, Ambulation Index, proportion of progression-free patients, area under curve analyses of EDSS progression 2) Relapse frequency: Definition of "relapse": Appearance or reappearance of one or more neurological	This study demonstrated the benefit of Copolymer 1 therapy in reduction of relapse rates and in proportion of patients who improved by ≥ 1.0 points on EDSS. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Johnson, Brooks, Cohen, et al., 1998	lymphoid irradiation; need for aspirin or chronic NSAIDs during trial; [other generic exclusions]				abnormalities persisting for at least 48 hours and immediately preceded by a relatively stable or improving neurological state of at least 30 days. A relapse was confirmed only when a patient's symptoms were accompanied by objective changes on the neurological examination consistent with an increase of at least a half a step on the EDSS, two points on one of the seven functional systems, or one point on two or more of the functional systems. Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Relapse rate: Cop 1 Placebo P-value Relapse rate 24 months 1.19 1.68 0.007 Annual relapse rate 0.59 0.84 Relapse free 33.6% 27.0% 0.098 Extension Relapse rate 1.34 1.98 0.002 Extension Annual relapse rate 0.58 0.81 3) Cognitive functioning: Brief Repeatable Battery of Neuropsychological Tests – consisting of 5 tests including measures of sustained attention and concentration (Paced Auditory Serial Addition Test and Symbol Digit Modalities Test), verbal learning and delayed recall (Buschke Selective Reminder Test), visuospatial learning and delayed recall (10/36 Spatial Recall Test), and semantic retrieval (Word	

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					List Generation Test) Definition of "improvement": Not defined Proportion of patients with "improvement": Mean neuropsychologic test scores were improved at 12 and 24 months compared with baseline for placebo and glatiramer groups. No differences were detected between the treatment groups for any of the neuropsychologic test results. Other (non-improvement) outcomes:	
Kappos, Polman, Pozzilli, et al., 2001 **and** **Freeman, Thompson, Fitzpatrick, et al., 2001**	Inclusion: Clinically or laboratory supported definite diagnosis of secondary progressive MS; EDSS 3.0-6.5; ≥ 2 relapses or ≥ 1.0-point increase in EDSS in previous 2 yr; age 18-55 Exclusion: None specified	RCT (parallel-group, double-blind, multicenter) Mean duration of treatment/follow up: Treatment lasted up to 36 mo; article reports results at study termination; mean follow-up time 1068 ± 176 days for IFNβ-1b and 1054 ± 199 days for placebo Provider specialty: NR (presumably neurologists) Location: 32 sites in Europe	No. of patients randomized: 718 Lost to follow up: 88 Withdrew from treatment: 132 Completed treatment and follow up: 498 Age (mean ± SD): IFNβ-1b: 41.1 ± 7.2 Placebo: 40.9 ± 7.2 Baseline EDSS (mean ± SD): IFNβ-1b: 5.1 ± 1.1 Placebo: 5.2 ± 1.1 Baseline relapse rate (% of patients without relapse in 2 yr preceding study):	1) Interferon β-1b (IFNβ-1b) by SC injection; initial dose 0.5 mL (4 MIU) every other day, increased after 2 wk to 1.0 mL (8 MIU) every other day for up to 3 yr (n = 360) 2) Placebo (n = 358)	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Time to confirmed progression in EDSS favored IFNβ-1b, p = 0.007 Percent of patients progression-free Placebo – 46.1% IFNβ-1b – 54.7% P = 0.031 2) Relapse frequency: Definition of "relapse": Previously defined Definition of "improvement": Not defined Proportion of patients with "improvement": Not assessed Other (non-improvement) outcomes: Percent of patients relapse-free: Placebo – 36.3% IFNβ-1b – 42.5% P = 0.083	These studies examined further analyses and quality-of-life parameters from the previously published trial conducted by the European Study Group in Interferon-β1b in Secondary-Progressive MS, 1998, above. Significant improvements in EDSS, relapse rate, and quality-of-life parameters were demonstrated. This study provides data on individual patient improvement only with regard to relapse rates. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
			IFNβ-1b: 31.9% Placebo: 28.2%		Percent of patients relapse-free or decrease in relapse rate: Placebo – 45.0% IFNβ-1b – 53.1% P = 0.031 3) Quality of life: The SIP is a generic self-report questionnaire of health-related quality of life, which examines the individual's perception of the impact of the disease process on behavior in everyday life. The total score ranges from 0 (best) to 100 (worst). The GEMS scale was developed specifically for this study and provides a global evaluation of the neurologist's perception of change in terms of disease status and disability. The scale provides 7 points ranging from "very much better" to "very much worse." No published information is available determining its measurement properties. Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: The difference in total SIP score for the two groups shows a non-statistically significant trend in favor of IFNβ-1b. The SIP physical dimension score demonstrates a statistically significant benefit in favor of IFNβ-1b therapy at 6 and 12 months. A significant treatment effect of IFNβ-1b was demonstrated in the psychosocial dimension scores at 18 months but not at the end of the study.	

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Khatri, McQuillen, Harrington, et al., 1985	Inclusion: Clinically definite MS; chronic progressive disease course (continuous worsening on serial neurological exams during previous 12 mo); patient insured, and insurance company would pay for plasma exchange Exclusion: None specified	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: 18 mo Provider specialty: Neurologists Location: 1 site in Milwaukee, WI	No. of patients randomized: 59 Dropouts: 4 Completed: 55 Age (mean, completers): Genuine: 37.8 Sham: 42.2 Baseline EDSS (mean, completers): Genuine: 6.6 Sham: 6.3 Baseline relapse rate: NR	1) Plasma exchange (n = 30); during each exchange, plasma volume equivalent to 5% of patient's body weight exchanged for 5% albumin solution and normal saline in equal ratios; exchanges performed once per week for 20 wk 2) Sham plasma exchange (patient's plasma returned after it had been separated) (n = 29); exchanges performed once per week for 20 wk Patients in both groups also received: a) Oral cyclophospha-mide (1.5 mg/kg per day, rounded to nearest 50 mg); b) prednisone (1 mg/kg every other day, gradually decreasing doses after 15th wk); and c) pooled human immune serum globulin (40 ml in 4 divided IM injections over 2 days after each exchange)	1) Physical functioning: Two scoring scales were used in measuring clinical change, the Kurtzke DSS and the Canter Scale, which measures changes in activities of daily living Definition of "improvement": ≥ 1-point improvement on DSS Proportion of patients with "improvement": At 5 mo, 14 plasmapheresis patients improved and 8 sham pheresis patients improved with details as follows: 5-mo evaluation: PP: 3 or more points: 5; 2 points: 5; 1 point: 4 Sham: 3 or more points: 0; 2 points: 4; 1 point: 4 11-mo evaluation: PP: 3 or more points: 3; 2 points: 4; 1 point: 4 Sham: 3 or more points: 0; 2 points: 1; 1 point: 4 Other (non-improvement) outcomes: Not delineated 2) Relapse frequency: Definition of "relapse": Not defined Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Not delineated 3) Cognitive functioning: Standard	This study evaluated plasmapheresis in the treatment of chronic progressive MS. The results suggest a benefit to plasmapheresis with regard to EDSS measured at 5 and 11 months. Observations suggest some improvement in cognitive function, although the details are not delineated. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					neurological examination Definition of "improvement": Not defined Proportion of patients with "improvement": 4 patients with cognitive deficits improved in these functions at the 15th PP treatment, but this did not occur in similar patients in the sham group	
Leary, Miller, Stevenson, et al., 2003	Inclusion: Primary progressive MS (progressive history without relapse or remission, ≥ 2 typical lesions on MRI brain or spinal cod, and oligoclonal bands in the CSF not present in parallel serum or abnormal visual evoked potentials); disease duration ≥ 2 yr; EDSS 2.0-7.0; age 18-60 Exclusion: Interferon, immunosuppressant, or chronic steroid therapy in previous 3 mo; pregnancy or lactation; seizure in previous 3 mo; history of severe depression	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: 2 yr Provider specialty: NR (presumably neurologists) Location: 1 site in London, UK	No. of patients randomized: 50 Dropouts: 7 withdrew from treatment; all but 1 of these followed up for 2 yr Completed: 43 completed treatment; 49 followed up for 2 yr Age (mean [with range]): IFNβ-1a 60: 47 (25-59) IFNβ-1a 30: 46.5 (29-58) Placebo: 43 (30-59) Baseline EDSS (median [with range]): IFNβ-1a 60: 5.5 (2.0-6.5) IFNβ-1a 30: 5.5 (3.5-7.0) Placebo: 4.5 (2.0-7.0) Baseline relapse	1) Interferon β-1a (IFNβ-1a) 60 µg weekly by IM injection for 2 yr (n = 15) 2) IFNβ-1a 30 µg weekly by IM injection for 2 yr (n = 15) 3) Placebo for 2 yr (n = 20)	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Primary endpoint was time to sustained progression in disability, and there was no statistically significant difference among the treatment arms	This study examined the efficacy of IFNβ-1a in the treatment of primary progressive MS with a primary endpoint of time to sustained progression and found no statistically significant treatment effect. No data are reported regarding individual patient improvement. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
			rate: NA			
Milanese, La Mantia, Salmaggi, et al., 1988	Inclusion: Clinically definite MS by Schumacher's criteria; relapsing-remitting (with ≥ 2 relapses in previous 3 yr) or progressive (with continuous worsening of neurological status over previous 1 yr) disease course Exclusion: Conditions which did not permit regular examination or which hampered patient's reliability (e.g., DSS > 7 or psychic disturbances); contraindications to immunosuppressive treatment; previous use of immuno-suppressive therapy; pregnancy	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: 1 yr (see "Comments") Provider specialty: Neurologists Location: 1 site in Milan, Italy	No. of patients randomized: 23 included in 1-yr analysis reported here (13 relapsing-remitting, 10 progressive) Dropouts: 0 (though 2 dropped out after 1 yr; see "Comments") Completed: 23 Age (mean): AZA-relapsing: 33.1 Placebo-relapsing: 34.1 AZA-progressive: 38.1 Placebo-progressive: 42.4 Baseline EDSS (mean): AZA-relapsing: 2.17 Placebo-relapsing: 2.43 AZA-progressive: 5.00 Placebo-progressive: 3.86 Baseline relapse rate (mean per yr): AZA-relapsing: 1.144 Placebo-relapsing: 0.890	1) Azathioprine (AZA) PO 2-2.5 mg/kg per day for 1 yr (n = 9) 2) Placebo for 1 yr (n = 14)	1) Physical functioning: Definition of "improvement": Not delineated Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: No statistically significant difference at 1 yr 2) Relapse frequency: Definition of "relapse": Schumacher criteria Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Relapse rate – Progressive MS: Pre- Final AZA 0.5 0.42 Placebo 0.32 0.42 Relapse rate – Relapsing-remitting MS: Pre- Final AZA 1.14 0.98 Placebo 0.89 0.92 No statistically significant differences in relapse rates	This study evaluated the efficacy of azathioprine in patients with relapsing-remitting and progressive MS. No statistically significant differences were detected in the first year of this 3-year trial. At the time of publication 17 of 38 patients had withdrawn from the study resulting in significant questions regarding the utility of 3-year data. No information is provided regarding individual patient improvement. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
			AZA-progressive: 0.500 Placebo-progressive: 0.318			
Millefiorini, Gasperini, Pozzilli, et al., 1997	Inclusion: Clinically definite or laboratory-supported relapsing-remitting MS; disease duration 1-10 yr; EDSS 2-5; at least 2 exacerbations in previous 2 yr; age 18-45 Exclusion: HIV-positive; previous cardiovascular disease; left ventricular ejection fraction < 50%; renal, liver, and/or respiratory dysfunction; diabetes; malignancy; psychiatric illness; pregnancy; women not using contraception; use of steroids in previous 3 mo; previous immunosuppressant therapy	RCT (parallel-group, double-blind [patients and assessors, not treating physicians], multicenter) Duration of study treatment/follow up: Treatment lasted 1 yr; patients followed for total of 2 yr Provider specialty: Neurologists Location: 8 sites in Italy	No. of patients randomized: 51 (all relapsing-remitting) Dropouts: 9 Completed: 42 completed all assessments (including MRIs) Age (mean ± SD): MTX: 30.9 ± 6.0 Placebo: 28.7 ± 6.5 Baseline EDSS (mean ± SD): MTX: 3.6 ± 0.9 Placebo: 3.5 ± 1.2 Baseline relapse rate (mean ± SD in previous 2 yr): MTX: 2.8 ± 1.2 Placebo: 2.8 ± 1.1	1) Mitoxantrone (MTX), 30-min IV infusion (8 mg/m^2) ever month for 1 yr (n = 27) 2) Placebo (n = 24)	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: % of patients who progressed by 1.0 point on EDSS – found statistically significant benefit of mitoxantrone at 2 yr 2) Relapse frequency: Definition of "relapse": Appearance of a new symptom or worsening of an old symptom, attributable to MS, accompanied by a documented new neurological abnormality, lasting more than 48 hours and preceded by stability or improvement for at least 30 days Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Number of exacerbation (mean ± SD): MTX: 0.89 ± 2.1 Placebo: 2.62 ± 1.9 p = 0.0002 Exacerbation-free patients: MTX: 17 (63%) Placebo: 5 (21%) p = 0.006	This study examined the efficacy of mitoxantrone in patients with relapsing-remitting MS and found statistically significant benefit of mitoxantrone with regard to EDSS progression and relapse rate reduction. No data are presented with regard to individual patient improvement. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? No – appears that there were none

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Multiple Sclerosis Study Group, 1990	Inclusion: Clinically definite MS for ≥ 1 yr; EDSS 3.0-7.0; age 18-55; chronic and progressive clinical deterioration of ≥ 1 grade, but not > 3 grades, on EDSS in previous 12 mo, with some decline in last 6 mo; no acute relapse in previous 3 mo; no immunosuppressive drugs in previous 3 mo; no unproven therapies for MS (e.g., hyperbaric oxygen, gangliosides, snake venom [!]) in previous 1 mo; no prior treatment with cyclophosphamide or radiation; no uncontrolled hypertension (SBP > 170 mmHg or DBP > 110 mmHg), malignancy, recent myocardial infarction, chronic pulmonary disease, active infection, hepatic or renal dysfunction, or other neurological disorders; not using medications known to interfere with study drugs Exclusion: Known sensitivity or adverse reactions to immunosuppressive	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: 2 yr Provider specialty: Neurologists Location: 12 sites in US	No. of patients randomized: 547 Dropouts: 120 (cyclosporine) + 87 (placebo) = 207 Completed: 340 Age (mean ± SD): Cyclosporine: 40.5 ± 7.7 Placebo: 40.6 ± 8.2 Baseline EDSS (mean ± SD): Cyclosporine: 5.4 ± 1.2 Placebo: 5.4 ± 1.2 Baseline relapse rate: NR	1) Cyclosporine PO (liquid suspension); initial dose of 6 mg/kg diluted in milk or orange juice and taken each morning with breakfast; dose adjusted to achieve whole-blood cyclosporine trough level of 400-600 ng/mL, later reduced to 300-500 ng/mL; maximum dose permitted was 10 mg/kg/day (n = 273) 2) Placebo (n = 274)	1) Physical functioning: Extensive evaluations performed including EDSS, incapacity status scales, functional system scores of the Multiple Sclerosis Minimal Record of Disability, standardized neurological examination, quantitative examination of neurological functional, Ambulation Index, physical examination, and clinical evaluation Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Mean change in EDSS – found benefit of cyclosporine therapy with p = 0.006 in patients completing study, and p = 0.002 in all patients. 2) Relapse frequency: Definition of "relapse": Not defined Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes:	This study evaluated cyclosporine therapy in chronic progressive MS patients. The study is complicated by a high dropout rate, but appears to demonstrate statistically significant benefit as measured by a reduction in progression in EDSS. This study does not present data on individual patient improvement. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes – a total of 37.3% of all patients withdrew by the end of the study, necessitating some modifications to the primary outcome assessments. These modifications were made prior to data analysis. 56% of patients randomized to receive cyclosporine completed 24 months of continuous therapy, whereas 68% of those randomized to placebo successfully completed the trial (p=0.003)

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	drug; severe dementia; paraplegia or gait ataxia sufficient to prevent walking; severe upper extremity ataxia preventing independent feeding or dressing					
Nose-worthy, O'Brien, Petterson, et al., 2001	Inclusion: One or more episodes of demyelinating optic neuritis occurring in the setting of clinically definite or laboratory-supported definite MS or in the presence of cranial MRI changes consistent with MS; first episode of optic neuritis between ages of 18 and 45; age < 50 at enrollment; fixed, apparently irreversible loss of visual acuity in at least one eye that met following criteria: a) visual acuity worse than 20/40 for a period of at least 6 mo and unchanged on at least 2 exams separated by at least 1 mo; b) optic disc pallor as detected by study neuro-ophthalmologist; c) abnormal visual field measured on Humphrey Field	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: Treatment lasted 12 wk + 5 days; patients followed for total of 12 mo Provider specialty: Ophthalmologists and neurologists Location: 1 site in Rochester, MN	No. of patients randomized: 55 (42 relapsing-remitting, 13 secondary progressive) Dropouts: 2 (both between 6 and 12 mo) Completed: 53 Age (mean ± SD): IV IgG: 38.0 ± 7.2 Placebo: 39.2 ± 6.7 Baseline EDSS (mean ± SD, excluding visual functional status scores): IV IgG: 3.6 ± 2.5 Placebo: 3.0 ± 2.5 Baseline relapse rate: NR	1) IV immunoglobulin (IV IgG) 0.4 g/kg daily for 5 days, then once per month for 3 months (total of 8 infusions) (n = 27) 2) Placebo (n = 28)	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Several measures of visual function were assessed, as well as EDSS. No measures demonstrated statistically significant benefit from therapy. 2) Relapse frequency: Definition of "relapse": Not defined Definition of "improvement": Not assessed Proportion of patients with "improvement": Not assessed Other (non-improvement) outcomes:	This study evaluated the efficacy of IV IgG in the treatment of optic neuritis in patients with MS. The study was terminated early due to negative results. No data are presented that demonstrate individual patient improvement. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	Analyzer with a mean deviation ≤ -4.00 and a pattern of defect consistent with optic neuritis; no adrenocorticotropic hormone or corticosteroids in previous 2 mo Exclusion: Primary progressive MS; nondemyelinating cause for visual loss; preexisting ocular abnormalities; serious intercurrent medical illness; concomitant use of experimental drug for MS or other disease; serum creatinine > 1.5 times normal; pregnancy or unwillingness to use contraception; known antibody deficiency syndrome; need for IV IgG administration					
Patti, L'Episcopo, Cataldi, et al., 1999	Inclusion: Definite MS; disease course relapsing-remitting (with ≥ 2 documented relapses in previous 2 yr and EDSS ≤ 3.5) or secondary progressive (with deterioration of ≥ 1.0 point on the EDSS over previous 2 yr and EDSS ≤ 7.0); emotionally stable;	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: 2 yr Provider specialty: Neurologists	No. of patients randomized: 98 (58 relapsing-remitting, 40 secondary progressive) Dropouts: 0 Completed: 98 Age (mean): Relapsing-	1) Natural interferon-β (nIFNβ) 6 MIU by IM injection three times per wk for 2 yr (n = 49) 2) Placebo for 2 yr (n = 49)	1) Physical functioning: Definition of "improvement": Decrease of 0.5 or 1.0 in EDSS Proportion of patients with "improvement": Relapsing-remitting patients: Placebo – 1 of 29 patients (3.4%) improved nIFNβ – 15 of 29 patients (52%) improved P = 0.002 Secondary progressive patients: Placebo – 1 of 20 patients (5%) improved nIFNβ – 8 of 20 patients (40%) improved	This study examined treatment effect of nIFNβ in relapsing-remitting and secondary-progressive MS. Statistically significant differences were found in the treatment group with regard to proportion of patients improving by 0.5 or 1.0 points on EDSS and in the proportion of patients relapse-free. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	negative for HIV, HbsAg, and Borreliosis; free of other immune or neurological diseases; clinically stable for ≥ 30 days; no ACTH or corticosteroids in previous 30 days; age 18-45 Exclusion: Pregnancy; prior treatment with azathioprine or cyclophosphamide (in previous 1 yr)	Location: 1 site in Catania, Italy	remitting (RR) patients: 36.6 Secondary progressive (SP) patients: 36.9 Baseline EDSS (mean): RR-nIFNβ: 3.06 RR-placebo: 3.1 SP-nIFNβ: 5.8 SP-placebo: 6.0 Baseline relapse rate (mean over previous 2 yr): RR-nIFNβ: 1.8 RR-placebo: 1.9 SP-nIFNβ: 0.4 SP-placebo: 0.6		P = 0.006 2) Relapse frequency: Definition of "relapse": Rapid onset of new symptoms or a worsening of preexisting symptoms persisting for 48 hours or more and were accompanied by objective changes on the neurologic examination – an increase of at least one grade in the score for at least one of the functional groups of EDSS Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: The probability of remaining exacerbation-free was significantly higher in the nIFNβ-treated group (presented in graphical form; p < 0.001)	Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes
Patzold, Hecker, and Pockling-ton, 1982	Inclusion: Confirmed MS; resident in district of study site Exclusion: None specified	RCT (parallel-group, open-label, single-center) Duration of study treatment/follow up: 2 yr Provider specialty: Neurologists Location: 1 site in Hanover, Germany	No. of patients randomized: 142 Dropouts: 27 before completing 1 yr; 17 more before completing 2 yr Completed: 115 completed 1 yr (53 intermittent, 52 intermittent-progressive, 10 progressive); 98 completed 2 yr (47 intermittent, 43 intermittent-progressive, 8 progressive)	1) Azathioprine PO, daily dose of 2 mg/kg for 2 yr (n = 74) 2) No azathioprine (n = 68)	1) Physical functioning (EDSS *not* assessed): Definition of "improvement": Not defined Proportion of patients with "improvement": Not assessed Other (non-improvement) outcomes: Patients were evaluated clinically and the severity of disease was calculated by means of an objective weighting scale corresponding to the data recorded by the examiner. In the untreated group on average MS deteriorated three times as rapidly as in the treated group. 2) Relapse frequency:	This study examined the efficacy of azathioprine in the treatment of MS. This trial suffers from two major design issues – lack of blinding, and lack of validated treatment outcome measures. The significance of the findings is unclear. This study does not provide data regarding individual patient improvement. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? No Described as "double-blind"? No Patients blinded? No Investigators blinded? No Outcome assessors blinded? No No. of withdrawals in each group stated?

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
			Age: NR Baseline EDSS: NR Baseline relapse rate: NR		Definition of "relapse": Definite worsening of condition lasting for 24 hr or more, or the occurrence or recurrence of symptoms and signs after a period of 4 wk in which these had either disappeared or improved Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: No. of relapses: Azathioprine: 2.4 ± 2.0 Control: 1.9 ± 1.3	Yes
PRISMS Study Group and the University of British Columbia MS/MRI Analysis Group, 1998 **and** **Liu and Blumhardt, 1999** **and** **Liu and Blumhardt, 2002** **and** **Patten and Metz, 2001**	Inclusion: Clinically definite or laboratory-supported definite MS of at least 1 yr duration; relapsing-remitting MS with ≥ 2 relapses in preceding 2 yr and EDSS score 0-5.0; adult Exclusion: Any previous systemic treatment with interferons, lymphoid irradiation, or cyclophosphamide; other immuno-modulatory or immunosuppressive treatment in previous 12 mo	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: 2 yr Provider specialty: Neurologists Location: 22 sites in Canada, Australia, and 7 European countries	No. of patients randomized: 560 Lost to follow up: 27 Withdrew from treatment: 31 Followed up to 2 yr: 533 Completed treatment to 2 yr: 502 Age (median with IQR): IFNβ-1a 44 µg: 35.6 (28.4-41.0) IFNβ-1a 22 µg: 34.8 (29.3-39.8) Placebo: 34.6 (28.8-40.4) Baseline EDSS (mean ± SD):	1) Interferon β-1a (IFNβ-1a) by SC injection, 44 µg (12 MIU), 3 times weekly (n = 184) 2) IFNβ-1a by SC injection, 22 µg (6 MIU), 3 times weekly (n = 189) 3) Placebo (n = 187)	1) Physical functioning: Definition of "improvement": In the categorical disability trend analysis sustained improvement was defined as a decrease of at least 1.0 EDSS point confirmed at 3 months and sustained until the end of the study Proportion of patients with "improvement": Not stated – in the categorical disability trend analysis data were not reported on the number of patients with sustained improvement. 31% of treated patients and 20% of placebo patients attained stable course. Other (non-improvement) outcomes: 22-mcg dose and 44-mcg dose patients both had mean reduction in EDSS compared with placebo of 0.25 2-yr change in EDSS: Mean / AUC Placebo +0.48 / +0.48 22-mcg dose +0.23 / +0.05 44-mcg dose +0.24 / +0.06	This study provides significant data regarding the benefit of treatment over placebo with regard to relapse rate and EDSS outcome measures. These data are reported as group improvement and no data are provided on individual patient improvement from baseline status. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
			IFNβ-1a 44 µg: 2.5 ± 1.3 IFNβ-1a 22 µg: 2.5 ± 1.2 Placebo: 2.4 ± 1.2 Baseline relapse rate (mean relapses in previous 2 yr [± SD]: IFNβ-1a 44 µg: 3.0 ± 1.1 IFNβ-1a 22 µg: 3.0 ± 1.1 Placebo: 3.0 ± 1.3		2) Relapse frequency (primary outcome measure): Definition of "relapse": As defined by Schumacher criteria, required the appearance of a new symptom or worsening of an old symptom over at least 24 hr that could be attributed to MS activity and was preceded by stability or improvement for at least 30 days Definition of "improvement": Proportion of patients with "improvement": - Not stated Other (non-improvement) outcomes: Relapses per patient: Placebo – 2.56 22 mcg dose – 1.82 44 mcg dose – 1.73 % reduction in relapses vs. placebo: 22 mcg dose – 29 44 mcg dose – 32 % relapse free over 1 year: Placebo – 22 22 mcg dose – 37 44 mcg dose – 45 % relapse free over 2 years: Placebo – 16 22 mcg dose – 27 44 mcg dose – 32 Moderate or severe relapses - % with no relapses: Placebo – 42 22 mcg dose – 61 44 mcg dose – 62 % with no admissions for MS:	

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					Placebo – 75 22 mcg dose – 77 44 mcg dose - 82 3) Cognitive functioning [describe scale/ instrument used]: Definition of "improvement": Not assessed Proportion of patients with "improvement": Not assessed 5) Quality of life: Center for Epidemiological Studies Depression Rating Scale was used to assess whether treatment with IFNβ-1a was associated with depression Other (non-improvement) outcomes: Proportion of patients exceeding cut-point did not vary significantly across treatment groups	
Rice, Filippi, and Comi, 2000	Inclusion: Clinically definite or laboratory-supported MS according to Schumacher or Poser criteria; chronic progressive disease course (slow progression of signs and symptoms over preceding 12 mo); EDSS 3.0-6.5; serum creatinine < 1.5 mg/dL and creatinine clearance ≥ 80% of age-adjusted normal; aspartate and alanine transaminase and alkaline phosphatase levels < twice the normal upper limit;	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: 12 mo Provider specialty: NR (presumably neurologists) Location: 6 sites in Canada and the US	No. of patients randomized: 159 (111 secondary progressive, 48 primary progressive) Dropouts: 4 Completed: 155 Age (mean): High-dose: 43.8 Low-dose: 44.6 Placebo: 44.2 Baseline EDSS (mean): High-dose: 5.6 Low-dose: 5.6 Placebo: 5.6	1) Cladribine by SC injection, 6 monthly courses of 0.07 mg/kg/day for 5 consecutive days (total dose 2.1 mg/kg), followed by 2 monthly courses of placebo (n = 52) 2) Cladribine by SC injection, 2 monthly courses of 0.07 mg/kg/day for 5 consecutive days (total dose 0.7 mg/kg), followed by 6 monthly courses of placebo (n = 53) 3) Placebo, 8 monthly courses (n = 54)	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Primary outcome measure was mean change in EDSS – no statistical difference in treatment groups observed 2) Relapse frequency: Definition of "relapse": Not assessed Definition of "improvement": Not delineated Proportion of patients with "improvement": Not assessed	This study evaluated two different doses of cladribine and found no statistically significant difference in clinical outcomes. No data are provided regarding individual patient improvement. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? No – 97% of all patients completed the study

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	neutrophil count > 1600/µL; platelet count > 130,000/µL; clinically normal ECG and chest X-ray; age 21-60 Exclusion: Significant history of medical disease in previous 2 yr; use of corticosteroids or other immunosup-pressants in previous 3 mo; total lymphoid irradiation; persistent leukopenia or thrombocytopenia after treatment with immunosuppressive agents; alcohol or drug abuse or attempted suicide in previous 1 yr; malignancy in previous 5 yr; pregnancy or nursing; HIV+; use of experimental drug or device in last 60 days; previous participation in cladribine trial		Baseline relapse rate: NR			
Romine, Sipe, Koziol, et al., 1999	Inclusion: Clinically definite relapsing-remitting MS for at least 1 yr; ≥ 2 relapses in previous 2 yr; EDSS ≤ 6.5 Exclusion: Treatment with immunosup-	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: Treatment lasted 8 mo; patients followed	No. of patients randomized: 52 Dropouts: 2 before 12 mo, plus 6 more before 18 mo Completed: 50 to 12 mo, 44 to 18 mo	1) Cladribine by SC injection; 5 consecu-tive daily injections of 0.07 mg/kg/day given monthly for 6 mo for total cumulative dose of 2.1 mg/kg; during remaining 2 mo of 8-mo treatment period, placebo given unless	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": Not assessed Other (non-improvement) outcomes: No significant differences between the two groups with regard to EDSS or SNRS scores over the 18-mo period	This study evaluated the efficacy of cladribine compared with placebo in patients with relapsing-remitting MS. No statistical difference was found with regard to EDSS scores. A modest benefit was found in favor of cladribine with regard to relapse rate and severity. The data were not evaluated with regard to clinical improvement of individual patients.

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	pressive drugs in previous 3 mo; serum creatinine > 1.5 mg/dL; serum glutamic-oxaloacetic transaminase/serum glutamic-pyruvic transaminase or alkaline phosphatase elevated to twice the upper limit of normal; neutrophil counts of < 1600/µL or platelet counts < 130,000/µL; previous total lymphoid irradiation or extensive myelosuppressive chemotherapy	for total of 18 mo Provider specialty: Neurologists Location: 1 site in La Jolla, CA	Age (mean, with range): Cladribine: 43.4 (30-52) Placebo: 39.8 (31-52) Baseline EDSS (mean, with range): Cladribine: 3.9 (2.0-6.5) Placebo: 3.8 (2.0-6.5) Baseline relapse rate (number in previous 1 yr): Cladribine: 1: 5 (19%) 2: 16 (59%) 3-4: 6 (22%) Placebo: 1: 13 (52%) 2: 5 (20%) 3-4: 7 (28%)	investigators had had to substitute placebo for a monthly dose earlier due to blood count inadequacy, in which case active drug could be given during mo 7 or 8 (n = 27) 2) Placebo (n = 25)	2) Relapse frequency: Definition of "relapse": Appearance of new symptoms or worsening of an existing symptom, attributable to MS and accompanied by objective worsening of neurological findings and must have been preceded by disease stability or improvement lasting for at least 30 days, and the worsening must have lasted at least 24 hours and occur in the absence of fever Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Relapse rate: Cladribine – 0.77 (95% CI, 0.37 to 1.41) Placebo – 1.67 (95% CI, 1.02 to 2.57)	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes
Schwartz, Coulthard-Morris, Cole, et al., 1997	Inclusion: Relapsing-remitting MS Exclusion: None specified	RCT (see under "Comments") Duration of study treatment/follow up: 1 yr Provider specialty: NR Location: NR; patients had applied to lottery to gain access to experimental drug	No. of patients randomized: NR Dropouts: NR Completed: 79 Age (mean): IFNβ-1b: 43.9 Control: 43.3 Baseline EDSS: NR Baseline relapse rate: NR	1) Recombinant interferon β-1b (IFNβ-1b); dose, route of administration, and treatment regimen not described (n = 34) 2) Usual care (n = 45)	1) Physical functioning: Not assessed 2) Relapse frequency: Not assessed 3) Cognitive functioning: Multiple scales used as below Definition of "improvement": Improvement was defined as population mean change Proportion of patients with "improvement": Not assessed Other (non-improvement) outcomes: Wechsler Memory Scale delayed visual recall demonstrated improvement in the	As recognized by the authors, the small sample size may have precluded the finding of statistical significance on some of the other measures of cognitive function Study design was retrospective, taking advantage of random allocation of IFNβ-1b in a treatment lottery; however, control condition was not standardized, and follow-up data were collected by survey and thus were subject to respondent bias QUALITY ASSESSMENT: Described as "randomized"? No

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					high-dose group compared with placebo ($p < 0.003$). Other measures failed to reach statistical significance. Individual patient data and percentage of patients improving not reported.	Method of randomization clearly described? No Concealment of allocation? No Described as "double-blind"? No Patients blinded? No Investigators blinded? No Outcome assessors blinded? No No. of withdrawals in each group stated? Yes
Sipe, Romine, Koziol, et al., 1994	Inclusion: Clinically definite or laboratory-supported definite chronic progressive MS for more than 2 yr Exclusion: Serum creatinine ≥ 132 µmol/L or creatinine clearance < 80% of age-adjusted normal; serum transaminases or hepatic alkaline phosphatase more than twice the upper limit of normal; neutrophil count < 1600 µL or platelet count < 130,000/µL; inadequate birth control; plans to father a child during study; treatment with corticosteroids or other immunosup-pressive medications in previous 6 mo; decreased marrow reserve as manifested by leukopenia or thrombocytopenia for > 6 wk after	RCT (designed as 2-yr crossover trial, but analyzed as parallel-group trial after 1 yr; double-blind [examining physicians and patients, *not* treating physicians], single-center, matched-pair design) Duration of study treatment/follow up: 1 yr Provider specialty: Neurologists Location: 1 site in La Jolla, CA	No. of patients randomized: 51 (49 initially entered + 2 replacements for dropouts) Dropouts: 3 cladribine patients (2 of whom were replaced), 1 placebo patient (included in analyses) Completed: 47 (48 analyzed) Age (mean, with range): Cladribine: 43.0 (28-53) Placebo: 42.7 (21-54) Baseline EDSS (mean ± SE): Cladribine: 4.7 ± 0.3 Placebo: 4.6 ± 0.3 Baseline relapse rate: NR	Central venous access device surgically implanted in all patients for study drug administration 1) Cladribine administered by continuous 7-day IV infusion at the rate of 0.1 mg/kg daily; total of 4 monthly courses given (n = 24) 2) Placebo infusion (n = 24)	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Paired differences in the two groups were significant in favor of cladribine: EDSS: Cladribine 4.4 ± 2.0; Placebo 5.6 ± 1.5; P-value $p < 0.01$ SNRS: Cladribine 74.8 ± 10.3; Placebo 62.6 ± 11.3; P-value $p < 0.001$ 2) Relapse frequency: Definition of "relapse": Not defined Definition of "improvement": Not defined Proportion of patients with "improvement": Not assessed Other (non-improvement) outcomes: None	This study examined the effect of cladribine therapy in patients with progressive MS and found a statistically significant benefit to cladribine therapy with regard to group differences in progression as measured by EDSS and SNRS. No data are presented with regard to improvement of individual patients. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	conclusion of immunosuppressive treatment					
SPECTRIMS Study Group, 2001	Inclusion: Clinically definite secondary progressive MS (defined as progressive deterioration of disability for ≥ 6 mo, with increase of ≥ 1 EDSS point over the last 2 yr [or 0.5 point between EDSS 6.0 and 6.5], with or without superimposed exacerbations, following an initial relapsing-remitting course); EDSS 3.0-6.5; pyramidal functional score ≥ 2; age 18-55 Exclusion: Immunosuppressive or immunomodulatory treatments during previous 3-12 mo (depending on drug); corticosteroid use or disease exacerbation in previous 8 wk; severe concurrent illness; pregnancy or lactation; unwilling-ness to use contraception	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: 3 yr Provider specialty: Neurologists Location: 22 sites in Europe, Canada, and Australia	No. of patients randomized: 618 Dropouts: 112 withdrew from treatment; 65 of these were followed up for 3 yr Completed: 506 completed treatment; 571 were followed up for 3 yr Age (mean ± SD): IFNβ-1a 44: 42.6 ± 7.3 IFNβ-1a 22: 43.1 ± 7.2 Placebo: 42.7 ± 6.8 Baseline EDSS (mean ± SD): IFNβ-1a 44: 5.3 ± 1.1 IFNβ-1a 22: 5.5 ± 1.1 Placebo: 5.4 ± 1.1 Baseline relapse rate (mean ± SD in previous 2 yr): IFNβ-1a 44: 0.9 ± 1.3 IFNβ-1a 22: 0.9 ± 1.4 Placebo: 0.9 ± 1.2	1) Interferon β-1a (IFNβ-1a) 44 µg by SC injection three times weekly for 3 yr (n = 204) 2) IFNβ-1a 22 µg by SC injection three times weekly for 3 yr (n = 209) 3) Placebo (n = 205)	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: The primary outcome, time to sustained progression, revealed no statistically significant difference among treatment arms. 2) Relapse frequency: Definition of "relapse": Appearance of a new symptom or worsening of an old symptom attributable to MS, accompanied by an appropriate new neurologic abnormality or focal neurologic dysfunction lasting at least 24 hours in the absence of fever and preceded by stability or improvement for at least 30 days Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Mean annual relapse rate: IFN 22 mcg Placebo IFN 44 mcg 0.50 0.71 0.50 p < 0.001 p < 0.001	This study examined the benefit of IFNβ-1a in the treatment of secondary progressive MS. There was no significant treatment effect on the primary outcome measure of time to confirmed progression. Significant benefits were demonstrated with regard to relapse rates. No data on improvement with regard to individual patients. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3a. Disease modifying therapies and long-term improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
van de Wyngaert, Beguin, D'Hooghe, et al., 2001	Inclusion: Definite clinical diagnosis of MS by Poser criteria; relapsing, secondary progressive disease course; at least partial recovery from last relapse at least 1 mo before study entry; EDSS 3.0-6.0; worsening of EDSS by 1 point in previous 12 mo; effective birth control; normal isotopic cardiac ventriculography and routine blood analysis at entry; age 18-50 Exclusion: Remittent disease course, primary progressive disease, or secondary progressive disease without relapses; major illness other than MS or immuno-suppressive drugs other than corticosteroids in previous 3 yr	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: Treatment lasted 32 mo; patients followed up for an additional 4 mo Provider specialty: Neurologists Location: 1 site in Belgium	No. of patients randomized: 49 Dropouts: 25 Completed: 24 Age (mean ± SD): MTX: 38.3 ± 6.9 MP: 39.2 ± 7.8 Baseline EDSS (mean, with range): MTX: 5.1 (3.0-6.0) MP: 5.0 (3.0-6.0) Baseline relapse rate (mean in previous 12 mo ± SD): MTX: 2.3 ± 1.0 MP: 2.2 ± 1.2	1) Mitoxantrone (MTX) 12 mg/m^2 initially given intravenously over one hour once per month for 3 mo; then given once every 3 mo, 10 times, until month 32; each treatment preceded by IV administration of 3 vials of alizapride (anti-emetic) (n = 28) 2) Methylprednisolone (MP) 1 g initially given intravenously over one hour between 8 and 10 a.m. once per month for 3 mo; then given once every 3 mo, 10 times, until month 32 (n = 21)	1) Physical functioning: Definition of "improvement": Not defined Proportion of patients with "improvement": 35% of patients receiving MTX improved clinically compared with 22% receiving placebo – difference not statistically significant Other (non-improvement) outcomes: 2) Relapse frequency: Definition of "relapse": Not defined Definition of "improvement": Not defined Proportion of patients with "improvement": Not delineated Other (non-improvement) outcomes: Mean number of relapses/patient/year was significantly lower in the MTX group after 2 and 3 years of treatment (p = 0.016 and 0.029, respectively)	This study examined the effectiveness of cladribine in relapsing, secondary progressive MS. The study demonstrated a non-significant trend in favor of cladribine with regard to the number of patients who improved. The precise definition of improvement was not given. The small sample size may have contributed to the lack of statistical significance. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Unclear Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3b. Symptom management and improvement

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Bass, Weinshenker, Rice, et al., 1988 **and** **Rice, 1989**	Inclusion: Clinically definite MS; spasticity interfered with activities of daily living; spasticity stable for ≥ 2 mo Exclusion: None specified	RCT (crossover, double-blind, single-center) Duration of study treatment/follow up: 9 wk with each treatment, 22 wk total (2-wk run-in, two 9-wk treatment periods, 2-wk washout) Provider specialty: Neurologists and physiotherapists Location: 1 site in London, Ontario, Canada	No. of patients randomized: 66 Dropouts: 4 excluded for protocol violations/ non-compliance; 14 more failed to complete both treatment periods Completed: 48 completed both treatment periods and were analyzed (MS diagnoses NR; of 62 not excluded for protocol violations/ non-compliance, 1 was "remitting" at entry, 19 were "progressive," and 42 were "stable") Age (mean, with range; n = 62 not excluded for protocol violations/ non-compliance): 51.1 (30-74) Baseline EDSS: NR	1) Tizanidine PO initiated at dose of 2 mg on the first day and 6 mg daily for the next three days; then increased by 6 mg every four days to a maximum of 32 mg/day (increased until spasticity controlled, AEs intolerable, or maximum dose reached); maintenance dose taken for 5 wk; tapered withdrawal during wk 9 of treatment 2) Baclofen PO initiated at dose of 5 mg on the first day and 15 mg daily for the next three days; then increased by 15 mg every four days to a maximum of 80 mg/day (increased until spasticity controlled, AEs intolerable, or maximum dose reached); maintenance dose taken for 5 wk; tapered withdrawal during wk 9 of treatment 2-wk washout period between treatments (in addition to 1-wk tapered withdrawal)	1) Symptom-specific functional status/ quality-of-life outcomes: Muscle strength (7-point ordinal scale); muscle tone (6-point ordinal scale) Definition of "improvement": ≥ 1-point change from baseline in right or left side Proportion of patients with "improvement": Similar percentages of patients improved, remained the same, and worsened on tizanidine compared to baclofen (p = NS) Other (non-improvement) outcomes: NR 2) Physical functioning (EDSS): Definition of "improvement": Decrease of ≥ 1 point from baseline Proportion of patients with "improvement": Tizanidine 9/48 (18%) Baclofen 6/48 (12%) (P = NS) Other (non-improvement) outcomes: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: Tizanidine (daytime somnolence, insomnia, xerostomia) 46% required dosage reduction; 4 withdrew (weakness) Baclofen (muscle weakness) 61% required dosage reduction; 7 withdrew (weakness)	Non-standard instruments used for assessing spasticity; much of data not shown QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes *Crossover trials only:* Period or carry-over effects? Not discussed Washout period? Yes (2 weeks) No. of patients in each sequence clearly described? No Were patients who did not complete all of the periods excluded from the analysis? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Brar, Smith, Nelson, et al., 1991	Inclusion: Clinically definite MS; EDSS ≤ 5.5; clinically stable for past 3 mo; mild to moderate spasticity in one or both lower extremities; age 24-54 Exclusion: Systemic disorders; impaired mentation; previous intolerance to baclofen	RCT (crossover, partially double-blind, single-center) Duration of study treatment/follow up: 10 wk total: 2 wk each with baclofen, stretching, and combination; 4 wk with placebo (after each period involving baclo-fen; included tapering of baclofen) Provider specialty: Neurologists and physical therapists Location: 1 site in Denver, CO	No. of patients randomized: 38 Dropouts: 8 Completed: 30 Age: NR Baseline EDSS: NR	1) Baclofen alone; titrated according to a predetermined schedule of 5-mg increments or decrements every day for 5 days to maximum of 20 mg/day; maximum dose then maintained for seven days 2) Stretching exercises + placebo; exercise instruction given by physical therapist; program included stretches for hamstrings, quadri-ceps, adductor, and plantarflexor muscles 3) Stretching exercises (as above) + baclofen (as above) 4) Placebo alone Placebo periods followed each period in which baclofen was used and included a period for tapering off baclofen	1) Symptom-specific functional status/ quality-of-life outcomes: Quadriceps hypertonicity; muscle tone (Ashworth scale); self-rated questionnaire of functional abilities Definition of "improvement": Not given Proportion of patients with "improvement": Ashworth Improved Baclofen 9 (30%) Stretch 5 (17%) Comb 12 (40%); p=0.10 v placebo Placebo 6 (20%) 100-yd walk / Stair climb / Household activities Baclofen 10% / 20% / 17% Stretch 30% / 7% / 23% Comb 10% / 23% / 23% Placebo 17% / 13% / 20% Other (non-improvement) outcomes: Quadriceps spasticity was significantly improved after both baclofen and combination treatment when compared to placebo ($p < 0.05$) 2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: None reported	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? No (only to baclofen vs. placebo) Investigators blinded? No (only to baclofen vs. placebo) Outcome assessors blinded? Unclear No. of withdrawals in each group stated? No *Crossover trials only:* Period or carry-over effects? Not discussed Washout period? No No. of patients in each sequence clearly described? No Were patients who did not complete all of the periods excluded from the analysis? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Canadian MS Research Group, 1987	Inclusion: At least 6-mo history of definite MS according to Schumacher criteria; ≥ 3-mo history of chronic, persistent, moderate to severe, daily fatigue (confirmed during 2-wk run-in) Exclusion: Pregnancy; hypersensitivity to amantadine; CHF or peripheral edema; hepatic or renal impairment; epilepsy; history of depression or other psychiatric disorders; acute anemia; thyroid disorders; diabetes; gastric or duodenal ulcers; alcohol or drug abuse	RCT (crossover, double-blind, multicenter) Duration of study treatment/follow up: 3 wk with each treatment, 10 wk total (2-wk placebo run-in, two 3-wk treatment periods, 2-wk placebo washout) Provider specialty: NR (presumably neurologists) Location: 11 sites in Canada	No. of patients randomized: 115 (57 relapsing-remitting, 33 relapsing-progressing, 22 chronic progressing, 3 benign) Dropouts: 6 Completed: 109 Excluded from all analyses: 2 (protocol violations) Excluded from some analyses: 21 (discovered post-randomization to have had insufficient baseline fatigue) "Efficacy-analyzable" population: 86 (41 relapsing-remitting, 28 relapsing-progressing, 15 chronic progressing, 2 benign) Age (mean ± SE; n = 86): 40.1 ± 1.0 Baseline EDSS (mean ± SE; n = 86): 4.3 ± 0.2	1) Amantadine PO 100 mg twice per day for 3 wk 2) Placebo for 3 wk 2-wk placebo washout period between treatments	1) Symptom-specific functional status/ quality-of-life outcomes: VAS fatigue score Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Change in VAS fatigue score baseline to end: Amantadine: 29 to 25 (23 to 26), -4.3 mm Placebo: 30 to 27 (25 to 29), -2.6 mm p = NS 2) Physical functioning: most affected activity VAS; effect on activities of daily living total score Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Most affected activity VAS favored amantadine $p < 0.05$ ADL total score amantadine 27 (SE 1.13) baseline to 24 (SE 1.06) end, change of -2.5 compared to placebo 26 (SE 0.74) baseline to 26 (SE 0.74) end; change of -0.3 (p = 0.09) 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: 66/115 (57%) reported AEs on amantadine; 62/115 (54%) reported AEs on placebo; 1 dropout for acute confusional state on amantadine	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Unclear Outcome assessors blinded? Unclear No. of withdrawals in each group stated? Yes *Crossover trials only:* Period or carry-over effects? Yes Washout period? Yes (2 wk) No. of patients in each sequence clearly described? No Were patients who did not complete all of the periods excluded from the analysis? Unclear

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Cartlidge, Hudgson, and Weightman, 1974	Inclusion: Spasticity; Ashworth score of 3-4 in at least one lower limb Exclusion: None specified	RCT (crossover, double-blind, single-center) Duration of study treatment/follow up: 4 wk with each treatment, 9 wk total (two 4-wk treatment periods, 1-wk washout) Provider specialty: Neurologists Location: Newcastle, UK	No. of patients randomized: 40 (34 MS "in remission but with severe residual neurological deficits," 2 hereditary spastic paraplegia, 1 spondylotic myelopathy, 1 traumatic paraplegia) Dropouts: 3 Completed: 37 Age (range): 22-61 Baseline EDSS: NR	1) Baclofen PO 30 mg per day for 2 wk, then 60 mg per day for 2 wk 2) Diazepam PO 15 mg per day for 2 wk, then 30 mg per day for 2 wk 1-wk washout between treatment periods	1) Symptom-specific functional status/ quality-of-life outcomes: Spasticity score (Ashworth scale) Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Low-dose Baclofen Diazepam N 37 37 Before/after 2.87/2.38 2.87/2.16 Change (SE) 0.49 (0.163) 0.71 (0.159) p-value < 0.01 < 0.001 High-dose N 26 23 Change (SE) 1.31 (0.227) 1.13 (0.202) p-value < 0.001 < 0.001 No differences between baclofen and diazepam. No period effect or treatment-period interaction 2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: Daytime sedation, weakness, gustatory disturbances (loss of taste and smell) 11 withdrew on high-dose baclofen 14 withdrew on high-dose diazepam	Adverse events at high dose levels resulted in high dropout rate QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? No Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes *Crossover trials only:* Period or carry-over effects? No Washout period? Yes (1 wk) No. of patients in each sequence clearly described? Yes Were patients who did not complete all of the periods excluded from the analysis? No

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Cohen and Fisher, 1989	Inclusion: Definite or probable MS according to Poser criteria; diagnosis established at least 6 mo prior to study entry; daily symptomatic fatigue for ≥ 3 mo Exclusion: EDSS > 6; moderate or major depression on Beck Depression Inventory; pregnancy; CHF; renal or hepatic impairment; epilepsy; anemia; thyroid disorders; diabetes; active gastric or duodenal ulcer; psychiatric disorder; alcohol or drug abuse; current use of stimulants, sedative-hypnotics, anti-depressants, major tranquilizers, beta-blockers, immuno-suppressants, or steroids	RCT (crossover, double-blind, single-center) Duration of study treatment/follow up: 4 wk with each treatment, 10 wk total (two 4-wk treatment periods, 2-wk washout) Provider specialty: NR Location: 1 site in Worcester, MA	No. of patients randomized: 29 (16 benign or relapsing-remitting, 13 chronic-deteriorating or relapsing-deteriorating) Dropouts: 7 Completed: 22 Age (mean ± SD): 44.5 ± 9.3 Baseline EDSS (mean ± SD, n = 22 completers): 4.0 ± 1.4	1) Amantadine PO 100 mg twice per day for 4 wk 2) Placebo for 4 wk 2-wk washout between treatment periods	1) Symptom-specific functional status/ quality-of-life outcomes: Fatigue (daily ratings; point scale 1-5) Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Amantadine mean fatigue score 3.2 ± 0.04 SE versus placebo 3.0 ± 0.03 SE (p = 0.58) 2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: 4 amantadine and 4 placebo patients reported AEs. At least 1 amantadine-treated patient withdrew due to nausea and anxiety; 1 placebo patient with constipation may have withdrawn.	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Unclear Investigators blinded? Unclear Outcome assessors blinded? Unclear No. of withdrawals in each group stated? Yes *Crossover trials only:* Period or carry-over effects? No Washout period? Yes (2 wk) No. of patients in each sequence clearly described? No Were patients who did not complete all of the periods excluded from the analysis? Yes
Crawford and McIvor, 1985	Inclusion: Primary diagnosis of MS; mental status optimal or only mildly to moderately deficient Exclusion: None specified	RCT (parallel-group, open-label, single-center) Duration of study treatment/follow up: 6 mo Provider	No. of patients randomized: 32 Dropouts: NR Completed: NR Age: Mean, 47.25; range, 20-63	1) Traditional, insight-oriented group psychotherapy (IOT; n = NR); two 1-hr sessions per wk for approximately 6 mo (50 sessions total) 2) Current events discussion group (CE,	1) Symptom-specific functional status/ quality-of-life outcomes: 2) Physical functioning: NR 3) Cognitive functioning: MMPI Depression-30 Scale (D-30); Anxiety Scale Questionnaire (ASQ); Internal-External Control Scale (IECS); Rosenberg Self-Esteem Scale (SES)	Little assessment of the clinical importance of changes observed in psychological scales QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? No

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
		specialty: NR (presumably psychologists) Location: 1 site in New York, NY	Baseline EDSS: NR; patients described as "moderately to severely disabled physically"	active control; n = NR); two 1-hr sessions per wk for approximately 6 mo (50 sessions total) 3) No treatment (n = NR)	Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: IOT CE Control p-value D-30 19.3 23.5 23.5 0.025 IECS 28.3 30.7 37 0.005 ASQ NR NR NR NS SES NR NR NR NS 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: NR	Patients blinded? No Investigators blinded? No Outcome assessors blinded? No No. of withdrawals in each group stated? No
Cutter, Scott, Johnson, et al., 2000	Inclusion: Laboratory-supported diagnosis of chronic progressive MS (MRI and/or CSF); clinical evidence of spasticity; veteran eligible for care at study site (Denver VAMC); age 18-85 Exclusion: Lack of clinically significant spasticity; inability to travel to study site for evaluations; potential to become pregnant during study; significant renal dysfunction	RCT (crossover, double-blind, single-center) Duration of study treatment/follow up: 26 days (6 days treatment with each intervention + 14-day washout period) Provider specialty: NR Location: Denver, CO (1 site)	No. of patients randomized: 22 Dropouts: 1 Completed: 21 Age: Range, 34-67 Baseline EDSS: Range, 6.0-9.0	1) Gabapentin PO; 300 mg three times per day for 2 days, then 600 mg three times per day for 2 days, finally 900 mg three times per day for 2 days (n = 22) 2) Placebo (n = 22) 14-day washout between treatment periods	1) Symptom-specific functional status/ quality-of-life outcomes: Spasm frequency scale; spasm severity scale, interference with function scale, painful spasm scale, global assessment scale Definition of "improvement": Spasm frequency – no spasms Interference with function – not defined Global assessment – not defined Proportion of patients with "improvement": Spasm frequency (p = 0.0001) Gabapentin Placebo B/l Post B/l Post None 0 (0%) 6 (28%) 0 (0%) 0 (0%) Mild 5 (24%) 12 (57%) 5 (24%) 7 (33%) Mod 11 (52%) 2 (9%) 11 (52%) 12 (57%) Sev 5 (24%) 1 (5%) 5 (24%) 2 (9%) Interference with function (p = 0.02) Gabapentin Placebo B/l Post B/l Post None 2 (9%) 10 (48%) 4 (19%) 4 (19%) Difficult 13 (62%) 10 (48%) 11 (52%) 12	Some impact on spasticity measures, but none on EDSS QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes *Crossover trials only:* Period or carry-over effects? No Washout period? Yes (14 days) No. of patients in each sequence clearly described? Yes Were patients who did not complete all of the periods excluded from the analysis? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					(57%) Imposs 6 (29%) 1(5%) 6 (29%) 5 (24%) Global assessment (p = 0.003) Gabapentin Placebo Post Post Lot better 11 (52%) 1 (5%) Little better 4 (19%) 4 (19%) Unchanged 6 (27%) 12 (57%) Worse 0 (0%) 4 (19%) Other (non-improvement) outcomes: Modified Ashworth Scale (p = 0.0005) 2) Physical functioning (EDSS): Definition of "improvement": Proportion of patients with "improvement": "No significant change in…EDSS with either gabapentin or placebo? Other (non-improvement) outcomes: 3) Cognitive functioning: Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Digit Span, Digit Symbol, adjective generation technique 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: Falls in 2 patients, 1 gabapentin, 1 placebo	

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Eyssette, Rohmer, Serratrice, et al., 1988	Inclusion: Chronic spasticity due to MS; age 18-70 Exclusion: None specified	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: Treatment lasted 8 wk; preceded by 3-day run-in Provider specialty: NR (presumably neurologists) Location: 6 sites in France	No. of patients randomized: 100 Dropouts: 14 Completed: 86 Age (mean ± SE): Tizanidine: 46.8 ± 1.6 Baclofen: 47.5 ± 1.7 Baseline EDSS: NR (60/100 patients were bedridden at entry)	1) Tizanidine (n = 50); initiated at 2 mg three times per day; daily dose then increased, if tolerated, by 2 mg every 2 days for first 2 wk, up to maximum dose of 24 mg/day; maximum dose then taken for 6 wk 2) Baclofen (n = 50); initiated at 5 mg three times per day; daily dose then increased, if tolerated, by 5 mg every 2 days for first 2 wk, up to maximum dose of 60 mg/day; maximum dose then taken for 6 wk	1) Symptom-specific functional status/ quality-of-life outcomes: Muscle tone (5-point scale); flexor spasms, clonus, strength, locomotor function Definition of "improvement": Flexor spasms & muscle tone – none described; clonus – no longer detectable Proportion of patients with "improvement": Flexor spasms 2 wk 8 wk Tizanidine (n = 36) 47% 55% Baclofen (n = 33) 48% 43% P = NS Muscle tone by muscle group improved in between 40% to 67% of patients; no statistically significant difference between tizanidine and baclofen for any muscle group or time point Clonus 2 wk 8 wk Tizanidine 8/35 (23%) 8/28 (29%) Baclofen 8/30 (27%) 6/28 21%) Other (non-improvement) outcomes: In ambulatory patients (40/100) there was no significant change in walking distance for tizanidine or baclofen 2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: Tizanidine: daytime drowsiness (n = 15), dry mouth (n = 14), fatigue (n = 8), orthostatic hypotension (n = 6), and insomnia (n = 7). Discontinued in 6: daytime drowsiness (n =	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					2); weakness and drowsiness (n = 2), syncope (n = 1) and bradycardia (n = 1). Baclofen (daytime drowsiness (n = 10), fatigue (n = 12), muscular weakness (n = 10), disturbances of affect (n = 9), and vomiting (n = 8). Discontinued in 4: rash (n = 1), vomiting (n = 1), disturbed affect (n = 1), and muscular weakness and syncope (n = 1).	
Feldman, Kelly-Hayes, Conomy, et al., 1978	Inclusion: Adults with an established diagnosis of MS; spontaneous flexor contractions or spasticity for ≥ 3 mo; free of infections, peripheral vascular disease, contractures, advanced arthritis, or other conditions that might hinder evaluation of joint movement Exclusion: Women of childbearing age; patients with bleeding tendencies, GI disease, or liver and renal impairment	RCT (crossover, double-blind, single-center) Duration of study treatment/follow up: 4 wk with each treatment; 10 wk total (1-wk placebo run-in, two 4-wk treatment periods, 1-wk placebo washout) Provider specialty: NR Location: Boston, MA	No. of patients randomized: 33 Dropouts: 10 Completed: 23 Age: Mean, 43; range, 38-53 Baseline EDSS: NR; disability said to have varied "from being ambulatory with a spastic gait to functional quadriplegia"	1) Baclofen; initiated at 5 mg three times per day for 3 days; increases then made at intervals not less than 3 days up to a maximum dose of 80 mg/day (or less if AEs occurred or maximum benefit achieved at lower dose) 2) Placebo (with dose adjustments as above) 1-wk placebo washout between treatment periods	1) Symptom-specific functional status/ quality-of-life outcomes (spasm frequency, clonus [knee], resistance to passive movement, functional assessment): Definition of "improvement": Not defined Proportion of patients with "improvement": ROM exercises / Spasm frequency Baclofen 15/23 (65%) / 9/16 (56%) Placebo 4/23 (17%) / 1/16 (6%) P < 0.05 / p < 0.05 Clonus / Barthel Baclofen 12/15 (80%) / 8/16 (50%) Placebo 1/15 (7%) / 7/16 (46%) P < 0.01 / p = NS Other (non-improvement) outcomes: 2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: Dry mouth (baclofen n = 5; placebo n = 1). Also observed: drowsiness, dizziness, anorexia, nocturia and constipation.	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? No *Crossover trials only:* Period or carry-over effects? Not discussed Washout period? Yes (1 wk) No. of patients in each sequence clearly described? No Were patients who did not complete all of the periods excluded from the analysis? Unclear

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Foley, Bedell, LaRocca, et al., 1987	Inclusion: Confirmed diagnosis of MS; DSS ≤ 8; no major cognitive deficits Exclusion: None specified	RCT (parallel-group, open-label, single-center) Duration of study treatment/follow up: 5 wk (6-mo follow up included only 10 patients and only patients in experimental group) Provider specialty: Experimental group: Advanced clinical psychology graduate student, supervised by 2 licensed clinical psychologists Control group: "Hospital staff who utilized standard methods in treating patients" Location: 1 site in Bronx, NY	No. of patients randomized: 41 (type of MS not specified; 60% of patients were experiencing a relapse at start of trial, 58% at end) Dropouts: 5 (missing data) Completed: 36 Age: Mean, 38.8 Baseline DSS: Mean, 6; range, 1-8	1) Stress inoculation therapy (SIT) (n = NR); combination of cognitive-behavioral therapy (focused on relieving affective distress and preventing maladaptive psychological responses to stress) and progressive muscle relaxation (shortened version); total of 6 sessions over 5 wk (length of individual session NR) 2) Current available care (CAC) (n = NR); patients received a variety of psychotherapeutic and medical interventions (including minimum of 2 hr of supportive psychotherapy) for 5 wk	1) Symptom-specific functional status/ quality-of-life outcomes (BDI; STAI-S; STAI-T; Hassles scale; PFC): Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: MANOVA showed significant treatment effect for composite of all outcome measures ($p < 0.002$): SIT / CAC / p-value BDI: 13.2 ± 10.5 / 21.6 ± 14.2 / < 0.05 STAI-S: 37.2 ± 13.8 / 50.5 ± 13.0 / < 0.05 STAI-T: 46.2 ± 13.1 / 51.9 ± 13.4 / NS Hassles: 57.5 ± 37.6 / 89.2 ± 67.1 / < 0.05 WCC: 16.2 ± 4.8 / 11.8 ± 4.6 / < 0.05 2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: NR	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? No Patients blinded? No Investigators blinded? No Outcome assessors blinded? No No. of withdrawals in each group stated? No
Francabandera, Holland, Wiesel-Levison, et al., 1988	Inclusion: Definite MS; followed at study site; EDSS 6.0-9.0; evidence of ability to benefit from rehabilitation (at least 3 specific rehabilitation goals); not institutionalized	RCT (parallel-group, open-label, single-center) Duration of study treatment/follow up: 3 mo	No. of patients randomized: 84 Dropouts: 11 did not enter treatment or were lost to follow up Completed: 73	1) Inpatient rehabilitation (n = 42); daily physical (two 45-min sessions per day) and occupational therapy (1 session per day); bladder management, speech therapy, and social	1) Symptom-specific functional status/ quality-of-life outcomes: Incapacity Status Scale (ISS) (part of Minimal Record of disability [16-item self-report inventory reflecting ambulation status and level of independence in self-care); need for home assistance (number of hours of assistance in ADLs)	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? No Patients blinded? No Investigators blinded? No Outcome assessors blinded? No

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	and able to return home after inpatient treatment; insurance or other resources to pay for inpatient or outpatient treatment Exclusion: None specified	Provider specialty: Neurologists, physical therapists, occupational therapists, nurses Location: 1 site in Bronx, NY	Age: NR Baseline EDSS: NR	services provided as needed; equipment needs assessed and addressed; individual care plan for each patient; coordinated, multidisciplinary approach 2) Outpatient rehabilitation (n = 42); physical and occupational therapy; bladder management, speech therapy, and social services as needed; equipment needs assessed and addressed; treatment administered through community-based visiting nurse services or public health nurse services Treatment of both groups supervised by neurologist at study site	Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: ISS: Entry / 3-mo / 3-mo adjusted / p-value Inpt: 28± 9 / 26± 9.4 / 24.3 / < 0.05 Opt: 24± 7.2 / 26± 8.5 / 27.2 Assistance Inpt: 62± 52 / 73± 62 / 76.9 / 0.17 Opt: 71± 56 / 77± 56 / 73.1 2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: NR	No. of withdrawals in each group stated? No
Fredrikson, 1996	Inclusion: Clinically definite MS; increased daytime frequency of voiding/ incontinence episodes; had previously tested anticholinergic drugs with unsatisfactory effect on bladder symptoms Exclusion: Hyper-tension, coronary	RCT (crossover, double-blind, single-center) Duration of study treatment/follow up: 2 wk with each treatment; 6 wk total (2-wk run-in, two 2-wk treatment periods, no washout)	No. of patients randomized: 27 Dropouts: 0 premature withdrawals; 1 patient excluded from analyses (appendectomy); 4 provided incomplete data for main outcome Completed: 22	1) Desmopressin nasal spray 20 µg daily 2) Placebo nasal spray No washout between treatment periods	1) Symptom-specific functional status/ quality-of-life outcomes: Number of voidings and incontinence episodes (a) during 6 hr after drug intake, (b) during 24 hr Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Voidings: Mean ± SD 6 hr / 24 hr	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes *Crossover trials only:* Period or carry-over effects? Not discussed

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	artery disease; diabetes; hepatic disease	Provider specialty: NR (presumably neurologists) Location: 1 site in Huddinge, Sweden	included in analysis of main outcome Age: Mean, 51; range, 24-69 Baseline EDSS: NR		Baseline 3.1± 1.0 10.7± 2.5 Placebo 3.1± 1.0 8.6± 2.3 Desmopressin 2.6± 1.0 8.4± 2.6 p-value < 0.05 NS 2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: NR	Washout period? No No. of patients in each sequence clearly described? No Were patients who did not complete all of the periods excluded from the analysis? Yes
Freeman, Langdon, Hobart, et al., 1997	Inclusion: Clinically or laboratory-supported definite MS; in progressive phase of the disease as established by neurologist; considered appropriate for inpatient rehabilitation Exclusion: Current or recent (within 1 mo) relapse; use of steroids in previous mo; required urgent admission on clinical grounds; other diseases; cognitive impairment such that unable to give informed consent	RCT (parallel-group, open-label, single-center) Duration of study treatment/follow up: Active treatment lasted average of 20 days; patients followed for total of 6 wk Provider specialty: Multi-disciplinary team Location: 1 site in London, UK	No. of patients randomized: 70 Dropouts: 4 Completed: 66 (60 secondary progressive, 6 primary progressive) Age (mean ± SD; n = 66 completers): Rehab: 43.2 ± 10.8 Wait-list: 44.6 ± 9.7 Baseline EDSS (median, with range): Rehab: 6.5 (5.0-9.0) Wait-list: 6.5 (6.0-8.5)	1) Comprehensive, short-term (mean, 20 days; range, 17-31), inpatient rehabilitation program; not described in detail, but said to involve multi-disciplinary team approach, interventions tailored to individual's needs, and patient-centered functional goal-setting approach (n = 32) 2) Wait-list control (n = 34)	1) Symptom-specific functional status/ quality-of-life outcomes: NR 2) Physical functioning (EDSS): Definition of "improvement": Proportion of patients with "improvement": EDSS – No statistically significant difference between the two groups in … EDSS change scores (p = 0.42)…"with change scores clustering closely around zero" FIM motor scores - 72% of people in the treatment group improved their overall level of disability, 3% stayed the same, and 25% deteriorated. In contrast, 29% of people in the control group improved their overall level of disability, 9% stayed the same, and 62% deteriorated (p < 0.001) Other (non-improvement) outcomes: LHS – 53% of the treatment group improved their total handicap score, 3% remained the same, and 44% deteriorated. In contrast 23% of the control group improved, 12% stayed the same, and 65% deteriorated (p = 0.01)	No difference was shown between treatment and control groups for those who were walking (p = 0.38), but there was a significant difference among wheelchair users (p = 0.03) QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? No Described as "double-blind"? No Patients blinded? No Investigators blinded? No Outcome assessors blinded? No No. of withdrawals in each group stated? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: NR	
From and Heltberg, 1975	Inclusion: Spasticity due to MS; inpatients Exclusion: None specified	RCT (crossover, double-blind, single-center) Duration of study treatment/follow up: 4 wk with each treatment, 10 wk total (two 4-wk treatment periods, 1-wk washout, 1-wk follow up) Provider specialty: Neurologists Location: 1 site in Copenhagen, Denmark	No. of patients randomized: 17 Dropouts: 1 Completed: 16 Age: Mean, 51; range, 38-68 Baseline EDSS: NR; only 2 patients had significant walking ability	1) Baclofen PO 10-mg tablets; dose titrated to optimal level during first 2 wk, then continued for 2 wk; mean optimal dose, 61.2 mg (range, 30-120 mg) 2) Diazepam PO 5-mg tablets; dose titrated to optimal level during first 2 wk, then continued for 2 wk; mean optimal dose, 26.8 mg (range, 10-40 mg) 1-wk washout between treatment periods	1) Symptom-specific functional status/ quality-of-life outcomes (flexor spasm, clonus): Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Baclofen Diazepam Flexor spasm 10/12 (83%) 12/14 (86%) Clonus 16/26 (62%) 18/28 (64%) 2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: Baclofen 8 (sedation [n = 5], weakness, depression, nausea) Diazepam 12 (sedation [n = 11], weakness) One patient discontinued treatment with baclofen due to AE (sedation).	No significant differences between baclofen and diazepam QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes *Crossover trials only:* Period or carry-over effects? Not discussed Washout period? Yes (1 wk) No. of patients in each sequence clearly described? Yes Were patients who did not complete all of the periods excluded from the analysis? Unclear

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Gambi, Rossini, Calenda, et al., 1983	Inclusion: Spinal spasticity Exclusion: None specified	RCT (crossover, double-blind, single-center) Duration of study treatment/follow up: 5 wk with each treatment, 13 wk total (2-wk run-in, two 5-wk treatment periods, 1-wk washout) Provider specialty: NR (presumably neurologists) Location: 1 site in Milan, Italy	No. of patients randomized: 24 (12 MS, 12 degenerative myelopathies) Dropouts: 2 (both MS) Completed: 22 (10 MS, 12 degenerative myelopathies) Age (mean ± SE, MS patients only): 38.2 ± 2 Baseline EDSS: NR	1) Dantrolene sodium PO; initiated at 25 mg twice per day and increased by slow weekly increments until therapeutic goal achieved (maximum dose permitted = 350 mg per day); treatment lasted 5 wk 2) Placebo, with dose adjustments as above, for 5 wk 1-wk washout between treatment period	1) Symptom-specific functional status/ quality-of-life outcomes: NR 2) Physical functioning: Hip flexor movement (degrees); degree of spasticity (6-point scale); muscular strength (6-point scale); clonus (6-point scale); knee and ankle tendon reflexes (6-point scale) Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Change in hip flexor movement (degrees) Dantrolene Placebo p-value Left hip 8.5± 3.7 1.5± 3.9 NS Right hip 9.5± 2.7 -1± 2.9 NS No influence on knee joint movements Dantrolene reduced spasticity of both lower limbs ($p < 0.05$; data not shown) No significant difference for muscular strength, clonus and tendon reflexes (data not shown) 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: 13/24 (59%) reported AEs (headache drowsiness, nausea, vomiting, gastric pain, malaise, muscular weakness). 2/24 (9%) on dantrolene and 3/24 (14%) on placebo withdrew due to AEs.	Few data shown Small study, especially when MS subgroup considered separately QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? No Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes *Crossover trials only:* Period or carry-over effects? Not discussed Washout period? Yes (1 wk) No. of patients in each sequence clearly described? No Were patients who did not complete all of the periods excluded from the analysis? Unclear

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Geisler, Sliwinski, Coyle, et al., 1996	Inclusion: Clinically or laboratory-supported definite MS according to Poser criteria; severe fatigue (Fatigue Severity Scale score ≥ 4.0); ambulatory; EDSS ≤ 6.5; age 18-50 Exclusion: EDSS > 6.5; severe depression (score > 35 on Center for Epidemiologic Studies Depression Scale); severe dementia (score < 15 on Mini-Mental State Examination); current or recent (within 2 mo) MS relapse; current or recent (within 2 mo) use of fatigue-producing medication (e.g., tricyclic anti-depressants, benzodiazepines)	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: 6 wk treatment, 10 wk total (2-wk run-in, 6 wk treatment, 2 wk follow up) Provider specialty: Neurologists Location: 1 site in Stony Brook, NY	No. of patients randomized: 45 (38 relapsing-remitting, 7 chronic progressive) Dropouts: NR (implied 0) Completed: NR (implied 45) Age (mean ± SD): Amantadine: 40 ± 6.4 Pemoline: 41 ± 6.2 Placebo: 40 ± 5.6 Baseline EDSS (mean ± SD): Amantadine: 3.1 ± 2.1 Pemoline: 2.6 ± 0.9 Placebo: 2.2 ± 1.7	1) Amantadine PO 100 mg twice daily for 6 wk (n = 16) 2) Pemoline PO 18.75 mg, once daily for 1st wk, twice daily for 2nd wk, then three times per day during weeks 3-6 (n = 13) 3) Placebo (double-dummy technique used) (n = 16)	1) Symptom-specific functional status/ quality-of-life outcomes: NR 2) Physical functioning: NR 3) Cognitive functioning: Attention (Digit Span, Trail Making Test, Symbol Digit Modalities Test); verbal memory (Selective Reminding Test); nonverbal memory (Benton Visual Retention Test), and motor speed (Finger Tapping Test) Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: All three treatment groups showed significant improvement on cognitive measures; however, only written SDMT (a measure of attention and visual search) showed a significant difference between treatment groups, with amantadine-treated group showing the greatest improvement. For other measures, the change scores were nearly identical between groups with no significant differences between the active drug groups and the placebo group. 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: NR	Study patients were subgroup of the patients examined in Krupp, Coyle, Doscher, et al., 1995, below QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Gillson, Richards, Smith, et al., 2002	Inclusion: Diagnosis of MS confirmed by neurologist exam and the presence of CNS sclerotic lesions on MRI; EDSS 5.0-6.5; Modified Fatigue Impact Scale (MFIS) score > 40; no relapse in previous 3 mo; age ≥ 18 Exclusion: Current or previous use of study drug; current use of antispasmodic agents, cortico-steroids, chemo-therapeutic agents, MAOIs, or histamine blockers; started antidepressants, interferons, or glatiramer acetate in past 3 mo; serious renal, hepatic, endocrine, cardiac, or pulmonary disease	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: 12 wk Provider specialty: NR Location: 1 site in Seattle, WA	No. of patients randomized: 29 (10 relapsing-remitting, 16 secondary progressive, 3 primary progressive; significant difference between treatment groups at baseline) Dropouts: 3 Completed: 26 Age: Mean, 47.4 Baseline EDSS: NR	1) Transdermal cream containing histamine diphosphate 1.65 mg + caffeine citrate 100 mg per 0.2 mL (Prokarin™); applied twice per day using a skin patch (n = 22) 2) Placebo cream (n = 7)	1) Symptom-specific functional status/ quality-of-life outcomes: Modified Fatigue Impact Scale (MFIS); timed walk test (25-foot); 9-hole peg test Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: MFIS p-value Week 0 4 8 12 within group PK 58±8.9 38± 18 38± 16 37± 15 < 0.001 Pl 61±7.5 NR NR 53± 11 NS p-value (between-group) < 0.02 No significant differences between the Prokarin™ group and the placebo group for secondary endpoints (25-foot timed walk, 9-hole peg test) 2) Physical functioning: NR 3) Cognitive functioning: Paced Auditory Serial Additions Test (PASAT) Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: No significant differences between the Prokarin™ group and the placebo group for PASAT 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: All AEs observed were mild – specific AEs included skin irritation,	Authors point out that baseline differences showed more relapsing-remitting patients in the Prokarin™ group QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					itching, and headache	
Hauser, Doolittle, Lopez-Bresnahan, et al., 1992	Inclusion: Clinically definite MS of either inactive (relapsing-remitting MS that had been clinically stable for > 2 yr) or very slowly progressive (chronic MS without change for ≥ 1 yr as assessed by Ambulation Index and EDSS) form; spasticity or spontaneous flexor spasms sufficient in degree to interfere with functional activities for ≥ 3 mo; ambulatory, with EDSS ≤ 6 and Ambulation Index ≤ 5; reasonable functional use of arms; good general health; age 18-55 Exclusion: Cancer or serious underlying medical illness; advanced arthritis, contractures, or other conditions hindering evaluation of joint movement; use of psychoactive drugs; antispasticity treatment within previous 1 mo; use of chemotherapeutic agents within previous 6 mo	RCT (crossover, double-blind, single-center) Duration of study treatment/follow up: 8 wk each treatment, 18 wk total (two 8-wk treatment periods, 2-wk washout) Provider specialty: Neurologists Location: 1 site in Boston, MA	No. of patients randomized: 26 Dropouts: 5 Completed: 21 Age (mean ± SE): 41 ± 6.5 Baseline EDSS (mean ± SE): 4.7 ± 1.5	1) Threonine (naturally occurring amino acid), 5 capsules three times per day for a total daily dose of 7.5 mg for 8 wk 2) Placebo for 8 wk 2-wk washout between treatment periods Patients also instructed to consume "a standard 75-g protein diet" during the study	1) Symptom-specific functional status/ quality-of-life outcomes: Ashworth Scale; Clinician Spasticity Scale (upper extremity muscle tone, lower extremity muscle tone, reflexes and spontaneous flexor spasms each graded improved [+1]/same[0]/worse [-1] then summed); Patient Spasticity Scale Definition of "improvement": Not described Proportion of patients with "improvement": Spasticity Clinician Scale Patient Scale Threonine 11/21 (52%) 8/21 (38%) Placebo 5/21 (24%) 4/21 (19%) p-value 0.04 0.18 Other (non-improvement) outcomes: 2) Physical functioning: EDSS; Ambulation Index Definition of "improvement": Proportion of patients with "improvement": Other (non-improvement) outcomes: 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life utcomes: NR 6) Adverse events: None reported	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes *Crossover trials only:* Period or carry-over effects? No Washout period? Yes (2 wk) No. of patients in each sequence clearly described? No Were patients who did not complete all of the periods excluded from the analysis? No

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Hilton, Hertogs, and Stanton, 1983	Inclusion: Women with MS who complained of nocturia (waking to void on two or more occasions each night) Exclusion: History of impaired renal function, ischemic heart disease, hypertension, or urinary infection	RCT (crossover, double-blind, single-center) Duration of study treatment/follow up: NR (1-wk run-in, but length of treatment not specified) Provider specialty: OB/GYNs Location: 1 site in London, UK	No. of patients randomized: 16 Dropouts: 0 Completed: 16 Age: NR Baseline EDSS: NR	1) Desmopressin nasal spray 20 µg daily at bedtime 2) Placebo nasal spray at bedtime No washout period described	1) Symptom-specific functional status/ quality-of-life outcomes: Subjective benefit in nocturia Definition of "improvement": Not described Proportion of patients with "improvement": Desmopressin 9/16 (56%) Placebo 1/16 (6%) P = 0.008 Other (non-improvement) outcomes: Urinary freq: Desmopressin; Placebo; p-value Daytime: 8.7± 3.4; 8.6± 2.5; ns Nighttime: 1.3± 1.0; 2.0± 0.9; < 0.001 2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: Headache (n = 3), nasal congestion (n = 1) No patients stopped treatment due to AEs	Treatment duration not described; apparently no washout period and no analysis reported for period or carry-over effects QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes *Crossover trials only:* Period or carry-over effects? Not discussed Washout period? No No. of patients in each sequence clearly described? Yes Were patients who did not complete all of the periods excluded from the analysis? No (no dropouts)
Hoog-straten, van der Ploeg, Burg, et al., 1988	Inclusion: Spasticity due to MS; spasticity stable for ≥ 2 mo; EDSS 4-7 Exclusion: Severe cardiac insufficiency; marked hypertension (DBP > 110 mmHg); severe hypotension; chronic alcoholism; history of mental illness; pretreatment	RCT (crossover, open label [only assessors of selected outcomes were blinded], single-center) Duration of study treatment/follow up: 6-7 wk with each treatment, 13.5-15.5 wk+	No. of patients randomized: 16 Dropouts: 5 Completed: 11 Age (mean ± SD): 54.9 ± 8.3 Baseline EDSS (mean ± SD): 6.1 ± 0.8	1) Tizanidine PO; dose titrated to optimal level (range, 12-24 mg daily) over first 2-3 wk, then continued for 4 wk 2) Baclofen PO; dose titrated to optimal level (range, 15-60 mg daily) over first 2-3 wk, then continued for 4 wk	1) Symptom-specific functional status/ quality-of-life outcomes: NR 2) Physical functioning: Spasticity (7-point scale); spasms (7-point scale); mobility (7-point scale) Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes:	Small study Unclear relationship between primary measures (spasticity, spasms, mobility) and variable analyzed (overall efficacy) QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? No Patients blinded? No

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	with diazepam or dantrolene	total (two 6- to 7-wk treatment periods, 1.5-wk+ washout period) Provider specialty: NR (presumably neurologists) Location: 1 site in Groningen, The Netherlands		Washout between treatment periods: taper off of study meds over 1-2 wk, followed by drug-free period of at least 3 days	Data not provided for spasticity. Overall efficacy variable showed no significant difference whether completers of both periods analyzed as cross-over (n = 11) or first-period only data (n = 14) analyzed. 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: AEs reported on baclofen (muscle weakness (n = 11), somnolence (n = 4), dry mouth, nausea (n = 3), urine incontinence (n = 3), dizziness) and on tizanidine (muscle weakness (n = 4), somnolence (n = 8), dry mouth (n = 5); flushed (n = 3); Severe AEs on baclofen (muscle weakness (n = 6); nausea (n = 1)) and tizanidine (somnolence (n = 1), depression (n = 1)) 3 patients discontinued treatment due to AEs on baclofen	Investigators blinded? No Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes *Crossover trials only:* Period or carry-over effects? No Washout period? Yes (1-2 wk+) No. of patients in each sequence clearly described? Yes Were patients who did not complete all of the periods excluded from the analysis? Yes
Hoverd and Fowler, 1998	Inclusion: MS and neurogenic bladder dysfunction (≥ 8 episodes of voiding per day); sufficient lower limb power to stand; cognitively unimpaired Exclusion: Diabetes; heart disease; hypertension; renal disease; use of diuretic therapy	RCT (crossover, double-blind, single-center) Duration of study treatment/follow up: 2 wk with each treatment; 6 wk total (2-wk run-in, two 2-wk treatment periods, no washout) Provider specialty: NR Location: 1 site	No. of patients randomized: 28 Dropouts: 4 (3 before treatment started) Completed: 24 Age: Mean, 43; range 18-65 Baseline EDSS: NR	1) Desmopressin nasal spray 20 µg at same time each day (between 8:00 AM and 2:00 PM) 2) Placebo nasal spray No washout between treatment periods	1) Symptom-specific functional status/ quality-of-life outcomes [describe scale/instrument used]: Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Urinary freq: Desmopressin / Placebo / p-value Day (6 hr): 2.4± 0.9 / 3.1± 1.4 / 0.008 Nighttime: 1.5± 1.2 / 1.4± 1.1 / 0.26 Vol (6 hr): 246± 99 / 342± 166 / 0.006 Vol (24 hr): 1218± 455 / 1272 ± 482 / 0.052	No washout period; no discussion of carry-over or period effects QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes *Crossover trials only:* Period or carry-over effects? Not discussed Washout period? No

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
		in London, UK			2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: Hyponatremia, malaise, headache nausea (required withdrawal from desmopressin)	No. of patients in each sequence clearly described? No Were patients who did not complete all of the periods excluded from the analysis? Yes
Hyman, Barnes, Bhakta, et al., 2000	Inclusion: Definite or probable MS; disabling spasticity affecting the hip adductor muscles of both legs (EDSS ≥ 7), which had been stable for ≥ 6 mo and which caused moderate pain or difficulty in nursing (hygiene score ≥ 2); age ≥ 18 Exclusion: Acute exacerbation of MS; contracture of the hip; hypersensitivity to botulinum toxin; myasthenia gravis; other neuromuscular junction diseases; pregnant; pre-menopausal and unwilling to use contraception; recent treatment with botulinum toxin (4 mo), phenol injection (4 mo), intrathecal	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: Single treatment; patients followed up for 12 wk Provider specialty: NR Location: 8 sites in Europe (6 UK, 1 Germany, 1 Austria)	No. of patients randomized: 74 Dropouts: 14 Completed: 60 Age (mean ± SD): BTX 1500: 46.8 ± 10.3 BTX 1000: 54.0 ± 9.9 BTX 500: 47.0 ± 12.2 Placebo: 50.7 ± 10.9 Baseline EDSS (median): BTX 1500: 7.50 BTX 1000: 7.50 BTX 500: 8.00 Placebo: 7.75	1) Botulinum toxin (Dysport®) IM 1500 units, one injection to hip adductor muscles of both legs (n = 17) 2) Botulinum toxin IM 1000 units, one injection, as above (n = 20) 3) Botulinum toxin IM 500 units, one injection, as above (n = 21) 4) Placebo, one injection, as above (n = 16)	1) Symptom-specific functional status/ quality-of-life outcomes: Hygeine assessment Definition of "improvement": Overall investigator and patient opinion at end of study – excellent, good or fair on 5-point scale where lowest categories are poor, no benefit Proportion of patients with "improvement": Overall opinion Outcome Invest Patient Placebo 7(44%) 7 (44%) BTX 500 14 (67%) 13 (62%) BTX 1000 9 (48%) 10 (53%) BTX 1500 6 (36%) 8 (47%) Other (non-improvement) outcomes: Outcome Hygiene assessment (median) Placebo 2.0 BTX 500 2.0 BTX 1000 1.0 BTX 1500 1.0 2) Physical functioning: Passive hip abduction; active hip abduction; modified Ashworth score; spasm frequency Definition of "improvement": Hip abduction - Not described	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? No

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	baclofen (14 days), or any investigational drug (3 mo)				Proportion of patients with "improvement": Outcome / Active Hip abd Placebo 2 (13%) BTX 500 1 (5%) BTX 1000 1 (6%) BTX 1500 2 (12%) Other (non-improvement) outcomes: Hip abduction Passive Deg (SD) / Active possible (%) Placebo 54 (20) 4 (27) BTX 500 56 (25) 5 (26) BX 1000 63 (24) 5 (31) BTX 1500 61 (25) 7 (41) p-value NS NS Ashworth Score (median) / Muscle Tone Max n (%) / Spasm Frequency Max n (%) Placebo 8.0 13 (87) 3 (20) BTX 500 4.0 13 (68) 3 (16) BTX 1000 12.0 13 (76) 7 (41) BTX 1500 8.0 10 (59) 4 (24) p-value NS NS NS 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: AEs reported by 32/58 (55%) BTX; 10/16 (62%) placebo Hypertonia (22%), weakness of non-injected muscles (14%), fatigue (7%), UTI (5%), headache (5%), micturition frequency (5%). back pain (5%), diarrhea (5%). Twice as many AEs reported by 1500 Unit group (mean 2.7/pt) compared with the 500 Unit group (mean 1.2/pt) Six patients had serious AEs;2 on BTX, 4 on	

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					placebo; none was believed to be drug related.	
Killestein, Hooger-vorst, Reif, et al., 2002	Inclusion: Progressive MS; disease duration > 1 yr; severe spasticity (mean Ashworth spasticity score ≥ 2 in at least one limb); EDSS 4-7.5 Exclusion: Other disease of clinical importance; use of other investigational drug; MS exacerbation; steroid treatment or use of cannabinoids in previous 2 mo; history of alcohol or drug abuse, depression, psychosis, or schizophrenia	RCT (crossover, double-blind, single-center) Duration of study treatment/follow up: 4 wk with each treatment; 20 wk total (three 4-wk treatment periods and two 4-wk washouts) Provider specialty: NR (presumably neurologists) Location: 1 site in Amsterdam, The Netherlands	No. of patients randomized: 16 (10 secondary progressive, 6 primary progressive) Dropouts: 0 Completed: 16 Age (mean ± SD): 46 ± 7.9 Baseline EDSS (mean ± SD): 6.2 ± 1.2	1) Synthetic delta-9-tetrahydrocannabinol (THC) PO; initiated at 2.5 mg twice daily for 2 wk; if well tolerated, then increased to 5 mg twice daily for 2 more wk 2) Cannabis sativa plant extract with delta-9-THC and cannabidiol PO; initiated at 2.5 mg twice daily for 2 wk; if well tolerated, then increased to 5 mg twice daily for 2 more wk 3) Placebo (with dose escalation after 2 wk, as above) 4-wk washout between treatment periods	1) Symptom-specific functional status/ quality-of-life outcomes: Multiple Sclerosis Functional Composite (MSFC) score; 9-hole Peg Test Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Compared to placebo, MSFC ($p = 0.09$) and 9-hole peg test ($p = 0.02$) scores were worse on delta-9-THC treatment 2) Physical functioning: EDSS, muscle tone (Ashworth score) Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Compared with placebo, active treatment did not result in significant differences of muscle tone or EDSS score 3) Cognitive functioning: Fatigue Severity Scale (FSS) Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: No significant changes in FSS scores 4) Work or employment outcomes: NR	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes *Crossover trials only:* Period or carry-over effects? Not discussed Washout period? Yes (4 wk) No. of patients in each sequence clearly described? No Were patients who did not complete all of the periods excluded from the analysis? No (no dropouts)

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					5) Generic quality-of-life outcomes: SF-36 Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Mental Health subscale (p = 0.02) and Psychological status domain (p = 0.02) improved during delta-9-THC treatment. Other SF-36 data not given. 6) Adverse events: AEs more common during plant-extract treatment than placebo (p = 0.01). Increased spasticity (n = 5). One serious AE (brief acute psychosis).	
Kinn and Larson, 1990	Inclusion: MS for > 5 yr; advanced urgency and urinary leakage due to detrusor hyperreflexia; normal liver and renal function tests Exclusion: Diabetes; heart disease; hypertension	RCT (crossover, double-blind, single-center) Duration of study treatment/follow up: 3 wk with each treatment, no washout period; trial preceded by a 7-day run-in period and a 12-day desmopressin dose-titration phase (doses increased every 3 days from 0.1 mg to 0.2, 0.4, and 0.8 mg per day) Provider specialty: Urologists	No. of patients randomized: 13 Dropouts: 1 Completed: 12 Age: Mean, 48; range, 28-68 Baseline EDSS: NR	1) Desmopressin PO at optimal daily dose (established during dose-titration phase) for 3 wk 2) Placebo for 3 wk No washout period described	1) Symptom-specific functional status/ quality-of-life outcomes: Micturition frequency within 6 hr Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Micturition frequency decreased significantly for desmopressin compared to run-in and placebo (p < 0.05) No. of voidings in 24 hr did not show difference (p = NS) Urine volume in 6 hr lower for desmopressin than run-in and placebo (325 mL vs 440 mL; p < 0.05) 2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? No *Crossover trials only:* Period or carry-over effects? Not discussed Washout period? No No. of patients in each sequence clearly described? No Were patients who did not complete all of the periods excluded from the analysis? Unclear

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
		Location: 1 site in Malmö, Sweden			5) Generic quality-of-life outcomes: NR 6) Adverse events: 1 withdrawal during run-in (on desmopressin) – tachycardia and pruritis	
Krupp, Coyle, Doscher, et al., 1995	Inclusion: Clinically or laboratory-supported definite MS; severe fatigue (Fatigue Severity Scale score ≥ 4.0), persisting as a problem after a 2-wk pre-trial monitoring phase; ambulatory; EDSS ≤ 6.0; age 18-52 Exclusion: Current or recent (within 2 mo) use of benzodiazepines, antidepressants, azathioprine, or cyclophosphamide; severe depression (score of ≥ 36 on the Center for Epidemiologic Studies Depression scale)	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: 6 wk treatment, 10 wk total (2-wk run-in, 6 wk treatment, 2 wk follow up) Provider specialty: Neurologists Location: 3 sites in metropolitan New York City area	No. of patients randomized: 119 Dropouts: 26 Completed: 93 (83 relapsing-remitting) Age (mean ± SD, n = 93 completers): Amantadine: 40.7 ± 7.1 Pemoline: 40.2 ± 8.2 Placebo: 41.4 ± 5.9 Baseline EDSS (mean ± SD; n = 93 completers): Amantadine: 2.7 ± 1.8 Pemoline: 3.1 ± 1.7 Placebo: 2.1 ± 1.2	1) Amantadine PO 100 mg twice daily for 6 wk (n = 31) 2) Pemoline PO 18.75 mg, once daily for 1st wk, twice daily for 2nd wk, then three times per day during weeks 3-6 (n = 27) 3) Placebo (double-dummy technique used) (n = 35)	1) Symptom-specific functional status/ quality-of-life outcomes: MS-FS; FSS Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: MS-FS Baseline End Change Aman 4.9 ± 0.24 4.4 ± 0.29 -0.5 Pemoline 4.7 ± 0.20 4.7 ± 0.18 -0.03 Placebo 4.7 ± 0.14 4.7 ± 0.20 +0.1 Aman vs. placebo; p = 0.04 Pemoline vs. placebo; p = 0.394 FSS Baseline End Change Aman 5.6 ± 0.17 5.2 ± 0.22 -0.45 Pemoline 5.7 ± 0.18 5.4 ± 0.27 +0.3 Placebo 5.6 ± 0.15 5.4 ± 0.20 -0.22 Aman vs. placebo; p = NS Pemoline vs. placebo; p = 0.845 2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: 5 AEs reported on amantadine (2 withdrawals for rash, anxiety); 6 AEs reported on pemoline (2 withdrawals for irritability, anxiety); 3 AEs reported on placebo (1 withdrawal due to sleep	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Unclear No. of withdrawals in each group stated? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					disturbance)	
Larcombe and Wilson, 1984	Inclusion: Diagnosis of MS by a neurologist; self-reported duration of depression ≥ 3 mo; no current or prior treatment with major tranquilizers or lithium; score of ≥ 20 on Beck Depression Inventory; definite or probable depression according to Feighner criteria; no other major psychological disorders; low suicide risk, as assessed by Beck criteria; score within normal range on revised version of the Paired Associate Learning sub-test of the Wechsler Memory Scale and on the Simpson Memory Pictures Test; age 20-65 Exclusion: None specified	RCT (parallel-group, open-label, single-center) Duration of study treatment/follow up: 6 wk treatment; 1-wk run-in and 1-wk post-treatment follow up Provider specialty: Psychologists Location: 1 site in Australia	No. of patients randomized: 20 Dropouts: 1 Completed: 19 Age (mean, with range, overall only): 42.5 (26-61) Baseline EDSS: NR; 8 patients required wheelchair for mobility	1) Cognitive-behavioral therapy (n = 9); weekly group sessions lasting 1.5 hr each for 6 wk 2) Wait-list control (n = 10)	1) Symptom-specific functional status/ quality-of-life outcomes: BDI; HRSD; Significant-Other Rating; Best Mood; Worst Mood; Average Mood Definition of "improvement": Proportion of patients with "improvement": Subjects in the cognitive-behavioral therapy condition improved significantly more than subjects in the waiting list control condition on each of: BDI $p < 0.01$ 27± 5.6 to 8.1 ± 5 vs. 29 ± 8.7 to 33 ± 9.7 Hamilton Rating Scale $p < 0.01$ 16± 5 to 2± 1.5 vs. 16.9± 6.4 to 17.4± 8.3 Significant-Other Rating Scale $p < 0.01$ 10.7 ± 4.4 to 5.9 ± 2.8 vs. 12 ± 2.7 to 11.7± 2.8 Worst Mood Rating $p < 0.05$ 25 ± 5.7 to 37 ± 6.5 vs. 20.9 ± 7.2 to 19.6 ± 5.4 No significant effect for: Best Mood 39.8 ±7 to 44.4 ± 6.0 vs. 30.8 ± 8.0 to 30 ± 6.8 Average Mood 34.7± 6.2 to 42.2 ± 5 vs. 27.3 ± 8.3 to 26.1± 5.8 Other (non-improvement) outcomes: 2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: NR	Differences between CBT and wait-list were not only statistically significant, but also clinically important at 1 mo. Longer follow up in CBT group only suggested benefits were maintained at least 2 mo, although these data were not controlled. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? No Patients blinded? No Investigators blinded? No Outcome assessors blinded? Unclear No. of withdrawals in each group stated? No

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Lee and Patterson, 1993	Inclusion: Spasticity and a clinical picture of predominant spinal cord involvement; increased lower extremity tone associated with upper motor neuron signs such as weakness, hyperreflexia, or extensor plantar responses; spasticity score (Ashworth Scale) ≥ 15 and stable over 4-wk run-in period Exclusion: Suspicion of an extra-pyramidal contribution to their increased tone	RCT (crossover, double-blind, single-center) Duration of study treatment/follow up: 2 wk with each treatment; 10 wk total (4-wk run-in, two 2-wk treatment periods, 2-wk washout) Provider specialty: NR (presumably neurologists) Location: 1 site in Belfast, Northern Ireland	No. of patients randomized: 41? Dropouts: 8 (4 during 4-wk run-in, 4 during treatment) Completed: 33 (26 MS, 5 spinal cord injury, 1 syringomyelia, and 1 spinal tumor) Age (range; n = 33 completers): 17-70 Baseline DSS (mean, with range; n = 33 completers): 7.4 (2-9)	1) L-threonine PO 6 g per day (four 500-mg capsules 3 times per day on an empty stomach) for 2 wk 2) Placebo for 2 wk 2-wk washout between treatment periods	1) Symptom-specific functional status/ quality-of-life outcomes: Spasticity Score – sum of 6 highest scoring lower extremity muscle groups according to Ashworth Scale; Spasm score (not described); Barthel Index Definition of "improvement": 10% reduction in Spasticity score Proportion of patients with "improvement": Only a few patients reported a symptomatic benefit. 16/33 "responded" to L-threonine; 3/33 to placebo; 8 had no response to either treatment; 2 responded to both treatments; 4 dropped out. Spasticity score 21.5 baseline; 18.9 post threonine; 20.6 post placebo (p = NR) Spasm score 3.8 to 2.6 on L-threonine and 3.4 to 3.0 on placebo (p = NR) No change in Barthel Index …was seen with either treatment. Other (non-improvement) outcomes: 2) Physical functioning: Kurtzke DSS Definition of "improvement": Proportion of patients with "improvement": No change in … Kurtzke DSS in either treatment Other (non-improvement) outcomes: 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: 4 patients dropped out; 2 for medical reasons (urosepsis, chest infection) believed to be unrelated to treatment. 2 dropped out	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes *Crossover trials only:* Period or carry-over effects? Not discussed Washout period? Yes (2 wk) No. of patients in each sequence clearly described? No Were patients who did not complete all of the periods excluded from the analysis? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					for non-medical reasons. Two other patients reported minor side-effects on L-threonine (indigestion and diarrhea); 1 reported headache on placebo.	
Levine, Jossmann, and DeAngelis, 1977	Inclusion: Spasticity caused by MS or spinal cord injury; severely disabled (confined to bed or bed and wheelchair) Exclusion: None specified	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: 5 wk treatment; 11 wk total (3-wk run-in, 5 wk treatment, 3 wk post-treatment follow up) Provider specialty: NR (presumably neurologists) Location: 1 site in Boston, MA	No. of patients randomized: 19 Dropouts: 1 Completed: 18 (12 MS, 6 spinal cord injury) Age (mean overall, n = 18 completers): 42.5 Baseline EDSS: NR "The patients being reported were severely disabled and were either bed or bed and wheelchair confined"	1) Baclofen (Lioresal) PO given in evenly divided daily doses for 5 wk as follows: wk 1, 15 mg; wk 2, 30 mg; wk 3, 45 mg; wk 4, 60 mg; wk 5, 80 mg (n = NR) 2) Placebo for 5 wk (n = NR)	1) Symptom-specific functional status/ quality-of-life outcomes: Ashworth scale Definition of "improvement": 10% drop in spasticity score Proportion of tests with "improvement": Dose Baclofen Placebo 15 mg 1/17 (6%) 1/15 (7%) 30 mg 4/16 (25%) 2/16 (13%) 45 mg 4/15 (25%) 4/17 (25%) 60 mg 8/15 (50%) 8/15 (50%) 80 mg 8/15 (50%) 6/15 (40%) p-value NR at any dose Other (non-improvement) outcomes: Avg change in spasticity scores Dose Baclofen Placebo 15 mg -2 -5 30 mg -7 -3 45 mg -11 -6 60 mg -13 -9 80 mg -12 -10 p-value NR at any dose 2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: Baclofen " was for the most part tolerated quite well. Side effects included occasional mild drowsiness and infrequent complaints of vertigo, weakness and fatigue."	Results of MS and SCI patients were not presented separately; however, baclofen "was 10% more effective in MS than in SCI; on the other hand placebo reaction was 36% greater in SCI than in MS." "Clinical grading of spasticity was found lacking in sensitivity to changes in skeletal muscle hypertonia appreciated by more objective bio-electric monitoring of integrated EMG." QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Lincoln, Dent, Harding, et al., 2002	Inclusion: Clinically definite, laboratory-supported, or clinically probable MS; resident within 20-mile radius of study site; able to undergo 30-min assessments Exclusion: None specified	RCT (parallel-group, single-blind [assessors only], single-center) Duration of study treatment/follow up: Only extended intervention (cognitive rehabilitation program) lasted 6 wk; all patients followed up for 8 mo Provider specialty: Psychologists Location: 1 site in Nottingham, UK	No. of patients randomized: 240 (107 relapsing-remitting, 94 secondary progressive, 19 primary progressive, 20 unknown) Dropouts: 17 Completed: 223 Age (mean ± SD): 43 ± 10 Baseline EDSS: NR; baseline Ambulation Index (median): Rehab: 4 Assessment: 4 Control: 3	1) Detailed cognitive assessment + cognitive rehabilitation program (n = 79); 3-hr assessment session using multiple instruments selected according to nature of patient's problems; results communicated to GP, hospital staff, patients, and families; cognitive rehabilitation program designed and implemented for any deficits identified 2) Detailed cognitive assessment, as above, but no subsequent intervention (n = 79); results of assessment communicated to GP, hospital staff, patients, and families 3) No psychological/ cognitive assessment beyond screening tests; results of screening tests not communicated to medical or rehabilitation staff, patients, or families (n = 82)	1) Symptom-specific functional status/ quality-of-life outcomes: Extended Activities of Daily Living Scale (EADL) Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: EADL — Control / Assess / Inter-vention / p-value 4-month — 48.0 / 43.0 / 45.0 / 0.23 8-month — 47.5 / 44.5 / 42.0 / 0.21 2) Physical functioning: NR 3) Cognitive functioning: General Health Questionnaire-28 (GHQ-28); Dysexecutive Syndrome Questionnaire (DEX); Everyday Memory Questionnaire (EMQ); Memory Aids Questionnaire (MAQ) Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: GHQ-28 — Control / Assess / Inter-vention / p-value 4-month — 21.0 / 21.0 / 22.0 / 0.73 8-month — 18.0 / 18.5 / 21.0 / 0.59 DEX 4-month — 17.0 / 16.0 / 20.0 / 0.77 8-month — 16.5 / 18.0 / 18.0 / 0.98 EMQ 4-month — 16.5 / 18.5 / 17.0 / 0.69 8-month — 14.0 / 15.0 / 15.0 / 0.76 MAQ 4-month — 10.0 / 11.0 / 10.0 / 0.92	Although 28% did not report cognitive problems on the GNDS, only 5% reported no cognitive problems and had no significant impairment on cognitive testing. Intervention was not intensive, carried out at home. Heterogeneous patient group, which leads to increased variance on outcome measures, more difficult to detect treatment effect QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? No Patients blinded? No Investigators blinded? No Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					8-month 10.0 9.0 10.0 0.80 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: SF-36 physical and mental composite scores Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: SF-36 Control Assess Inter-vention p-value 4-month Physical 25.6 27.1 31.4 0.45 Mental 44.7 44.7 46.9 0.55 8-month Physical 30.0 32.1 30.7 0.55 Mental 47.3 49.3 46.9 0.76 6) Adverse events: NR	
Livesley, 1992	Inclusion: Spasticity as a component of a chronic neurological disease (stable for ≥ 6 mo); high level of cognitive awareness; inpatient or outpatient Exclusion: None specified	RCT (parallel-group, single-blind [patients only], single-center) Duration of study treatment/follow up: 6 wk Provider specialty: Physiotherapist Location: 1 site in Nottingham, UK	No. of patients randomized: 40 (37 MS, 2 spinal injuries, 1 stroke) Dropouts: 1 Completed: 39 Age (mean ± SD): ENS: 48 ± 8.8 Sham ENS: 47 ± 11.2 Baseline EDSS: NR	1) Electrical neuromuscular stimulation (ENS); quadriceps and hamstrings treated for 12 min every working day for 6 wk; frequency gradually increased from 3 Hz (2 min) to 10 Hz (5 min) to 35 Hz (5 min) during each treatment session (n = 20) 2) Sham ENS; as above, but stimulator deactivated (n = 20)	1) Symptom-specific functional status/ quality-of-life outcomes: Functional ambulation classification appendix; Spasticity self-rating Definition of "improvement": Rated better on scale of worse, same, or better Proportion of patients with "improvement": Treatment 9/20 (45%) Sham 4/19 (21%) Other (non-improvement) outcomes: Functional ambulation (median) Treatment Sham Entry Exit Entry Exit p-value 4 4 5 5 NS 2) Physical functioning: Rivermead motor assessment; Range of movement at hip,	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? No Patients blinded? Unclear Investigators blinded? No Outcome assessors blinded? No No. of withdrawals in each group stated? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					knee and ankle (degrees) Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Rivermead motor assessment (median) Treatment Sham Entry Exit Entry Exit p Gross 8 9 11 11 NS Leg 8 8 7 9 NS Joint ROM (degrees) Treatment Sham Entry Exit Entry Exit p Hip flex 98± 19 102±21 100±17 100±18 NS Hip ext 8.5± 6 8.5± 6 7± 6 7.5± 7 NS Hip abd 33± 11 35± 10 29± 13 34± 13 NS Knee fl 121±25 126±19 122±18 120±24 NS Knee ex 1± 3 2.5±5.5 0.5± 2 0.5± 2 NS Ank dor 18±6.5 26±6 21±12 18±4 NS Ank pla 21±17 14±5 12.5±7 19±8 NS 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: NR	
Mendoza, Pittenger, and Weinstein, 2001	Inclusion: Advanced MS; resident in a skilled nursing facility specializing in the treatment of patients with advanced MS Exclusion: Primary admitting diagnosis not MS; unable to	RCT (parallel-group, open-label, single-center) Duration of study treatment/follow up: 2 mo Provider	No. of patients randomized: 20 Dropouts: 0 (though post-study data not collected from 1 patient because of a medical complication)	1) Active treatment (n = 10); extended battery of cognitive tests, plus specific problem-solving strategy: Individual CNA assigned to each patient, provided with special training, and charged with keeping	1) Symptom-specific functional status/ quality-of-life outcomes: NR 2) Physical functioning: NR 3) Cognitive functioning: Beck Depression Inventory Definition of "improvement": Change score greater than 2 SD	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? No Patients blinded? No Investigators blinded? No Outcome assessors blinded? No No. of withdrawals in each group stated?

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	read test stimuli; co-morbid major mental disorder; unable to answer test questions at a sufficiently high verbal level; performance on Kaufman Short Neuropsychological Assessment Procedure Mental Status Subtest in the impaired range	specialty: Certified nursing assistants (CNAs), social workers, and psychologists Location: 1 site in Dorchester, MA	Completed: 20 Age (mean): Active: 54.6 Control: 64.7 Baseline EDSS: NR; 2 groups "equivalent in terms of general physical status"	a notebook, attached to patient's chair, in which information was recorded on patient's comments or concerns, special assistance required, etc. 2) Control (n = 10); no change to previous treatment routine	Proportion of patients with "improvement": Treatment 6/10 (60%) Control 1/9 (11%) Other (non-improvement) outcomes: BDI Pre Post Treatment 11.3 5.5 Control 9.3 8.6 p-value NS 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: NR	Yes
Mohr, Boudewyn, Goodkin, et al., 2001	Inclusion: Confirmed diagnosis of MS (Poser criteria); relapsing-remitting or secondary progressive disease course confirmed by a neurologist; diagnosis of major depressive disorder based on Structured Clinical Interview for the DSM-IV; score ≥ 16 on 17-item Hamilton Rating Scale for Depression; score ≥ 16 on Beck Depression Inventory; willingness to abstain from psychological or pharmacological treatment for depression other than that provided as part of study	(Pseudorandomized, parallel-group, open-label, single-center) Patients allocated to group therapy based on threshold number during 4-week period; if fewer than 6 pts enrolled, then they were randomized to CBT or sertraline. Duration of study treatment/follow up: 16 wk; 43 patients also followed up at 6 mo Provider specialty: Neurologists and psychologists	No. of patients randomized: 63 Dropouts: 11 Completed: 52 Age (mean ± SD, overall only): 43.9 ± 10.0 Baseline EDSS (mean, with range, overall only): 2.4 (0 to 8.0)	1) Cognitive-behavioral therapy focused on improving coping skills (in relation to both depression and MS); individual sessions (50 min each) once weekly for 16 wk (n = 20 at start, 19 at end) 2) Supportive-expressive group therapy, focused on facilitating expression and providing social support; sessions involved 5-9 patients and 2 therapists; weekly 90-min sessions for 16 wk (n = 22 at start, 18 at end) 3) Sertraline PO, initiated at 50 mg per day, increased by 50 mg every 4 wk until	1) Symptom-specific functional status/ quality-of-life outcomes: BDI, HRSD (Hamilton) Definition of "improvement": 50% decrease in symptoms and symptoms severity on HRSD Proportion of patients with "improvement": CBT 10 (50%) SEG 3 (14%) Sertraline 5 (24%) Other (non-improvement) outcomes: ITT BDI – SEG significantly less effective than CBT (P = 0.003) and sertraline (p = 0.047) BDI-18 – SEG less effective than CBT (p = 0.0007) and marginally less effective than sertraline (p = 0.84) HRSD - CBT more effective than SEG (p = 002); no significant differences between SEG and sertraline (p = 0.45) or between CBT and sertraline (p = 0.13) 2) Physical functioning: EDSS Definition of "improvement": None	QUALITY ASSESSMENT: Described as "randomized"? No Method of randomization clearly described? Yes Concealment of allocation? No Described as "double-blind"? No Patients blinded? No Investigators blinded? No Outcome assessors blinded? No No. of withdrawals in each group stated? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	Exclusion: Other serious psychological disorders; dementia (below 5th percentile in 3 or 6 areas of neuropsychological functioning); severe suicidality; treatment with corticosteroids in previous 14 days; initiation of treatment with interferon in previous 2 mo; current MS exacerbation; other disorders of CNS; current or planned pregnancy; current psychological or pharmacological treatment for depression	Location: 1 site in San Francisco, CA		dosage of 200 mg was reached or until full remission achieved as judged by treating clinicians; patient visits lasting 10-15 min every 4 wk; treatment lasted 16 wk (n = 21 at start, 15 at end)	Proportion of patients with "improvement": NR Other (non-improvement) outcomes: 3) Cognitive functioning: Symbol Digit Modalities Test, Digit Span; Ret Auditory Verbal Learning Test, 7/24, Controlled Oral Word Association, California Card Sort Test Definition of "improvement": None Proportion of patients with "improvement": NR Other (non-improvement) outcomes: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: NR	
Mohr, Likosky, Bertagnolli, et al., 2000	Inclusion: Diagnosis of a relapsing form of MS; score of ≥ 15 on the Depression-Dejection scale of the Profile of Mood States; treatment for depression (if any) initiated at least 3 mo before start of study with continuation intended Exclusion: Dementia (score < 5th percentile on the Short Word List); other neurological disorder	RCT (parallel-group, open-label, single-center) Duration of study treatment/follow up: 8 wk Provider specialty: Neurologists and psychologists Location: 1 managed care program in northern California	No. of patients randomized: 32 (all relapsing) Dropouts: 9 Completed: 23 Age: Mean, 42.4 Baseline EDSS: NR; 56% walked without aids, 34% walked with aids, and 9% used a wheelchair	1) Telephone-administered cognitive-behavioral therapy (n = 16); eight weekly 50-min sessions; included training in thought monitoring, increasing pleasant events, and managing fatigue, as needed for individual patients 2) Usual care (n = 16)	1) Symptom-specific functional status/ quality-of-life outcomes: Profile of Modd States Depression-Dejection scale Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Completers Pre Post CBT 34.8± 13.5 13.8± 12.8 Usual 26.0± 8.1 24.3± 10.7 P = 0.003 ITT Pre Post CBT 33.1± 12.4 18.7± 13.8 Usual 27.9± 12.1 26.7± 13.7 P = 0.01 2) Physical functioning: NR	No change in control condition over 6 wk, but statistically significant change in treatment condition. Post-treatment scores in treatment groups approached upper end of population sample norms. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? No Patients blinded? No Investigators blinded? No Outcome assessors blinded? No No. of withdrawals in each group stated? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: NR	
Mondrup and Pedersen, 1984a **and** **Mondrup and Pedersen, 1984b**	Inclusion: Spastic paresis in a stable phase for ≥ 2 mo Exclusion: Markedly impaired liver or renal function; severe hypertension (DBP > 110 mmHg); orthostatic hypotension; chronic alcoholism; diabetes; cardiac disease; overt psycho-pathology; epilepsy; disease with dominating cerebellar symptoms; pregnancy	RCT (crossover, double-blind, single-center) Duration of study treatment/follow up: 2 wk with each treatment, 4 wk total (no washout described) Provider specialty: Neurologists Location: 1 site in Aarhus, Denmark	No. of patients randomized: 17 Dropouts: 1 Completed: 16 (14 MS, 2 hereditary spastic paraplegia) Age (completers): Median, 45.5; range, 30-62 Baseline EDSS: NR	1) Progabide PO administered three times per day; maximum dose reached after 3-5 days; treatment lasted 2 wk; median daily dose 24.3 mg/kg (range, 14.3-32.7 mg/kg) 2) Placebo, with dose adjustments as above, for 2 wk No washout described	1) Symptom-specific functional status/ quality-of-life outcomes: Overall therapeutic effect (includes evaluation of gait and other ADLs; 4-point scale) Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Overall therapeutic effect Investigator p < 0.01 Patient p < 0.01 2) Physical functioning: Spastic hypertonia (angle at which stretch reflex appears by mobilization of limb at gravity speed in steps of 15 degrees); tendon reflexes-patellar (4-point scale) Achilles (3-point scale); flexor spasms frequency (5-point scale) and discomfort (4-point scale); flexor reflex (4-point scale); muscle strength (6-point scale); Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: p-value Spastic hypertonia < 0.01 Tendon reflexes Patellar < 0.01 Achilles NS	No washout period was described, and no test for treatment-period interaction was described – there is potential for carry-over effect QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes *Crossover trials only:* Period or carry-over effects? Not discussed Washout period? No No. of patients in each sequence clearly described? No Were patients who did not complete all of the periods excluded from the analysis? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					Clonus Patellar NS Foot NS Flexor reflex NS Flexor spasms Frequency < 0.05 Discomfort NS Muscle strength Upper NS Lower NS 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: "No side-effects were registered"	
Mueller, Gruenthal, Olson, et al., 1997	Inclusion: Laboratory-supported definite MS, including characteristic MRI findings; spasticity and leg cramps severe enough to interfere with daily activities, including sleep; age 18-50 Exclusion: Pregnancy; significant renal disease	RCT (crossover, double-blind, single-center) Duration of study treatment/follow up: 2 days with each treatment; 15 days total (two 2-hr run-ins [on 1st day of treatment during each period], two 2-day treatment periods, 11-day washout) Provider specialty: NR (neurologists and others?) Location: 1 site in Louisville, KY	No. of patients randomized: 15 Dropouts: 0 Completed: 15 Age (mean, with range): 42.2 (31-59) Baseline EDSS (median): Prior to gabapentin: 12 Prior to placebo: 13	1) Gabapentin PO 400 mg three times per day for 2 days 2) Placebo three times per day for 2 days 11-day washout between treatment periods	1) Symptom-specific functional status/ quality-of-life outcomes: Visual Faces Scale, Ashworth Scale; clonus; reflexes; Response to Noxious Stimuli Definition of "improvement": None Proportion of patients with "improvement": NR Other (non-improvement) outcomes: VFS / Ashworth / Clonus Placebo b/l 2 / 22 / 1 Gabapentin b/l 2 / 23 / 1 Placebo 2 / 23 / 1 Gabapentin 1 / 22 / 1 p-value 0.008 / 0.007 / 0.1 Reflexes / Noxious Placebo b/l 14 / 2 Gabapentin b/l 14 / 2 Placebo 14 / 2 Gabapentin 13 / 2 p-value 0.28 / 0.25	Improvements on objective scales were statistically significant, but not as dramatic as patients self-evaluations QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes *Crossover trials only:* Period or carry-over effects? Yes Washout period? Yes (11 days) No. of patients in each sequence clearly described? No Were patients who did not complete all of the periods excluded from the analysis? No (no dropouts)

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					2) Physical functioning: EDSS Definition of "improvement": None Proportion of patients with "improvement": NR Other (non-improvement) outcomes: EDSS Placebo b/l 13 Gabapentin b/l 12 Placebo 12.5 Gabapentin 10 p-value 0.03 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: NR	

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Newman, Nogues, Newman, et al., 1982	Inclusion: Disabled by spasticity; neurologically stable Exclusion: None specified	RCT (crossover, double-blind, single-center) Duration of study treatment/follow up: 6 wk with each treatment, 13 wk total (two 6-wk treatment periods, 1-wk washout) Provider specialty: Neurologists Location: 1 site in Newcastle, UK	No. of patients randomized: 36 (32 MS, 4 syringomyelia) Dropouts: 10 Completed: 26 Age (mean ± SD, completers): 45.9 ± 9.4 Baseline EDSS: NR	1) Tizanidine PO in 2-mg capsules; dose increased over 2 wk to 8 capsules daily (16 mg), then maintained at this level for a further 1 mo (dose could be lowered if not tolerated) 2) Baclofen PO in 5-mg capsules; dose increased over 2 wk to 8 capsules daily (40 mg), then maintained at this level for a further 1 mo (dose could be lowered if not tolerated) 1-wk washout between treatment periods	1) Symptom-specific functional status/ quality-of-life outcomes: NR 2) Physical functioning: Muscle tone (Ashworth); EDSS; Pedersen score Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Overall score of lower limb muscle tone: Tizanidine 9/26 (35%) $p < 0.02$ Baclofen 8/26 (31%) $p > 0.05$ Difference between treatments p = NS No significant difference in muscle power Flexor, extensor, and adductor spasms in the lower limbs were improved more in baclofen group (p = NS) No significant change in Kurtzke scores or Pedersen scores 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: AEs experienced by 17/26 (65%) on tizanidine and 17/26 (65%) on baclofen. Drowsiness, muscle pains, dizziness, weakness, abdominal pain, bowel or bladder disturbance, sleeplessness, depression. Similar AE profiles for both drugs.	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? No *Crossover trials only:* Period or carry-over effects? No Washout period? Yes (1 wk) No. of patients in each sequence clearly described? No Were patients who did not complete all of the periods excluded from the analysis? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Nielsen, Sinkjaer, and Jakobsen, 1996	Inclusion: Clinically definite or laboratory-supported definite MS by Poser criteria; EDSS < 7.0; stable neurological condition for ≥ 6 mo; lower limb spasticity ≥ 2 on Ashworth score for at least one joint; preserved walking performance for 10 m Exclusion: Epilepsy; other neurological disorders; pregnancy; implanted spinal metal, drug infusion pump, or pacemaker; previous exposure to magnetic stimulation	RCT (parallel-group, double-blind [patients and assessors, not treating clinicians], single-center/ multicenter) Duration of study treatment/follow up: 7 days treatment; follow-up evaluations 1, 8, and 16 days after last treatment Provider specialty: NR (neurologists?) Location: 1 site in Aarhus, Denmark	No. of patients randomized: 38 Dropouts: 3 Completed: 35 Age (median, with range): Active: 44 (34-67) Sham: 44 (26-66) Baseline EDSS: NR	1) Repetitive magnetic stimulation twice daily for 7 consecutive days (n = 21); magnetic coil place in midline of back at mid-thoracic level; subjects stimulated in supine position for 25 min with repeated periods of stimulation for 8 sec at 25 Hz, followed by 22 sec of repose; magnetic field strength gradually increased to 0.7 Tesla within a few minutes 2) Sham stimulation twice daily for 7 consecutive days (n = 17)	1) Symptom-specific functional status/ quality-of-life outcomes: Clinical score = muscle tone (Ashworth score) + reflex activity; self-score Definition of "improvement": None Proportion of patients with "improvement": Mag stim / Sham Self-score 9/18 (50%) / 10/17 (59%) Clin score 14/18 (78%) / 10/17 (59%) p-values NR Other (non-improvement) outcomes: Mag stim / Sham / p-value Self-score 1.1± 1.6 / 1.5± 1.8 / NS Clinical 1d -3.3± 4.7 / 0.7± 2.5 / 0.003 Improvements in clinical score extinguished at 8 and 16 days after treatment 2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: NR	Treating clinicians were not blinded to treatment group No definition of threshold for defining "improvement" QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? No Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes
O'Hara, Cadbury, De Souza, et al., 2002	Inclusion: Diagnosis of MS confirmed by GP Exclusion: None	RCT (parallel-group, single blinded [assessors only, not treating clinicians or patients], multicenter) Duration of study treatment/follow	No. of patients randomized: 183 Dropouts: 14 Completed: 169 (80 relapsing-remitting, 82 chronic progressive, 7 unknown)	1) Professionally guided self-care program (n = 73); two 1- to 2-hr group or individual discussions of self-care strategies during 1st mo; supported by an information booklet developed for the study in line with	1) Symptom-specific functional status/ quality-of-life outcomes: Standard Day Dependency Record (SDDR) subscales SDDRO & SDDRE Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes:	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? No Patients blinded? No Investigators blinded? No Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
		up: 6 mo Provider specialty: NR Location: Multiple local sites in London, UK	Age (mean ± SD): Active: 52.5 ± 11.2 Control: 50.4 ± 10.4 Baseline EDSS: NR	consumer priorities; information covered physical, social, and psychological domains of life 2) No-treatment control (n = 96)	Change from baseline to follow up: Intervention Control p-value SDDRO 0.5 0.8 0.6 SDDRE -0.3 0.6 0.04 2) Physical functioning: Barthel Index Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Intervention Control Barthel 0 (0,0) 0 (-1,0) 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: SF-36 Change from baseline to follow up: Intervention Control p-value Mental hlth 3.7 -1.2 0.04 Pain 2.4 -1.1 0.32 Phys role -6.4 -6.2 0.31 Phys fn 0.6 -1.4 0.5 Role emo -4.2 -3.1 0.9 Social fn 0.8 -3.3 0.33 Vitality 1.5 -4.2 0.05 Gen hlth 7.4 4.8 0.32 6) Adverse events: NR	
Ørsnes, Sørensen, Larsen, et al., 2000	Inclusion: clinically definite MS; stable disease for ≥ 1 mo; increased stretch reflexes and hyperreflexia; moderate functional deficits; able to walk unaided and without	RCT (crossover, double-blind, single-center) Duration of study treatment/follow up: Approximately 24 days with each treatment;	No. of patients randomized: 14 (5 relapsing-remitting, 4 primary progressive, 5 secondary progressive) Dropouts: 0	1) Baclofen PO; dose initiated at 5 mg three times per day and increased by 5 mg every 3 days to maximum of 15 mg three times per day or maximum tolerated dose; after 11 days at	1) Symptom-specific functional status/ quality-of-life outcomes: Ashworth index Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes:	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	support for at least 1 min Exclusion: Use of drugs that could affect spasticity	approximately 62 days total (no run-in described, two 24-day treatment periods, 2-wk washout) Provider specialty: NR (presumably neurologists) Location: 1 site in Copenhagen, Denmark	Completed: 14 Age (median, with age): 42 (24-57) Baseline EDSS (median, with range): 5 (3.5-6.0)	this dose, treatment tapered over "about 1 wk" 2) Placebo, dosing schedule as above, for approximately 24 days 2-wk washout between treatment periods	Tendon Reflexes / Muscle tone Ashworth Baclofen Before 13.6 (2.8) 1.9 (1.5) During 11.7 (4.1) 2.8 (2.4) Placebo Before 13.7 (3.5) 3.1 (2.1) During 13.1 (3.1) 3.2 (2.3) p-value 0.14 0.33 2) Physical functioning: EDSS, Ambulation Index (AI), Neurologic Rating Scale (NRS), MS-impairment scale (MSIS) Definition of "improvement": Not defined Proportion of patients with "improvement": EDSS & AI: Baclofen 1/14 (7%) Placebo 3/14 (21%) Other (non-improvement) outcomes: No significant differences between baclofen and placebo in EDSS, AI, NRS or MSIS 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: NR	No. of withdrawals in each group stated? Yes *Crossover trials only:* Period or carry-over effects? No Washout period? Yes (2 wk) No. of patients in each sequence clearly described? Yes Were patients who did not complete all of the periods excluded from the analysis? No (no dropouts)
Patti, Ciancio, Reggio, et al., 2002	Inclusion: Clinically definite or laboratory-supported MS; primary or secondary progressive form of MS; EDSS 4.0-8.0; age 18-65 Exclusion: One or more exacerbations	RCT (parallel-group, single-blind [assessors only], single-center) Duration of study treatment/follow up: 12 wk	No. of patients randomized: 111 Dropouts: 5 Completed: 106 Age: Mean, 45.6; range, 25-60	1) Comprehensive outpatient rehabilitation program for 6 wk + self-exercise treatment for 6 wk (n = 58); rehabilitation program included physiotherapy, occupational therapy,	1) Symptom-specific functional status/ quality-of-life outcomes: Fatigue Impact Scale (FIS) Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes:	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? No Patients blinded? No Investigators blinded? No Outcome assessors blinded? Yes No. of withdrawals in each group stated?

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	in previous 3 mo; cognitive impairment (Mini-Mental State Examination score ≤ 24); history of cardiovascular, respiratory, ortho-pedic, psychiatric, or other medical condition precluding participation; pregnancy; treatment with immunosup-pressives, inter-ferons, copolymer, 4-amminopyridine, or experimental drugs in preceding 6 mo; rehabilitation therapy in previous 3 mo	Provider specialty: NR (presumably neurologists) Location: 1 site in Catania, Italy	Baseline EDSS: Mean, 6.2; range, 4-8	speech therapy (if needed), and complementary and alternative therapies 2) Control = 12-wk self-exercise treatment (n = 53)	Change from T0 to T1 Treatment Control p-value FIS -18.8± 14.3 0.6± 0.9 < 0.001 2) Physical functioning: EDSS Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: "Changes in EDSS scores clustered nearly around 0 in both groups at weeks 6 and 12." 3) Cognitive functioning: Tempelaar Social Experience Checklist (SET); Beck Depression Inventory (BDI) Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Change from T0 to T1 Treatment Control p-value SET -2.6± 6.0 -0.3± 0.8 < 0.001 BDI -2.2± 3.4 0.1± 1.0 < 0.001 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: SF-36 Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: SF-36 Change from T0 to T1 Treatment Control p-value PF 6.9± 18 -0.1± 0.3 < 0.001 RP 14± 24 -0.2± 0.5 < 0.001	Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					BP 15± 20 -0.1± 0.6 < 0.001 GH 5.8± 10 -0.2± 0.5 < 0.001 VT 7.4± 12 -0.1± 0.5 < 0.05 SF 12± 15 -0.1± 0.3 < 0.001 RE 6.2± 24 -0.1± 0.3 < 0.05 MH 7.7± 16 -0.1± 0.5 < 0.05 6) Adverse events: NR	
Penn, Savoy, Corcos, et al., 1989	Inclusion: Severe, disabling spasms caused by MS or spinal-cord injury; not responsive to oral doses of anti-spastic medication; agreed to implantation of drug pump after pre-trial test dose of intrathecal baclofen Exclusion: None specified	RCT (crossover, double-blind, single-center) Duration of study treatment/follow up: 3 days with each treatment; pre-trial test with bolus intrathecal dose; no washout Provider specialty: Physiatrists, motor physiologists, and neurosurgeons Location: 1 site in Chicago, IL	No. of patients randomized: 20 (10 MS, 10 spinal-cord injury) Dropouts: 0 Completed: 20 Age (mean, with range): 41.5 (23-62) Baseline EDSS: NR; 9/10 MS patients wheelchair-bound; all 10 "functionally dependent"	1) Baclofen by intrathecal infusion via surgically implanted pump; daily dose 1.5-2 times the effective bolus intrathecal dose (typically 100-150 µg per day) given by continuous infusion over 3 days 2) Placebo by same route for 3 days No washout between treatment periods	1) Symptom-specific functional status/ quality-of-life outcomes: Ashworth score; Spasm score Definition of "improvement": Not defined Proportion of patients with "improvement": 9/10 patients had clinically important improvement – 1 had no improvement during dbl blind trial, but did show improvement at higher dosage during open trial Other (non-improvement) outcomes: Ashworth Placebo 4.0± 1.0 Baclofen 1.2± 0.4 Change 2.8 (p < 0.0001) Spasm score Placebo 3.3± 1.2 Baclofen 0.4± 0.8 Change 2.9 (p < 0.0005) 2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: During 26 mo follow up, 2 catheters dislodged, 1 pump failed at 4 mo, pain at	Study was effectively unblinded due to the effect of the drug. Most results not given separately for SCI and MS patients. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes *Crossover trials only:* Period or carry-over effects? Not discussed Washout period? No No. of patients in each sequence clearly described? No Were patients who did not complete all of the periods excluded from the analysis? Unclear

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					implantation site	
Petajan, Gappmaier, White, et al., 1996	Inclusion: Confirmed diagnosis of clinically definite MS; EDSS ≤ 6.0; not involved in any form of regular physical activity for previous 6 mo; no history of cardio-vascular, respiratory, orthopedic, metabolic, or other medical condition that would preclude participation in exercise program Exclusion: None specified	RCT (parallel-group, open-label, single-center) Duration of study treatment/follow up: 15 wk Provider specialty: Neurologists (and physical therapists/ exercise physiologists) Location: 1 site in Salt Lake City, UT	No. of patients randomized: 54 Dropouts: 8 Completed: 46 Age (mean ± SE): Exercise: 41.1 ± 2.0 Control: 39.0 ± 1.7 Baseline EDSS (mean ± SE): Exercise: 3.8 ± 0.3 Control: 2.9 ± 0.3	1) Exercise program (n = 21); 3 supervised training session per week for 15 wk; each session consisted of 5-min warm-up at 30% VO_2max, 30 min at 60% VO_2max, 5-min cool-down, and 5-10 min stretching focusing on posterior muscles of lower leg, thigh, and back 2) No treatment (patients agreed not to alter their level of physical exercise) (n = 25)	1) Symptom-specific functional status/ quality-of-life outcomes: Fatigue Severity Scale (FSS); Sickness Impact Profile (SIP) Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: "No changes were observed for exercise or non-exercise groups on the FSS" Significant improvement in exercise group compared to non-exercise group for physical dimension subscale of the SIP. In other dimensions (ambulation, mobility, and body care and movement) exercise patients improved compared to baseline, but not significantly compared to non-exercise group. No changes for psychosocial dimension subscale. 2) Physical functioning: EDSS; ISS; VO2max Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: EDSS Exercise Non-exercise Baseline 3.8± 0.3 2.9± 0.3 15-week 3.7± 0.3 2.8± 0.3 p = NS ISS Exercise Non-exercise Baseline 9.0± 0.9 8.1± 0.9 15-week 6.8± 1.1 8.3± 0.9 p = NS	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? No Patients blinded? No Investigators blinded? No Outcome assessors blinded? No No. of withdrawals in each group stated? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					VO2max Exercise Non-exercise Baseline 24.2± 1.4 26.0± 1.3 15-week 29.4± 1.3 26.4± 1.4 p < 0.01 3) Cognitive functioning: Profile of Mood States (POMS) Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: POMS – Lower scores for depression (5,10 wk), anger (5,10 wk), and fatigue (10 wk) subscales from baseline to post-treatment in exercise group; no between-group differences 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: NR	
Pozzilli, Brunetti, Amicosante, et al., 2002	Inclusion: Clinically definite MS; resident in Rome service area of Italian National Health Service Exclusion: None specified	RCT (parallel-group, open-label, multicenter) Duration of study treatment/follow up: 1 yr Provider specialty: Multidisciplinary care teams for home-care patients; neurologists for hospital patients	No. of patients randomized: 201 (40 relapsing-remitting, 41 primary progressive, 120 secondary progressive) Dropouts: 13 Completed: 188 Age (mean ± SD): Home: 47.0 ± 10.3 Hospital: 46.7 ±	1) Home-based management (n = 133); patients managed through home visits and telephone calls; multidisciplinary care team designed individualized clinical care plan and coordinated home services; care included observation, administration of IV drugs, nursing care, rehabilitation,	1) Symptom-specific functional status/ quality-of-life outcomes: SF-36, Fatigue Severity Scale (FSS); Functional Independence Measure (FIM) Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: SF-36 Diff CI p-value Phys fn 0.27 -0.53 to 1.06 0.55 Role phys 3.67 -1.19 to 8.53 0.09 Bodily pain 3.46 2.4 to 4.5 0.0001 Gen Health 5.01 4.5 to 5.5 0.0001	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Unclear Described as "double-blind"? No Patients blinded? No Investigators blinded? No Outcome assessors blinded? No No. of withdrawals in each group stated? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
			13.3 Baseline EDSS (mean ± SD): Home: 6.0 ± 2.0 Hospital: 5.8 ± 2.2	education, psychological support, and social services; treatment continued for 1 yr 2) Traditional hospital care (n = 68); patients followed as usual in their MS referral centers for 1 yr	Vitality 0.28 -0.38 to 0.94 0.41 Social fn 1.09 0.51 to 1.67 0.001 Role, emo 12.4 9.8 to 14.9 0.0001 Mental hlth -0.10 -0.25 to 0.05 0.19 Phys component score 1.19 1.04 to 1.34 0.0001 Mental comp score 0.75 0.58 to 0.91 0.0001 No significant differences between intervention and control groups for FSS or FIM 2) Physical functioning: EDSS Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: No significant differences between intervention and control groups for EDSS 3) Cognitive functioning: MMSE, State-trait Anger Expression Inventory (STAXI); State-Trait Anxiety Inventory (STAI); Clinical Depression Questionnaire (CDQ) Definition of "improvement": Proportion of patients with "improvement": No significant differences between intervention and control groups for MMSE, STAXI, STAI Trend in favor of intervention group for changes in depression as measured by the CDQ score; intervention (-7.8%); control (+0.7%) (p = 0.11) Other (non-improvement) outcomes: No significant differences between intervention and control groups for MMSE	

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: NR	
Prasad, Smith, and Wright, 2003	Inclusion: MS; voiding dysfunction, (such as frequency or urgency) associated with elevated residual volume of > 100 mL and < 500 mL; attending a continence advisory clinic or a neuro-rehabilitation clinic; reasonable hand dexterity; intact abdominal sensation; able to walk short distances indoors without aids Exclusion: Urinary symptoms caused by infection	RCT (crossover, open-label, two-center) Duration of study treatment/follow up: 2 wk with each treatment; 8 wk total (no run-in described, three 2-wk treatment periods, two 1-wk washouts) Provider specialty: NR (rehabilitation medicine) Location: 2 sites in Edinburgh, Scotland	No. of patients randomized: 30 Dropouts: 2 (post-randomization, but pre-treatment) Completed: 28 Age (mean ± SD): 49 ± 9.2 Baseline EDSS: NR	1) Abdominal vibration; provided by low-cost, commercially available body massager (Queen Square Bladder Stimulator); used against supra-pubic region (2.5 cm above public symphysis) during and for 1 min after voiding; treatment continued for 2 wk 2) Abdominal pressure; applied using same massager as above, but without batteries, for 2 wk 3) No treatment for 2 wk 1-wk washout between treatment periods	1) Symptom-specific functional status/ quality-of-life outcomes: Frequency of micturition (per 72 hr); incontinence; frequency of incontinence; post-void residual urine volume (ml) Definition of "improvement": No incontinence/72 hr Proportion of patients with "improvement": Vibration 20/28 (71%) Abd pressure 12/28 (43%) No treatment 16/28 (57%) Other (non-improvement) outcomes: Frequency per 72 hr ± SD Vibration 25± 8.9 Abd pressure 26± 9 No treatment 27± 10.3 Mean episodes of incontinence Vibration 1.3 (0-3) Abd pressure 1.6 (0-20) No treatment 1.9 (0-20) Post-void residuals (ml) (± SD) Vibration 126± 121 (p = 0.002 vs NT) Abd pressure 191± 132 (p = 0.059 vs Vib) No treatment 231± 119 2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? No Patients blinded? No Investigators blinded? No Outcome assessors blinded? No No. of withdrawals in each group stated? Yes *Crossover trials only:* Period or carry-over effects? Not discussed Washout period? Yes (1 wk) No. of patients in each sequence clearly described? No Were patients who did not complete all of the periods excluded from the analysis? No (no dropouts)

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					6) Adverse events: NR	
Rinne, 1980	Inclusion: Stable spasticity (≥ 1 yr) due to MS or myelopathy Exclusion: None specified	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: 6 wk Provider specialty: NR (presumably neurologist) Location: 1 site in Turku, Finland	No. of patients randomized: 30 (all MS) Dropouts: 4 Completed: 26 Age (mean ± SD): Tizanidine: 42 ± 3 Diazepam: 40 ± 2 Baseline EDSS: NR	1) Tizanidine PO 2-mg capsules (n = 15); dose gradually increased (at 2-wk intervals) to maximum of nine capsules (18 mg) daily, taken in three divided doses; treatment lasted 6 wk 2) Diazepam PO 2.5-mg capsules (n = 15); dose gradually increased (at 2-wk intervals) to maximum of nine capsules (22.5 mg) daily, taken in three divided doses; treatment lasted 6 wk	1) Symptom-specific functional status/ quality-of-life outcomes: NR 2) Physical functioning: Muscle tone (Ashworth scale) Definition of "improvement": Marked, moderate or slight improvement on scale including no change and deterioration, based on muscle tone Proportion of patients with "improvement": Tizanidine 10/16 (63%) Diazapam 9/15 (60%) Other (non-improvement) outcomes: 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: AEs reported by 10/15 (67%) on tizanidine and 12/15 (80%) on diazepam Muscle weakness, drowsiness required withdrawal in 4 patients (diazepam) Overall tolerance was significantly better on tizanidine than diazepam ($p < 0.05$)	Article describes three separate trials. Trials 1 and 3 included patients with MS and chronic myelopathy; neither reported results separately for patients with MS. Results summarized here are for Trial 2, which included only patients with MS. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes
Rossini, Pasqualetti, Pozzilli, et al., 2001	Inclusion: Primary and secondary clinically definite MS; stable neurological deficits for ≥ 2 mo Exclusion: History of previous epileptic	RCT (crossover, double-blind, single-center) Duration of study treatment/follow up: 6 mo with each treatment,	No. of patients randomized: 54 Dropouts: 5 Completed: 49 (43 secondary progressive, 6	1) 4-aminopyridine (4-AP) 8 mg taken orally 4 times per day for 6 mo (dose gradually raised to this level over 1st mo) 2) Placebo for 6 mo	1) Symptom-specific functional status/ quality-of-life outcomes: Fatigue Severity Scale (FSS) Definition of "improvement": None Proportion of patients with "improvement": NA	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	seizures; EEG epileptiform activity; treatment with corticosteroids or immunosuppressants in previous 60 days	12 mo total (no run-in described, no washout between treatments) Provider specialty: NR (presumably neurologists) Location: 1 site in Rome, Italy	primary progressive) Age (mean ± SD; n = 49 completers): 43.9 ± 8.9 Baseline EDSS (mean ± SD; n = 49 completers): 6.2 ± 0.8	No washout between treatment periods	Other (non-improvement) outcomes: No significant difference in FSS improvements between 4-AP and placebo (p = 0.19) 2) Physical functioning: EDSS Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: EDSS Mean Difference ± SD Placebo -0.05± 0.37 4-AP -0.05± 0.50 p = NS Similarly no significant difference for any of the EDSS Functional Systems (FS) 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: None observed	Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes *Crossover trials only:* Period or carry-over effects? No Washout period? No No. of patients in each sequence clearly described? Yes Were patients who did not complete all of the periods excluded from the analysis? Yes
Rudick, Breton, and Krall, 1987	Inclusion: Definite MS by Schumacher criteria; at least grade-3 spasticity (Ashworth Scale) or spasms associated with significant discomfort or functional impairment Exclusion: Epilepsy; significant medical illnesses	RCT (crossover, double-blind, single-center/ multicenter) Duration of study treatment/follow up: 4 wk with each treatment; 12 wk total (two 4-wk treatment periods, 2-wk run-in, 2-wk	No. of patients randomized: 32 Dropouts: 7 Completed: 25 Age (mean, with range): 45.3 (24-67) Baseline EDSS (mean ± SD): 6.3	1) Progabide, dose increased to 30 mg/kg/ day over 10 days, then to 45 mg/kg/day over 10 days of weeks 3-4; treatment lasted total of 4 wk 2) Placebo for 4 wk 2-wk washout between treatment periods	1) Symptom-specific functional status/ quality-of-life outcomes: Ashworth Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Ashworth Baseline 10.3 Progabide 8.0 Placebo 9.6	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes *Crossover trials only:* Period or carry-over effects? No

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
		washout) Provider specialty: NR (presumably neurologists) Location: 1 site in Rochester, NY	± 1.7		P < 0.01 progabide vs placebo Measure p-value Timed 8-meter walk 0.62 Zip-a-garment test 0.45 Dial-a-phone test 0.74 Pick-up-coins test 0.25 Spasm count 0.28 Reflex scores 0.20 Arm+leg power 0.77 2) Physical functioning: EDSS Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: No significant change 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: 8 serious AEs included fever and weakness or transaminase elevation (associated with rash, hepatomegaly or fever)	Washout period? Yes (2 wk) No. of patients in each sequence clearly described? Yes Were patients who did not complete all of the periods excluded from the analysis? Yes
Sachais, Logue, and Carey, 1977	Inclusion: Spasticity secondary to MS; inpatients or outpatients; age ≥ 18; no muscle relaxant, anti-hypertensive, or psychoactive drugs for at least 7 days prior to start of trial Exclusion: Evidence	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: 5 wk Provider specialty: Neurologists	No. of patients randomized: 166 Dropouts: 60 Completed: 106 Age (mean [with range], completers): Baclofen: 43 (20-	1) Baclofen PO (n = 85). Dosing for *inpatients:* Wk 1: 10 mg three times per day for 3 days, 15 mg three times per day for 4 days Wk 2: 20 mg three times per day Wk 3-5: 1-2 10-mg	1) Symptom-specific functional status/ quality-of-life outcomes: impairment of sexual performance (4-point scale); interference with daily activities (4-point scale); overall disability (6-point scale) Definition of "improvement": None Proportion of patients with "improvement": NA	Large numbers of patients were excluded from analysis due to use of "disallowed" medications, presumably to treat spasticity symptoms QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	or history of renal, hepatic, or active GI disease; clinically evident joint contractures; psychiatric illness unrelated to MS; seizure disorders; drug or alcohol abuse; clinically significant lab abnormalities; pregnant and nursing women and those likely to become pregnant	Location: 16 sites in US	64) Placebo: 43 (21-65) Baseline EDSS: NR	tablets could be added to daily dose as needed; total daily dose not to exceed 80 mg Dosing for *outpatients:* Wk 1: 5 mg three times per day for 3 days, 10 mg three times per day for 4 days Wk 2: 15 mg three times per day for 3 days, 20 mg three times per day for 4 days Wk 3-5: One or two 10-mg tablets could be added to daily dose as needed; total daily dose not to exceed 80 mg 2) Placebo (n = 81)	Other (non-improvement) outcomes: Baclofen / Placebo / p-value Sex perf -0.13 / +0.09 / NS ADLs -0.16 / -0.16 / NS Overall disability -0.36 / -0.25 / NS 2) Physical functioning: MD rated flexor spasm pain, frequency (5-point scale); muscle tone (5-point scale) during flexion and extension at ankle, knee and hip; patellar reflexes, right and left (5-point scale); global severity (6-point scale) Definition of "improvement": MS assessment Proportion of patients with "improvement": Baclofen / Placebo / p Flexor spasms 17 (42%) / 6 (16%) / < 0.02 Ankle clonus 12 (27%) / 5 (11%) / NS Other (non-improvement) outcomes: Baclofen / Placebo / p-value Flex spasm Pain -1.1 / -0.08 / < 0.001 Freq -0.63 / -0.14 / < 0.05 Musc tone Ank flex -0.39 / -0.04 / < 0.005 Ank ext -0.45 / -0.21 / NS Knee f -0.46 / -0.11 / < 0.01 Knee e -0.50 / +0.02 / < 0.001 Hip abd -0.34 / -0.21 / NS Hip ext -0.33 / -0.12 / NS Reflexes L knee -0.60 / +0.04 / < 0.005 R knee -0.70 / -0.02 / < 0.001 Global -0.26 / -0.19 / NS 3) Cognitive functioning: Depression; euphoria, irritability (4-point scale) Definition of "improvement": None	Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Mental state Baclofen Placebo p-value Depression -0.23 -0.21 NS Euphoria -0.13 -0.37 NS Irritability -0.26 -0.68 NS 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: Somnolence occurred in 75% of baclofen-treated and 36% of placebo-treated patients. Vertigo, weakness, urinary frequency, nausea, vomiting and constipation were other frequent AEs that were more common in baclofen- than placebo-treated patients.	
Sawa and Paty, 1979	Inclusion: Clinically definite MS or chronic myelopathy (presumed MS); otherwise well Exclusion: Use of drugs that could affect muscle tone (e.g., diazepam or steroids) in previous 7 days	RCT (crossover, double-blind, single-center) Duration of study treatment/follow up: 3 wk with each treatment, 7 wk total (no run-in described, two 3-wk treatment periods, 1-wk washout) Provider specialty: NR (presumably neurologists) Location: 1 site in London, Ontario, Canada	No. of patients randomized: 21 Dropouts: 3 Completed: 18 Age (mean, reported only by sex): Men (n = 15): 49 Women (n = 6): 36 Baseline EDSS: NR	1) Baclofen 10 mg tablets; dose gradually increased from 15 mg per day (three 5-mg doses) to 60 mg per day, or until intolerable side effects resulted; treatment continued for 3 wk 2) Placebo for 3 wk 1-wk washout between treatment periods	1) Symptom-specific functional status/ quality-of-life outcomes [describe scale/instrument used]: Definition of "improvement": None Proportion of patients with "improvement": 13/18 exhibited an objective improvement in spasticity on baclofen; none on placebo Other (non-improvement) outcomes: 2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: Withdrawals 1 due to weakness (baclofen)	No quantitative data presented and no statistical comparison between groups QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes *Crossover trials only:* Period or carry-over effects? Not discussed Washout period? Yes (1 wk) No. of patients in each sequence clearly described? No Were patients who did not complete all of the periods excluded from the

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					Reported AEs Sedation 6 (29%) Headache 3 (14%) Mood changes 4 (19%) Dizziness 2 (10%) Weakness 3 (14%) Nausea 5 (24%) Vomiting 2 (10%) Abdominal pain 2 (10%) Malaise 2 (10%)	analysis? Unclear
Schiffer, Herndon, and Rudick, 1985	Inclusion: Confirmed MS according to Poser criteria; episodes of involuntary laughing or weeping Exclusion: None specified	RCT (crossover, double-blind, single-center) Duration of study treatment/follow up: 30 days with each treatment; total approxi-mately 6 wk (two 30-day treatment periods, 1-wk run-in; 1-wk washout) Provider specialty: NR (neurologists and psychiatrists) Location: 1 site in Rochester, NY	No. of patients randomized: 17 Dropouts: 5 Completed: 12 (5 relapsing, 7 progressive) Age (mean, with range; n = 12 completers): 44.3 (22-67) Baseline EDSS: NR; 5/12 completers not ambulatory	1) Amitriptyline; initial dose 25 mg per day, increased to 75 mg per day over first 5 days; mean dose, 57.8 mg per day, with no patient exceeding 75 mg per day; treatment continued for 30 days 2) Placebo for 30 days 1-wk washout between treatment periods	1) Symptom-specific functional status/ quality-of-life outcomes: NR 2) Physical functioning: NR 3) Cognitive functioning: No. episodes of pathological laughing or crying; Beck Depression Inventory; Hamilton Rating Scale for Depression Definition of "improvement": Not reported Proportion of patients with "improvement": 8/12 (67%) on amitriptyline 1/12 (8%) on placebo Other (non-improvement) outcomes: No significant change in BDI or HRSD 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: Drowsiness and dry mouth requiring reduction of dosage in 4/8 responders	One-tailed statistical tests for effectiveness of drug QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? No *Crossover trials only:* Period or carry-over effects? No Washout period? Yes (1 wk) No. of patients in each sequence clearly described? No Were patients who did not complete all of the periods excluded from the analysis? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Schiffer and Wineman, 1990	Inclusion: Definite MS according to Poser criteria; definite major depressive disorder (diagnosis made in accordance with the Research Diagnostic Criteria and the Schedule for Affective Disorders and Schizophrenia) Exclusion: Depressive episode occurred during period of acute corticosteroid administration; current use of psychotropic drugs	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: 30 days Provider specialty: NR Location: 1 site in Rochester, NY	No. of patients randomized: 32 Dropouts: 4 Completed: 28 (completed at least 2 wk of 30-day protocol; mean study duration over 29 days in both groups) Age (mean, with range): Desipramine: 37.8 (22-55) Placebo: 39.1 (22-75) Baseline EDSS (mean ± SD): Desipramine: 4.4 ± 2.1 Placebo: 4.8 ± 2.4	1) Desipramine + psychotherapy (n = 14); desipramine PO 25 mg; dose raised at 2-day intervals over first 7 days to 6 capsules per day (3 twice per day) or to maximum dose permitted by side effects; serum levels checked and dose adjustments made during 2nd week; psychotherapy administered in weekly 45-min sessions; treatment continued for total of 30 days 2) Placebo + psychotherapy (as above) for 30 days (n = 14)	1) Symptom-specific functional status/ quality-of-life outcomes: NR 2) Physical functioning: NR 3) Cognitive functioning (BDI, HRSD): Definition of "improvement": Blind clinical judgment of "sufficient improvement in depressive features so as to permit a definite improvement in psychosocial function" Proportion of patients with "improvement": 11/13 desipramine 6/14 placebo p = 0.05, Fisher's exact test Other (non-improvement) outcomes: BDI Baseline End Desipramine 18.4± 5.9 11.4± 8.0 Placebo 18.6± 8.6 15.5± 11.3 p = 0.16 HRSD Baseline End Desipramine 28.3± 5.8 12.7± 5.8 Placebo 24.9± 8.6 20.1± 13.6 p = 0.02 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: 12/14 desipramine patients reported AEs; commonly postural hypotension, dry mouth (n = 5), constipation 7/14 placebo patients reported AEs; dry mouth (n = 5)	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? No Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? No

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Schmidt, Lee, and Spehlmann, 1975 **and** **Schmidt, Lee, and Spehlmann, 1976**	Inclusion: MS; moderate or severe spasticity clearly interfering with physical function, but relatively less ataxia or weakness; condition stable for ≥ 6 mo; no ACTH or corticosteroids in previous 6 mo; no muscle relaxants or sedatives in previous 2 wk Exclusion: Severe dementia, ataxia, or tremor	RCT (crossover, double-blind, single-center) Duration of study treatment/follow up: 4 wk with each treatment, 12 wk total (2-wk run-in, two 4-wk treatment periods, 2-wk washout) Provider specialty: Neurologists Location: 1 site in Evanston, IL	No. of patients randomized: 46 Dropouts: 4 Completed: 42 Age: NR Baseline DSS: Mean, 5.5	1) Dantrolene sodium PO; dose gradually increased according to a fixed schedule in three increments over a 2-wk period (low dose); this process then continued over another 2-wk period (high dose); usual doses at end of low- and high-dose titrations were 25 mg and 75 mg four times per day, respectively (reductions permitted for side effects) 2) Diazepam PO; gradually increased over two 2-wk periods, as above; usual doses at end of low- and high-dose titrations were 2 mg and 5 mg four times per day, respectively (reductions permitted for side effects) 2-wk washout between treatment periods	1) Symptom-specific functional status/ quality-of-life outcomes: NR 2) Physical functioning: Spasticity, deltoid strength, hip flexor strength, station stability, hand coordination, hand speed, foot speed, stretch reflexes, clonus, and walking speed. Score calculations for each function by summing individual values from R and L sides and multiple trials. Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Lo DS / Hi DS / Lo DZ / Hi DZ Spasticity 10.0 / 9.54 / 9.40 / 9.14 Deltoid str 48.5* / 47.4# / 49.6 / 50.2 Hip flex 120* / 122 / 156 / 127 Hand coord 145 / 147 / 141 / 134* Stability 43.2 / 45.9* / 39.1 / 34.1 Hand speed 238 / 250 / 239 / 227 Foot speed 242 / 240 / 233 / 226 Reflexes 20.5* / 19.4* / 22.5 / 22.1 Clonus 3.77 / 3.15 / 3.50 / 3.41 Walk speed 11.3 / 10.6 / 13.8 / 17.1 *P < 0.05 compared to corresponding dose of comparator drug #p < 0.10 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: Dantrolene / Diazepam / p Impaired gait 52% / 75% / NS Drowsiness 31% / 67% / NS Imbalance 17% / 36% / NS	Multiple comparisons without statistical correction increases likelihood of finding significant associations by chance QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? No *Crossover trials only:* Period or carry-over effects? Not discussed Washout period? Yes (2 wk) No. of patients in each sequence clearly described? No Were patients who did not complete all of the periods excluded from the analysis? Unclear

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					Incoordination 10% 29% NS At least 1 of 4 withdrawals was due to AEs	
Smith, Birnbaum, Carter, et al., 1994	Inclusion: Stable spasticity secondary to MS; spasticity severe enough to cause significant discomfort of functional impairment and to produce score ≥ 2 on Ashworth Scale for muscle tone or ≥ 2 for muscle spasm type and frequency in most severely affected muscle group; age 18-70 Exclusion: Use of any other muscle relaxant or drugs with muscle-relaxant properties; current or recent (within 3 mo) acute MS relapse; fibrous contractures	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: 16 wk total (2-wk run-in, 3-wk dose titration, 9 wk at plateau dose, 1-wk dose tapering, followed by post-treatment evaluation) Provider specialty: Neurologists Location: 14 sites in US	No. of patients randomized: 257 Dropouts: 98 Completed: 159 (220 analyzable) Age (mean ± SD; n = 220 analyzable): Tizanidine: 44.5 ± 9.4 Placebo: 46.1 ± 9.6 Baseline EDSS: NR	1) Tizanidine PO, dose titrated over 3 wk from 2 mg/day to maximum of 36 mg/day (12 mg three times daily); optimal dose continued through plateau phase (9 wk); dose then tapered over 1 wk and discontinued (n = 111) 2) Placebo (n = 109)	1) Symptom-specific functional status/ quality-of-life outcomes: Ashworth Definition of "improvement": Decrease in total Ashworth Score Proportion of patients with "improvement": Tizanidine /111 (58%) Placebo /109 (60%) P = 0.83 Other (non-improvement) outcomes: Ashworth adj. mean change (± SD) Tizanidine -2.03 ± 7.22 Placebo -2.73 ± 7.17 P = 0.46 Spasms & clonus response ratio (% change): Tizanidine -0.44± 0.45 -61.1± 118 Placebo -0.26± 0.44 -41.0± 102 P = 0.028 p = NS 2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: 101 (91%) tizanidine 66 (61%) placebo Dry mouth, asthenia, somnolence, dizziness, increased SGOT/AST Serious AE – hepatitis (n = 1), hallucinations (n = 1) Discontinuations:	36 patients disqualified because of inadvertent contamination – placebo patients accidentally given active drug QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					14/111 (13%) tizanidine 6/109 (6%) placebo	
Smolenski, Muff, and Smolenski-Kautz, 1981	Inclusion: MS; hospitalized; stable spasticity for ≥ 2 mo Exclusion: History or evidence of cardiac, renal, or hepatic disease; severe hypertension; epilepsy; chronic alcoholism; diabetes; overt psycho-pathology	RCT (parallel-group, double-blind, single-center) Duration of study treatment/follow up: 6 wk Provider specialty: NR (presumably neurologists) Location: 1 site in Bern, Switzerland	No. of patients randomized: 21 Dropouts: 0 Completed: 21 Age (mean ± SD): Tizanidine: 53 ± 11 Baclofen: 55 ± 10 Baseline EDSS: NR	1) Tizanidine PO 4 mg capsules; dose initiated at 2 capsules per day and gradually increased during first few weeks to optimal level (usually between 3 and 6 capsules per day in 3 divided doses); treatment continued for 6 wk (n = 11) 2) Baclofen PO 10 mg capsules; dose initiated at 2 capsules per day and gradually increased during first few weeks to optimal level (usually between 3 and 6 capsules per day in 3 divided doses); treatment continued for 6 wk (n = 10)	1) Symptom-specific functional status/ quality-of-life outcomes: Muscle strength, Ashworth, spasms Definition of "improvement": Not described Proportion of patients with "improvement": Ashworth (muscle tone) Reported by muscle group Tizanidine Baclofen Left leg 8/11 9/10 Right leg 6/11 8/10 Left foot 8/11 8/10 Right foot 8/10 8/10 Spasms (reported by muscle group): Tizanidine Baclofen Flex left leg 6/8 4/7 Flex right leg 5/8 6/8 Ext left leg 7/9 6/8 Ext right leg 7/9 8/9 Abd left leg 4/7 5/8 Abd right leg 4/7 7/9 Other (non-improvement) outcomes: Overall spastic state, spasms and clonus were similarly improved with both medications 2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: Tizanidine (tiredness, weakness, dry mouth, ataxia)	Multiple measures QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					Baclofen (weakness, dry mouth, nausea, pyrosis) No withdrawals due to AEs	
Snow, Tsui, Bhatt, et al., 1990	Inclusion: Stable, chronic MS; chair- or bed-bound (EDSS 8.0-9.5); resident at one of two long-stay institutions; spastic contraction of adductor muscles that interfered with sitting, positioning in bed, cleaning, or urethral catheterization; not currently taking anti-spastic medication (most unresponsive in past) Exclusion: None specified	RCT (crossover, double-blind, two-center) Duration of study treatment/follow up: Single injections given for each treatment, with follow up at 2 and 6 wk; 3 mo between two treatment periods/injections Provider specialty: NR (presumably neurologists) Location: 2 sites in Vancouver, British Columbia, Canada	No. of patients randomized: 10 Dropouts: 1 Completed: 9 Age (mean, with range): 40.2 (23-61) Baseline EDSS: 8.0 to 9.5	1) Botulinum-A toxin, single IM injection of 400 mouse units (160 ng) 2) Placebo injection 3 mo between injections	1) Symptom-specific functional status/ quality-of-life outcomes: Spasticity score = Ashworth (muscle tone)+spasm frequency; Hygiene score. Definition of "improvement": None defined Proportion of patients with "improvement": Other (non-improvement) outcomes: Spasticity score @ 6 wk Botulinum 7.9± 4.9 4.7± 4.3 Placebo 6.8± 5.3 7.1 ± 4.8 p-value 0.009 Hygiene score @ 6 wk better for botulinum than placebo (p = 0.02) 2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: NR	Small preliminary study; severely spastic patients with very high EDSS scores QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? No Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes *Crossover trials only:* Period or carry-over effects? No Washout period? Yes (3 mo) No. of patients in each sequence clearly described? Yes Were patients who did not complete all of the periods excluded from the analysis? Yes
Solari, Filippini, Gasco, et al., 1999	Inclusion: Clinically definite or laboratory-supported MS; EDSS 3.0-6.5; age 18-65 Exclusion: 1 or more exacerbations in preceding 3 mo; cognitive impairment likely to interfere with	RCT (parallel-group, single-blind [evaluating physician only], single-center) Duration of study treatment/follow up: Inpatient program lasted 3	No. of patients randomized: 50 (11 relapsing-remitting, 8 primary progressive, 31 secondary progressive) Dropouts: 5	1) Inpatient physical rehabilitation program (n = 27); twice daily exercise periods of 45 min each for 3 consecutive wk; for patients with EDSS ≤ 4.5, main goals were normalization of postural control,	1) Symptom-specific functional status/ quality-of-life outcomes: NR 2) Physical functioning: EDSS; Functional Independence Measure (FIM) motor domain Definition of "improvement": EDSS – 1-step improvement FIM motor – 2- or more step improvement	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? No Patients blinded? No Investigators blinded? No Outcome assessors blinded? Yes No. of withdrawals in each group stated?

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	study adherence (Mini-Mental State Examination score ≤ 23.8, after adjustment for age and education); history of cardio-vascular, respiratory, orthopedic, psychiatric, or other medical conditions precluding participa-tion; pregnancy; treatment with immunosuppres-sants, interferons, copolymers, 4-aminopyridine, or experimental drugs in previous 6 mo; rehabilitation therapy in previous 3 mo	wk; patients followed for total of 15 wk Provider specialty: Neurologists and physiotherapists Location: 1 site in Milan, Italy	Completed: 45 Age (mean ± SD): Rehab: 44.6 ± 10.2 Control: 44.9 ± 10.6 Baseline EDSS (median, with range): Rehab: 5.5 (3.0-6.5) Control: 5.5 (3.5-7.0)	facilitation of normal gait pattern, increasing range of movement, and maximizing muscle power and endurance; for those with EDSS > 4.5, program also included instruction in use of mobility aids and orthoses and refinement of compensatory strategies. Patients given home exercise program at conclusion of inpatient program. 2) Home exercise program (control) (n = 23)	Proportion of patients with "improvement": EDSS 1/27 study group; 0/23 control group FIM motor Intervention Control 3 weeks 13/27 (48%) 2/23 (9%) (p = 0.994) 9 weeks 12/27 (44%) 1/23 (4%) (p = 0.001) Other (non-improvement) outcomes: 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: SF-36 Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: SF-36 component Intervention Control p 3wk Physical 3.8± 6.7 3.3± 8.4 0.7 Mental 5.2± 7.0 -0.77± 7.3 0.008 9 wk Physical 3.7± 10 1.6± 12 Mental 4.8± 9.9 -5.3± 15 15 wk Physical 3.2± 6.5 0.26± 7.9 Mental 2.1± 9.7 -1.8± 7.8 6) Adverse events: NR	Yes
Stien, Nordal, Oftedal, et al., 1987	Inclusion: Definite MS (McAlpine 1972); resident at one of several nursing homes for neurological patients; in stable phase of the	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: 6 wk	No. of patients randomized: 40 Dropouts: 2 Completed: 38	1) Tizanidine 4 mg capsules (n = 19); dose gradually increased over first 2 wk to maximum of 5 capsules per day (20 mg, given in 3 divided	1) Symptom-specific functional status/ quality-of-life outcomes: Functional disability (Pedersen) Definition of "improvement": None Proportion of patients with "improvement":	Study power too low to detect differences between these drugs QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	disease for ≥ 3 mo Exclusion: Mental diseases; overt signs of dementia	Provider specialty: Neurologists Location: Multiple sites (number NR) in Oslo, Norway	Age (median, with range; n = 38 completers): Tizanidine: 50 (29-70 Baclofen: 45 (26-66) Baseline EDSS: NR	doses); during last 4 wk, daily dose carefully adjusted for each patient, weighing anti-spastic effect vs. side effects; mean daily dose, 23 mg; range, 4-36 mg 2) Baclofen 10 mg capsules (n = 21); dose gradually increased over first 2 wk to maximum of 5 capsules per day (50 mg, given in 3 divided doses); during last 4 wk, daily dose carefully adjusted for each patient, weighing anti-spastic effect vs. side effects; mean daily dose, 59 mg; range, 20-90 mg	NA Other (non-improvement) outcomes: Neither tizanidine nor baclofen induced significant changes in functional disability (Pedersen) [data not shown] 2) Physical functioning: Tendon reflexes; muscle tone (Ashworth scale); provoked or spontaneous spasm activity; muscle strength in extremities; Kurtzke's scale Definition of "improvement": Not described Proportion of patients with "improvement": Tizanidine Baclofen p-value Clonus 7/18 (39%) 9/20 (45%) NS Musc tone 13/18 (72%) 13/20 (65%) NS Spasms 12/18 (67%) 13/20 (65%) NS Strength 2/18 (11%) 2/20 (10%) NS Other (non-improvement) outcomes: Neither tizanidine nor baclofen induced significant changes in neurological disability (Kurtzke's scale) [data not shown]. 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: AEs were "mild" and dose-dependent Tizanidine n = 6 (tiredness, weakness, sleepiness, dry mouth) Baclofen n = 5 (weakness, tiredness) Withdrawals due to AE: tizanidine (n = 1) subjective stiffness; baclofen (n = 1) gastroenteritis	Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Stuifbergen, Becker, Blozis, et al., 2003	Inclusion: Physician-diagnosed MS for at least 6 mo; female sex; age 20-70 Exclusion: Pregnancy; concurrent medical conditions for which changes in exercise and diet would be contraindicated	RCT (parallel-group, open-label, multicenter) Duration of study treatment/follow up: Active treatment lasted 5 mo; patients followed up for total of 8 mo Provider specialty: Clinical nurse specialist and woman with MS (intervention facilitators), dietician, fitness instructor, nurse practitioner associated with a woman's wellness center, and a counselor Location: Outpatients recruited from two large metropolitan areas	No. of patients randomized: 142 Dropouts: 29 failed to provide minimal data needed to be included in analysis Completed: 113 Age: Mean ± SD, 45.8 ± 10.1; range, 21-70 Baseline EDSS: NR	1) Wellness intervention (n = 56); two phases – a) an educational and skill-building lifestyle change program (8 sessions over 8 wk that presented information, guided participants in self-assessment of behaviors, resources, and barriers, and supported specific strategies aimed at building self-efficacy for health behaviors; b) supportive telephone follow-up (biweekly calls for 3 mo) 2) Usual care (n = 57)	1) Symptom-specific functional status/ quality-of-life outcomes: NR 2) Physical functioning: NR 3) Cognitive functioning [describe scale/ instrument used]: Definition of "improvement": Proportion of patients with "improvement": Other (non-improvement) outcomes: Self-rate [results?] 4) Work or employment outcomes: Proportion employed Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: By month 8, women in the intervention group were more likely to be employed than women in the control group ($p < 0.05$) 5) Generic quality-of-life outcomes: Self-Rated Abilities Scale (measure of self-efficacy); Barriers Scale; Personal Resources Questionnaire (measure of social support); Health Promoting Lifestyle Profile-II (HPLP-II); SF-36 Definition of "improvement": Proportion of patients with "improvement": Other (non-improvement) outcomes: Control Interv p-value Self-efficacy 84± 19 94± 14 < 0.01 Barriers 32± 8.4 31± 7.5 NS PRQ 143± 22 145± 22 NS	Authors acknowledge that population was a convenience sample and may reflect selection bias; may not be representative of MS population at large because of recruitment through MS Society. Such women may be more interested in health behaviors than other women with MS. QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? No Patients blinded? No Investigators blinded? No Outcome assessors blinded? No No. of withdrawals in each group stated? No

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
					HPLP-II Total 147± 23 158± 22 < 0.01 SF-36 scales PF 40±31 51± 29 NS RP 41± 42 47± 44 NS BP 64± 28 67± 25 < 0.05 GH 60± 24 57± 25 NS VT 41± 22 44± 22 NS SF 70± 24 70± 26 NS RE 66± 42 76± 36 NS MH 71± 20 75± 15 < 0.05 6) Adverse events: NR	
United Kingdom Tizanidine Trial Group, 1994	Inclusion: Spasticity secondary to clinically definite, laboratory-supported, or probable MS; stable disease during previous 1 mo; no concomitant neurological illness likely to alter muscle tone; age 18-75 Exclusion: Use of immunosuppressant drugs during previous 1 mo or cortico-steroids during previous 3 mo; uncontrolled hypertension (SBP > 180 mmHg, DBP > 120 mmHg) or hypotension (SBP < 90 mmHg, DBP < 60 mmHg); systemic disease; abnormalities on routine clinical lab tests; active	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: 12 wk treatment (3 wk dose titration, followed by 9 wk at maximum tolerated dose), plus 1-wk tapering period; last follow up visit at 14 wk Provider specialty: NR Location: 16 sites throughout the UK	No. of patients randomized: 187 (102 clinically definite MS, 58 laboratory-supported, 27 probable) Dropouts: 32 excluded from completers' analysis for more than minor protocol violations; 51 withdrew prematurely Completed: 155 included in completers' analysis; 136 completed entire study Age (mean ± SD): 47 ± 9 Baseline EDSS: NR	1) Tizanidine PO (n = 94), titrated over a 3-wk period between 2 and 36 mg daily to the maximum tolerated dose; this dose then maintained for 9 more weeks; dose then tapered over 1-wk period 2) Placebo (n = 93) (with dose titration, as above)	1) Symptom-specific functional status/ quality-of-life outcomes: Intermediate motor skills (turning, lying, and transfer); upper extremity functions; ADL (items from Kurtzke Incapacity Status Scale); impact of spasticity on quality of life (5-point scale) Definition of "improvement": Not described Proportion of patients with "improvement": Tizan Pbo p-value Intermed fn 20% 10% NS Upper limb fn 6% 5% NS Impact on PT 40% 21% NS Nursing care 22% 4% 0.09 Other (non-improvement) outcomes: 2) Physical functioning: Muscle tone (Ashworth scale) Definition of "improvement": Decrease by at least 1 point on Ashworth Proportion of patients with "improvement": Tizanidine 67/94 (71%) Placebo 46/93 (50%) Other (non-improvement) outcomes:	Used intention-to-treat analysis QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	bedsores, infection, or contractures				ITT analysis Muscle tone EDSS Baseline Week 12 change Tizanidine 1.85± 9.4 14.6± 10.1 0.1 Placebo 16.8± 11.1 15.3± 10 0 P-value < 0.004 NS Strength Baseline Week 12 change Tizanidine 71± 16 73± 16 +4 Placebo 72± 14 74± 13 +3 P-value NS Spasms (freq) Baseline Week 12 change Tizanidine 6.3± 6.6 5.5± 7.0 -13 Placebo 5.2± 5.8 4.4± 6.0 -15 P-value NS DTRs Baseline Week 12 change Tizanidine 18± 7.1 16± 7.1 -9 Placebo 17± 6.5 17± 6.8 -4 P-value NS Timed walk (sec for 8m) Baseline Week 12 change Tizanidine 20± 20 21± 34 +4 Placebo 28± 31 25± 26 -10 P-value NS 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: Tizanidine Placebo Total no. AEs 669 261 No. pts with AEs 82 (87%) 57 (61%) Dropouts due to AEs 12 (13%) 5 (5%) Dry mouth; drowsiness, tiredness	

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Vahtera, Haaranen, Viramo-Koskela, et al., 1997	Inclusion: Clinically definite MS by Poser criteria; in stable phase of disease; EDSS ≤ 6.5; current symptoms of lower urinary tract disorder; post-void residual volume ≤ 100 mL on ultrasound Exclusion: Pregnancy; cardiac pacemaker or any metallic implant near the treated area; history of pelvic malignancy; dementia; any nervous system disorder other than MS	RCT (parallel-group, open-label, single-center) Duration of study treatment/follow up: 6.5 mo Provider specialty: NR Location: 1 site in Masku, Finland	No. of patients randomized: 80 Dropouts: 0 lost to follow up; in active group, 25/40 exercising regularly at 6 mo, 12/40 exercising irregularly, and 3/40 not exercising at all Completed: 80 (see immediately above on compliance) Age (mean, with range): Active: 43.4 (25-57) Control: 44.2 (26-68) Baseline EDSS (mean, with range): Active: 4.4 (1.0-6.5) Control: 4.3 (1-6.5)	1) Pelvic floor rehabilitation (n = 40); consciousness of action of pelvic floor muscles stimulated using electrical stimulation at 6 sessions over 2 wk; at final session, patients taught by biofeedback to exercise pelvic floor muscles and advised to continue these exercises 3-5 times per week for at least 6 mo 2) No-treatment control (n = 40)	1) Symptom-specific functional status/ quality-of-life outcomes [describe scale/instrument used]: Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Incontinence and nocturia at week 3 and months 2 and 6 were significantly less frequent in treatment than control group ($p < 0.05$) No differences in frequency of acute UTIs Urinary symptom related handicap at month 6 lower for treatment than control (traveling, social shame, need of diapers) ($p < 0.05$) 2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: None reported	Uncertain validity of symptom measures; multiple assessments and statistical tests; potential for type I error QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? No Patients blinded? No Investigators blinded? No Outcome assessors blinded? No No. of withdrawals in each group stated? Yes
Valiquette, Herbert, and Meade-D'Alisera, 1996	Inclusion: Clinically definite or laboratory-supported definite MS by Poser criteria; relapsing-remitting or progressive forms of disease; MS in remission for at least 3 mo; 2 or more	RCT (crossover, double-blind, single-center) Duration of study treatment/follow up: 2 wk with each treatment; 6 wk total (2-wk	No. of patients randomized: 17 (5 relapsing-remitting, 4 relapsing-progressive, 8 chronic progressive)	1) Desmopressin administered as a nasal spray, one 10-µg dose per day at bedtime for 2 wk 2) Placebo nasal spray for 2 wk	1) Symptom-specific functional status/ quality-of-life outcomes: Proportion of nights with nocturia; proportion of nights with incontinence; number of episodes of nocturia per night; maximum uninterrupted sleep hours Definition of "improvement": None	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	episodes of nocturia in typical night or (for patients with limited mobility) any number of micturitions or episodes of incontinence per night; age 18-70 Exclusion: Evidence or history of hypertension, thrombotic events, or cardiovascular, thyroid, or renal disease; use of pulsed steroid therapy or short course of immuno-suppressive therapy in previous 3 mo	run-in, two 2-wk treatment periods, no washout) Provider specialty: NR (neurologists?) Location: 1 site in West Haverstraw, NY	Dropouts: 6 Completed: 11 Age (mean, with range): 48.9 (26-70) Baseline EDSS (mean, with range): 6.7 (2.5-8.5)	No washout between treatment periods	Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Nocturia, mean* Mean diff -0.74 p-value < 0.01 Incontinence -0.36 0.08 Nocturia, freq -2.2 < 0.01 Max uninterrupted Sleep (hrs)* 4.28 < 0.01 *Carry-over effect observed, only period 1 data analyzed. 2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: Hyponatremia requiring discontinuation (n = 4)	No. of withdrawals in each group stated? No *Crossover trials only:* Period or carry-over effects? Yes Washout period? No No. of patients in each sequence clearly described? Yes Were patients who did not complete all of the periods excluded from the analysis? Yes
Wassem and Dudley, 2003	Inclusion: MS Exclusion: None specified	RCT (parallel-group, open-label, single-center) Duration of study treatment/follow up: Active treatment lasted 4 wk; patients followed up for total of 4 yr Provider specialty: Advance practice nurses	No. of patients randomized: 27 Dropouts: 11 Completed: 16 Age: Mean, 44; range, 18-54 Baseline EDSS: Mean, 3.36; range, 0-9	1) Intensive outpatient intervention (n = NR); four weekly 2-hr group sessions; included education about MS, instruction in relaxation techniques, and discussion of dietary concerns, symptom management, psychosocial issues, memory and cognitive problems, etc. 2) Usual care (n = NR)	1) Symptom-specific functional status/ quality-of-life outcomes: Fatigue, sleep and pain severity (VAS) Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Fatigue levels were lower for intervention than control at most data collection points (p = 0.09) Sleep disturbance scores were significantly better for intervention compared to control (p = 0.07) Pain levels were not significantly different for intervention compared to control (P = NS)	Study used alpha = 0.10 rather than conventional level of 0.05 for hypothesis testing QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? No Patients blinded? No Investigators blinded? No Outcome assessors blinded? No No. of withdrawals in each group stated? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
		Location: 1 site in Utah			Sum of symptom severity scores improved for intervention compared to control (p = 0.03) 2) Physical functioning: Modified DSS Definition of "improvement": Proportion of patients with "improvement": Other (non-improvement) outcomes: 3) Cognitive functioning: Self-Efficacy for Adjustment Behaviors (SEAB) scale (26 behaviors x 4-point responses ranging from 0 [*no confidence in being able to perform the behavior*] to 4 [*total confidence* …]); Psychosocial Adjustment to Illness Scale-Self-Report (PAIS-SR); Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: SEAB scores were not significantly different for intervention compared to control (p = 0.55) PAIS-SR scores were not significantly different for intervention compared to control (p = 0.72) 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: NR	

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Weinshenker, Penman, Bass, et al., 1992	Inclusion: Clinically definite MS; severe fatigue for ≥ 3 mo; age 18-65 Exclusion: Pregnant or not practicing birth control; epilepsy; psychiatric disease; drug abuse; major medical illness	RCT (crossover, double-blind, two-center) Duration of study treatment/follow up: 5 wk with each treatment, 12 wk total (two 5-wk treatment periods, 2-wk washout) Provider specialty: NR Location: 2 sites in Ontario, Canada	No. of patients randomized: 46 Dropouts: 5 Completed: 41 Age (mean ± SD): 42.6 ± 10.6 Baseline EDSS (mean ± SD): 3.6 ± 2.0	1) Pemoline PO in 18.75-mg capsules; dose gradually increased during first week from 1 capsule (18.75 mg) to maximum of 4 capsules (75 mg) per day; maintenance dose then continued for additional 4 wk 2) Placebo, with dose adjustments as above, for total of 5 wk 2-wk washout between treatment periods	1) Symptom-specific functional status/ quality-of-life outcomes: NR 2) Physical functioning: EDSS; fatigue (50-mm VAS); relief of fatigue (4-point scale) Definition of "improvement": Excellent/good versus fair/poor rating on relief of fatigue Proportion of patients with "improvement": Trend toward better relief of fatigue on pemoline than placebo (p = 0.06) Other (non-improvement) outcomes: All patients remained within 1.0 point on the EDSS score during the course of the study (except for patients who were withdrawn due to exacerbations. No significant difference in fatigue (VAS) between pemoline and placebo. 3) Cognitive functioning: Modified Beck self-rating depression inventory Definition of "improvement": Proportion of patients with "improvement": Other (non-improvement) outcomes: 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: AEs experienced by > 25% while receiving pemoline: Irritability (n = 15); insomnia (12), anorexia (17), and nausea (13).	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? No Concealment of allocation? Unclear Described as "double-blind"? Yes Patients blinded? Yes Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes *Crossover trials only:* Period or carry-over effects? No Washout period? Yes (2 wk) No. of patients in each sequence clearly described? Yes Were patients who did not complete all of the periods excluded from the analysis? Yes

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
Wiles, Newcombe, Fuller, et al., 2001	Inclusion: Definite or probable MS; difficulty walking, but able to walk 5 meters with or without a mechanical aid; not in a current relapse; free of other major general medical or surgical disorders and pregnancy; age ≥ 18 Exclusion: None specified	RCT (crossover, single-blind [assessors only], single-center) Duration of study treatment/follow up: 8 wk with each treatment, 48 wk total (three 8-wk treatment periods, two 8-wk washouts, one 8-wk follow-up period) Provider specialty: Neurophysio-therapists Location: 1 site in Cardiff, UK	No. of patients randomized: 42 Dropouts: 2 Completed: 40 Age: Mean, 47.2; range, 28.2-68.8 Baseline EDSS: Mean, 6.0	1) Home physio-therapy; two 45-min sessions per wk for 8 wk; individualized problem-solving approach, focusing on specific functional activities 2) Hospital outpatient physiotherapy, as above, but focusing on specific facilitation techniques 3) No physiotherapy for 8 wk 8-wk washout period between treatment periods	1) Symptom-specific functional status/ quality-of-life outcomes: Rivermead mobility index; balance time; Walk A; 9-hole peg Definition of "improvement": None Proportion of patients with "improvement": NA Other (non-improvement) outcomes: Treatment None / Hosp / Home Mobil Index: 9.1 ± 3.9 / 10.5 ± 3.5, p < 0.001 / 10.6 ± 2.9, p < 0.001 Bal time: 15.0 ± 13.8 / 19.9 ± 13.2, p = 0.004 / 19.7 ± 13.2, p = 0.001 Walk A: 148 ± 129 / 138 ± 108, p = 0.003 / 138 ± 110, p = 0.002 9-hole peg: 207 ± 85 / 190 ± 69, p = 0.014 / 194 ± 70, p = 0.076 Global Mobility: 46 ± 11 / 44 ± 11, p < 0.001 / 44 ± 14, p < 0.001 2) Physical functioning: NR 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: NR	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? No Patients blinded? No Investigators blinded? No Outcome assessors blinded? Yes No. of withdrawals in each group stated? No *Crossover trials only:* Period or carry-over effects? No Washout period? Yes (8 wk) No. of patients in each sequence clearly described? No Were patients who did not complete all of the periods excluded from the analysis? Yes
Zajicek, Fox, Sanders, et al., 2003	Inclusion: Clinically definite or laboratory-supported MS; stable disease for previous 6 mo (in the opinion of the treating physician); problematic spasticity (Ashworth score ≥ 2	RCT (parallel-group, double-blind, multicenter) Duration of study treatment/follow up: Treatment lasted 14 wk; patients followed	No. of patients randomized: 657 No. treated and included in ITT analysis: 630 (452 secondary progressive, 145 primary	1) Cannabis extract containing delta-9-tetrahydrocannabinol (THC) and cannabidiol PO (n = 211); each capsule contained 2.5 mg of delta-9-THC equivalent, 1.25 mg of cannabidiol, and < 5%	1) Symptom-specific functional status/ quality-of-life outcomes: NR 2) Physical functioning: Ashworth scale – overall (upper and lower extremity); subjective spasticity (improved, same, deteriorated); mobility (10-m walk time) Definition of "improvement": None provided	"There was a degree of unmasking among patients in the active treatment groups" which should have been expected to bias the study toward showing a benefit; may be responsible for a statistically significant subjective effect, but no significant objective effect on spasticity.

Evidence Table 3b. Symptom management and improvement (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Interventions	Outcomes/Results	Comments/Quality Scoring
	in two or more lower limb muscle groups); age 18-64 Exclusion: Ischemic heart disease; active sources of infection; use of medication that could affect spasticity; not able to avoid driving while on study; fixed-tendon contractures; severe cognitive impairment; history of psychotic illness; other major illness; pregnancy; any previous use of delta-9-tetrahydro-cannabinol; use of cannabis in previous 30 days	for an additional (15th) wk Provider specialty: NR (presumably neurologists) Location: 33 neurology and rehabilitation centers in the UK	progressive, 33 relapsing-remitting) Dropouts (from ITT population): 19 Completed: 611 Age (mean ± SD): Cannabis: 50.5 ± 7.6 Delta-9-THC: 50.2 ± 8.2 Placebo: 50.9 ± 7.6 Baseline EDSS: 0-3.5: 3 4-5.5: 23 6-6.5: 299 7-9: 299 NR: 6	other cannabinoids; initiated at one capsule (2.5 mg delta-9-THC equivalent) twice daily, then increased by one capsule twice daily every wk, as tolerated, during 5-wk dose titration period; maximum daily dose 25 mg (10 capsules) 2) Synthetic delta-9-tetrahydrocannabinol (THC) PO (n = 206); initiated at one capsule (2.5 mg) twice daily, then increased by one capsule twice daily every wk, as tolerated, during 5-wk dose titration period; maximum daily dose 25 mg (10 capsules) 3) Placebo, with dose titration as above (n = 213)	Proportion of patients with "improvement": Cannabis extract 61% Delta-9-THC 60% Placebo 46% p = 0.003 Other (non-improvement) outcomes: Ashworth score: No treatment effect overall (p = 0.4); estimated difference in mean reduction in total Ashworth score: Cannabis extract 0.32 (-1.04 to 1.67) Delta-9-THC 0.94 (-0.44 to 2.31) Reduction in 10-m walk time from baseline to visit 7 Cannabis extract 4% (0 to 10%) Delta-9-THC 12% (6 to 21%) Placebo 4% (-2 to 7%) P = 0.015 3) Cognitive functioning: NR 4) Work or employment outcomes: NR 5) Generic quality-of-life outcomes: NR 6) Adverse events: NR	QUALITY ASSESSMENT: Described as "randomized"? Yes Method of randomization clearly described? Yes Concealment of allocation? Yes Described as "double-blind"? Yes Patients blinded? Unclear Investigators blinded? Yes Outcome assessors blinded? Yes No. of withdrawals in each group stated? Yes

Evidence Table 4. Association of clinical findings with work ability

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
Beatty, Blanco, Wilbanks, et al., 1995	Inclusion: Clinically definite MS by Poser criteria; adequate vision to read a newspaper; judged able to complete a 2.5- to 3-hr battery of neuro-psychological tests; age < 65 Exclusion: History of alcohol or drug abuse; serious head injury; learning disability; recent or complicated heart attack; uncontrolled hypertension; metabolic disease; CNS disease other than MS; major psychiatric illness; history of depression (if major episode preceded onset of MS-like symptoms); MS relapse in previous 1 mo	Cross-sectional study Location/recruitment: Patients recruited from practices of collaborating neurologists (n = 50) and from support groups (n = 52) in the areas of Tulsa and Oklahoma City, OK Data collection: Work status self-reported by study participants; not clear how clinical data (medication use, time since diagnosis, etc.) collected; testing described below performed in a single 2.5- to 3-hr session, usually (94% of the time) conducted in patient's home; following tests administered: 1) Beck Depression Inventory 2) Brief test of visual acuity 3) Ambulation Index 4) Handedness inventory 5) Neuropsychological testing in 7 domains: -Verbal ability (Shipley Institute of Living Scale Vocabulary Test) -Attention/	N = 102 Age (mean ± SD): Overall: 44.2 ± 7.8 (range, 29-62) Employed subjects: 39.9 ± 6.1 Retired subjects: 46.8 ± 7.8 Baseline measures of physical and mental functioning: Ambulation Index (mean ± SD): Overall: 3.4 ± 2.6 Employed: 1.8 ± 1.8 Retired: 4.3 ± 2.6 Beck Depression Inventory (mean ± SD): Overall: NR Employed: 10.4 ± 7.5 Retired: 13.4 ± 8.8 Baseline work status: Employed: 38 (33 full-time, 3 part-time, 2 at least half-time college students; homemakers not considered to be employed) Retired: 64 (all had once worked at full-time jobs and retired prematurely)	1) Physical: Ambulation Index Visual Acuity 2) Mental: Beck Depression Inventory Cognitive testing in 7 domains (see under "Study Design" for details; investigators also calculated a global measure of the severity of cognitive impairment = number of cognitive domains in which patient "impaired") 3) Laboratory: None 4) Radiographic: None 5) Other: Age Years of education Age at diagnosis Time since diagnosis Sex Use of symptomatic medication	No direct measure of work capacity or ability Work status measured through self-report 49% of the variance in employment status was explained by walking ability, age, two measures of memory, and one test of verbal fluency. Partial R^2: ▪ Ambulation Index: 0.25 ▪ Short Term Memory-Correct: 0.13 ▪ Selective Reminding Test-Delay Recall: 0.04 ▪ Age (29-62 years): 0.03 ▪ Letter fluency: 0.03	Cross-sectional design - temporal relationship between exposure and outcome of employment status not assessed; Duration of "retirement" at time of study was not considered; All participants had been previously employed; however, employment status at time of diagnosis was not considered; Sample size may be too small to detect true differences between groups. Authors note study limitation regarding absence of a measure of upper limb dexterity. Functional losses of fine motor control of the hands, which might not be reflected in scores on the Ambulation Index, may have contributed to premature retirement of clerical and skilled trade workers. Authors note that patients with global cognitive deficits can continue to work at intellectually demanding jobs. QUALITY ASSESSMENT: Study described as "population-based"?: Yes Follow up > 80%?: No Work outcomes assessed using a widely used scale?: Work status Work outcomes assessed in a blind fashion?: No If subgroups with different work ability identified: a) was there adjustment for important prognostic factors? Yes b) was there independent validation?: NA

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
		concentration (Digit Span from the Wechsler Adult Intelligence Scale-Revised) -Information processing speed (letter fluency, category fluency, and Symbol Digit Modalities Test -Naming (15-item version of Boston Naming Test) -Visuospatial perception (Benton Line Orientation Test) -Memory (Brown Peterson Short Term Memory Test, New Map Test, Selective Reminding Test) -Problem solving/ abstraction (Wisconsin Card Sorting Test, Shipley Institute of Living Scale Abstraction Test, and Conceptual Quotient)				
Beukelman, Kraft, and Freal, 1985	Inclusion: MS diagnosis from at least one physician; follow-up services from either the University of Washington MS Clinic, the Puget Sound Chapter	Cross-sectional study Location/recruitment: Survey mailed to "persons diagnosed as having multiple sclerosis and residing in Western Washington [state]" Data collection:	N = 656 returned questionnaires (90% response rate) Age: 1% ≤ 25 23% 25-39 39% 40-54 37% ≥ 55 Baseline measures of	1) Physical: None 2) Mental: Self-reported expressive communication disorder 3) Laboratory: None 4) Radiographic: None	No direct measure of work capacity or ability Work status measured through self-report Those with communication disorder (n = 149, 23% of total sample) were asked whether their communication disorder interfered with employment; 3% responded positively.	Comparison groups were not mutually exclusive (communication-disordered patients vs. all study subjects); Measurement of "communication disorder" was self-reported; Employment status prior to disease onset not considered; Cross-sectional design - temporal relationship between exposure and outcome of employment status not assessed;

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
	of the National MS Society, or the Neurological Disease Epidemiologic Study; moderate to severe symptoms Exclusion: None specified	8-page questionnaire requesting information on symptom characteristics and patterns, employment, daily living activities, rehabilitation needs, presence and severity of an expressive communication disorder, and use of communication augmentation equipment	physical and mental functioning: NR Baseline work status: NR	5) Other: None	Employment patterns of communication-disordered group vs. total sample: 1) Full-time employment: Communication-disordered: 7% Total sample: 17% Chi-square $p < 0.001$ 2) "Disabled employment": Communication-disordered: 56% ("larger percentage . . . as compared to the total sample") Total sample: NR 3) Part-time employment: Communication-disordered: 3% Total sample: 4%	No discussion section provided by authors where points about study bias and limitations discussed. As pointed out by the authors, study subjects may be less critical of their communication limitations than a third-party pathologist, who may be more objective. No data were provided about overall employment patterns among the population, so interpretation of study findings is limited. QUALITY ASSESSMENT: Study described as "population-based"?: No Follow up > 80%?: NA Work outcomes assessed using a widely used scale?: Work status Work outcomes assessed in a blind fashion?: No If subgroups with different work ability identified: a) was there adjustment for important prognostic factors? No b) was there independent validation?: NA

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
Canadian Burden of Illness Study Group, 1998a **and** **Canadian Burden of Illness Study Group, 1998b**	Inclusion: Clinically or laboratory-supported definite MS according to Poser criteria; age ≥ 18 Exclusion: Treatment with interferon-β; pregnancy or delivery in last 3 mo; any major acute or chronic disorder in last 3 mo; other neurological illness; recent participation in a drug trial	Cross-sectional study (cost analysis designed to estimate annual and lifetime costs of MS from the Canadian societal perspective); some data collected retrospectively for previous 3 mo Location/recruitment: Patients recruited from 14 MS outpatient clinics across Canada Data collection: Patients assessed using EDSS and SF-36; other data collected from patients and their families, clinic charts, hospital charts, and summaries of medical history from other institutions; cost data from various sources	N = 198 (62 "mild" MS [EDSS ≤ 2.5], 68 "moderate" [EDSS 3.0-6.0], 68 "severe" [EDSS ≥ 6.5]) Types of MS (incomplete data): Mild: 79% relapsing-remitting Moderate: 43% relapsing-remitting, 43% secondary progressive Severe: 57% secondary progressive, 41% primary progressive Age (mean ± SD): Mild MS: 39.8 ± 9.5 Moderate: 45.2 ± 10.7 Severe: 49.6 ± 12.2 Baseline measures of physical and mental functioning: See above for breakdown into EDSS categories; median EDSS scores within each category were: Mild: 2.0 Moderate: 4.5 Severe: 7.5 Baseline work status: Full-time: 23% Part-time: 12% Unemployed: 44% Other: 21%	1) Physical: EDSS scores 2) Mental: None 3) Laboratory: None 4) Radiographic: None 5) Other: None	No direct measure of work capacity or ability Work status measured through self-report 1) Current employment status by EDSS category : EDSS ≤ 2.5: 23 (37%) Full-time 13 (21%) Part-time 18 (29%) Unemployed 8 (13%) Other EDSS 3-6: 19 (28%) Full-time 7 (10%) Part-time 30 (44%) Unemployed 12 (18%) Other EDSS ≥ 6.5: 3 (4%) Full-time 4 (6%) Part-time 39 (57%) Unemployed 22 (32%) Other 2) Employment change because of MS (self-report): 37% of those with EDSS ≤ 2.5 62% of those with EDSS 3.0-6.0 82% of those with ≥ 6.5 3) Employment status compared to general population: 37% with mild MS were employed full-time versus 85% in age-matched comparator Canadian population 4) Lost workdays in a 1-yr period (dependent on number of people working – not very informative): EDSS ≤ 2.5: 49	Cross-sectional design - temporal relationship between exposure and outcome of employment status not assessed; Sample size too small to examine changes between groups; Employment status prior to disease onset not considered. Authors consider changes in employment status due to MS; however, study participants who may have been "unemployed" prior to disease onset were included in the analysis for EDSS vs. employment status. QUALITY ASSESSMENT: Study described as "population-based"?: Yes Follow up > 80%?: NA Work outcomes assessed using a widely used scale?: Work status Work outcomes assessed in a blind fashion?: No If subgroups with different work ability identified: NA a) was there adjustment for important prognostic factors? No b) was there independent validation?: NA

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
					EDSS 3-6: 109 EDSS ≥ 6.5: 40	
Dyck and Jongbloed, 2000 **and** **Jongbloed, 1996**	Inclusion: Women with definitive diagnosis of MS; working age (age 19-60) Exclusion: None specified	Cross-sectional study Location/recruitment: Questionnaire survey of all women with MS, age 19-60, who had attended MS clinic British Columbia, Canada Data collection: All data collected by postal questionnaire; three different questionnaires used: 1) Women currently in paid employment (n = 252) completed Questionnaire A; 2) Those who had been employed at time of diagnosis, but were no longer employed (n = 163), completed Questionnaire B; 3) Those who were not employed at time of diagnosis (n = 119) completed Questionnaire C. Questionnaires A and B included questions on age, education, marital status, income, housing, transportation, use of adaptive aids, visibility of MS, employment	N = 534 eligible respondents (66% response rate) Age (mean): Currently employed: 39.6 Now unemployed: 43.3 Unemployed at diagnosis: NR Baseline measures of physical and mental functioning: Use of scooter: Currently employed: 5.8% Currently unemployed: 30.5% Unemployed at diagnosis: NR Use of wheelchair: Currently employed: 8% Currently unemployed: 36.6% Unemployed at diagnosis: NR Baseline work status (self-reported): Currently employed: 47% Currently unemployed: 31% Unemployed at diagnosis: 22%	1) Physical: Use of mobility aids Visibility of MS 2) Mental: None (except self-reported barriers/helps to employment) 3) Laboratory: None 4) Radiographic: None 5) Other: Age Age at diagnosis Level of education Household income Job title at time of diagnosis Marital status Household composition Size of city of residence Home ownership Type of employment (self-employed, permanent, temporary, etc.) Place of employment Questionnaires also asked subjects (in open-ended way?) to identify factors contributing to their maintaining or leaving	No direct measure of work capacity or ability Work status measured through self-report Work status (self-report): 47% currently employed 31% no longer employed 22% never employed "Statistically significant differences in highest level of education": Attended university (yes/no): 25.3% - currently employed 14.8% - no longer employed (statistical test and level not provided) Comparing currently employed with no longer employed in a regression model: Mobility aids used and employment status controlling for education and age in model: $R^2 = 0.20$ Factors contributing to maintaining employment – 44% of currently employed women were limited in the kind and amount of work they could do because of MS including: NR – fatigue "most common" 16% - difficulty with standing and stairs 15% - walking 12% - writing 11% - memory/concentration 17% no longer working indicated "inability to negotiate reduced work hours" with their manager as reason for quitting work	Sample size is sufficient for comparing work ability between groups; Employment status prior to onset of MS was considered; Cross-sectional design - temporal relationship between exposure and outcome of employment status not assessed; Qualitative aspects of the study helped guide the quantitative analyses; Discussion section focused on work issues specific to women. Vague measurement of physical function Authors note that a study limitation included the absence of cognitive function measurements in the study QUALITY ASSESSMENT: Study described as "population-based"?: Yes Follow up > 80%?: NA Work outcomes assessed using a widely used scale?: Work status Work outcomes assessed in a blind fashion?: Unclear If subgroups with different work ability identified: a) was there adjustment for important prognostic factors? Yes b) was there independent validation?: NA

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
		history since diagnosis, and difficulties experienced at work. Questionnaire A asked women (in open-ended way?) to identify work-related and social/ family factors that allowed them to continue working; Questionnaire B asked women (in open-ended way?) to identify factors that contributed to their leaving employment; content of Questionnaire C not described. Study questionnaires developed on basis of in-depth interviews with 54 women with MS in first (qualitative) phase of study		employment		
Edgley, Sullivan, and Dehoux, 1991	Inclusion: Respondent to survey in *MS Canada;* currently or previously employed; age 18-55 Exclusion: None specified	Cross-sectional study Location/recruitment: Survey printed in summer 1989 issue of *MS Canada*, a newsletter distributed to approximately 25,000 individuals across Canada (of whom approximately 20,000 have MS) Data collection: All data collected by	N = 602 eligible respondents; 562 included in multivariate analysis of covariance Age: Mean, 43 Baseline measures of physical and mental functioning: 1) Mobility status: No problems with ambulation: 13% Some unsteadiness: 35%	1) Physical: Mobility status (1-5 = no problems, some unsteadiness, assistive device required, wheelchair required for long distances, unable to walk) 2) Mental: Self-perceived cognitive problems (0-4 = never, rarely, sometimes, often,	No direct measure of work capacity or ability Work status measured through self-report 1) Determinants of employment status: Mobility (mean [SD]): Unemployed: 3.1 (1.2) Employed: 2.2 (1.0) $p < 0.001$ Results on Perceived Deficit Questionnaire (mean [SD]): Unemployed: 1.6 (0.7)	Cross-sectional design - temporal relationship between exposure and outcome of employment status not assessed; Evaluation of cognitive abilities "self-perceived"; All participants had been previously employed; however, employment status at time of diagnosis was not considered; Sample size information is inconsistent throughout text, especially Table 1.0; Occupation was coded according the Blishen Socioeconomic Index for Occupations, but interpretation of scale

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
		questionnaire survey; items included were sex, age, occupation, level of education, duration of illness, mobility status, self-perceived cognitive problems (Perceived Deficits Questionnaire), and self-perceived primary reason for unemployment (open-ended question)	Assistive device required: 15% Wheelchair required for long distances: 27% Unable to walk: 10% 2) Perceived cognitive problems: Never: 0 Rarely: 23% Sometimes: 48% Often: 27% Almost always: 2% Baseline work status: Employed: 200 or 201 Unemployed: 402 or 401 (discrepancy between text and Table 1) Only subjects employed at diagnosis or employed at time of study were included	almost always; composite score obtained by summing 4 subscales of the Perceived Deficits Questionnaire) 3) Laboratory: None 4) Radiographic: None 5) Other: Sex Age Years of education Number of people living at home Type of occupation (coded according to Blishen Socio-economic Index for Occupations) Duration of illness Self-perceived primary reason for unemployment (open-ended question)	Employed: 1.4 (0.7) $p < 0.001$ 2) Study participants who indicated that they had quit working because of MS symptoms were asked an open-ended question about types of symptoms (n = 313; 78%): ▪ Ambulation difficulties (41%) ▪ Fatigue (39%) ▪ Memory problems (12%) ▪ Emotional problems (10%) ▪ Visual difficulties (12%) ▪ Problems with coordination (6%) ▪ Pain (2%) ▪ Incontinence (1%) 22% left employment for reasons unrelated to MS. Women (26%) were significantly more likely than men (11%) to cite reasons unrelated to MS as the primary cause of unemployment (chi-square = 9.3, $P < 0.01$).	not provided. QUALITY ASSESSMENT: Study described as "population-based"?: Yes Follow up > 80%?: NA Work outcomes assessed using a widely used scale?: Work status Work outcomes assessed in a blind fashion?: No If subgroups with different work ability identified: a) was there adjustment for important prognostic factors? Yes b) was there independent validation?: Yes/No/Unclear/NA
Freal, Kraft, and Coryell, 1984	Inclusion: Physician diagnosis of MS Exclusion: None specified	Cross-sectional study Location/recruitment: Subjects recruited by third parties, including hospitals, National MS Society chapters, a local MS association, and an epidemiological MS research study group (all in western Washington state)	N = 656 completed initial questionnaire; 309 completed follow-up questionnaire on fatigue (60% response rate on follow-up questionnaire) Age: NR Baseline measures of physical and mental functioning: In follow-up population (n = 309):	1) Physical: Fatigue 2) Mental: None 3) Laboratory: None 4) Radiographic: None 5) Other: None	No direct measure of work capacity or ability Work status measured through self-report Responses to open-ended question about how study participants (n = 309 responding to fatigue questionnaire) had changed work or lifestyle to cope with fatigue (only work-related factors reported here): 30 (10%) quit work	The main purpose of this study was to examine how individuals with MS deal with fatigue; the occupational component was secondary; Missing information about baseline work status hinders interpretation; Employment status prior to disease onset not considered. QUALITY ASSESSMENT: Study described as "population-based"?: Yes Follow up > 80%?: NA

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
		Data collection: All data collected by survey questionnaires; initial questionnaire gathered data on MS symptoms experienced and whether or not these symptoms interfered with activities of daily living; follow-up questionnaire on fatigue sent to all subjects identifying fatigue as a symptom; this questionnaire asked about characteristics of fatigue, its frequency, environmental variables affecting fatigue, relationship of other MS disease variables to fatigue, and affect of fatigue on subjects' lives	35% could walk without aids 32% used canes, walkers, or furniture when walking 33% used wheelchairs or were bedridden Baseline work status: NR		10 (3%) changes in work 9 (3%) rest and work changes 6 (2%) quit work and social activities	Work outcomes assessed using a widely used scale?: Work status Work outcomes assessed in a blind fashion?: No If subgroups with different work ability identified: a) was there adjustment for important prognostic factors? No b) was there independent validation?: NA
Genevie, Kallos, and Struening, 1987	Inclusion: Member of New York City Chapter of the National MS Society; employed at time of MS diagnosis and not yet retired Exclusion: Incomplete data	Cross-sectional study Location/recruitment: Survey questionnaires mailed to all members of the New York City Chapter of the National MS Society Data collection: All data collected by survey questionnaire; 10-page instrument captured data on demographic	N = 333 eligible respondents Age: Median, 44 Baseline measures of physical and mental functioning: NR Baseline work status: Employed: 41% (21% at job they held when diagnosed, 20% had changed jobs) Unemployed (but not	The following variables were examined for their relationship to job retention in correlation and stepwise multiple regression analyses. Symptom severity (16 items) was graded on a scale of 0 ("not at all severe") to 5 ("very severe"). Functional impairment (8 items) was measured on a scale of 1 ("can do without difficulty") to 5	No direct measure of work capacity or ability Work status measured through self-report 1) 31% of the variance in job retention was accounted for by demographic characteristics, symptom severity, and functional impairment. 2) 32% of the variance in job retention was accounted for by demographic characteristics, symptom severity, functional impairment, and vocational	SSDI was included as a predictor of "no" work. Authors infer that income from other sources, such as SSDI, is a disincentive to work. However, SSDI may be a result of one's inability to work and not a disincentive. It would be difficult to disentangle the relationship between SSDI and work incentive, especially in a cross-sectional study design. All study participants were employed at time of diagnosis of MS. QUALITY ASSESSMENT:

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
		characteristics, symptom severity (at time of diagnosis and present), functional impairment, vocational improvement, job change, sources of income, and medical, psychological, and vocational needs of patient	retired): 48% (36% voluntarily, 12% dismissed because of MS) Subjects required to have been employed at time of MS diagnosis and not yet retired	("cannot do at all"). 1) Physical: Numbness/tingling Speech Vision Pain Fatigue Functional impairment Incontinence Ambulation 2) Mental: Affective lability Cognition Motor disturbance 3) Laboratory: None 4) Radiographic: None 5) Other: Sex Age Family income Education Time since diagnosis Vocational improvement Job change Sources of income (savings/investments, SSDI, SSI, spouse)	activity. 3) 49% of the variance in job retention was accounted for by demographic characteristics, symptom severity, functional impairment, vocational activity, and various sources of income (12% of this [49% of] variance was explained by SSI or SSDI being an income source).	Study described as "population-based"?: Yes Follow up > 80%?: NA Work outcomes assessed using a widely used scale?: Work status Work outcomes assessed in a blind fashion?: No If subgroups with different work ability identified: a) was there adjustment for important prognostic factors? Yes (see note above) b) was there independent validation?: NA

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
Grima, Torrance, Francis, et al., 2000	Inclusion: History of relapsing-remitting MS (including some patients who had entered a secondary progressive phase within past 2 yr); EDSS < 7 (ambulatory); not in a clinical trial; age ≥ 18 Exclusion: None specified	Cross-sectional study (estimating costs of relapsing-remitting MS to Canadian health care system and society, measuring health utilities of patients, and examining influence of EDSS scores on these outcomes); some data collected retrospectively for previous 12 mo Location/recruitment: Patients recruited during regular visits to MS clinics at two sites in Ontario, Canada Data collection: Patient survey (patient information, resource use, and health utilities), chart review (resource use, medications, lab tests, procedures), and EDSS status assessment. Note: resource use data not collected on patients in relapse at time of study visit.	N = 195 (153 in remission at time of study visit [44 of whom could recall a relapse in the previous 6 mo] and 42 in relapse at time of visit) Age (mean ± SD): Remission patients: 41 ± 15 Relapse patients: 36 ± 14 Baseline measures of physical and mental functioning (EDSS): Remission patients: 1 – 24% 2 – 27% 3 – 22% 4 – 10% 5 – 5% 6 – 12% Relapse patients: NR Baseline work status: Remission patients: Full-time: 29% Part-time due to MS: 4% Part-time not due to MS: 7% Unemployed due to MS: 37% Unemployed not due to MS: 20% No response: 2% Relapse patients: NR	1) Physical: EDSS scores (assessed by neurologist at time of study visit) 2) Mental: None 3) Laboratory: None 4) Radiographic: None 5) Other: None	No direct measure of work capacity or ability Work status measured through self-report 1) EDSS 1 (n = 37): 51% - work full-time 3% - work part-time, unable to work full-time due to MS 8% - work part-time for other reasons 16% - not working due to MS 22% - not working for other reasons EDSS 2 (n = 41): 37% - work full-time 7% - work part-time, unable to work full-time due to MS 10% - work part-time for other reasons 15% - not working due to MS 32% - not working for other reasons EDSS 3 (n = 33): 15% - work full-time 0% - work part-time, unable to work full-time due to MS 9% - work part-time for other reasons 52% - not working due to MS 18% - not working for other reasons 6% - NR EDSS 4 (n = 16): 31% - work full-time 0% - work part-time, unable to work full-time due to MS 6% - work part-time for other reasons 50% - not working due to MS 13% - not working for other reasons EDSS 5 (n = 7): 0% - work full-time 0% - work part-time, unable to work	No information about employment status prior to disease onset; Cross-sectional design - temporal relationship between exposure and outcome of employment status not assessed; Details of subject selection criteria and process are limited; Details of how information about employment was collected are sparse; Multivariate analysis considering known and suspected risk factors for high EDSS and employment status was not conducted. The primary purpose of this study was to examine cost and quality of life among individuals with MS. Details about employment are limited. QUALITY ASSESSMENT: Study described as "population-based"?:-Yes Follow up > 80%?: NA Work outcomes assessed using a widely used scale?: Work status Work outcomes assessed in a blind fashion?: Unclear If subgroups with different work ability identified: a) was there adjustment for important prognostic factors? No b) was there independent validation?: NA

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
					full-time due to MS 0% - work part-time for other reasons 86% - not working due to MS 14% - not working for other reasons EDSS 6 (n = 19): 5% - work full-time 11% - work part-time, unable to work full-time due to MS 0% - work part-time for other reasons 75% - not working due to MS 5% - not working for other reasons 5% - NR	
Grønning, Hannisdal, and Mellgren, 1990	Inclusion: Diagnosed with clinically definite, probable, or possible MS; resident of one of two counties in Norway Exclusion: No occupational data on file	Retrospective cohort study Univariate and multivariate survival (time-to-response) analyses used to study variables at onset of MS as possible predictors of time to unemployment Location/recruitment: Included MS patients seen in neurological departments and clinics in two counties in Norway Data collection: All data taken from patient files recorded from 1974-82; observation time from onset of MS to last follow up varied from 1-33 yr, with mean of 10 yr	N = 79 (49 remittent, 12 remittent-progressive, 18 progressive) Age at MS onset: Mean, 30; range, 13-55 Measures of physical and mental functioning at MS onset: NR Work status at MS onset: Housewives: 20% Light work (secretaries, nurses, teachers, engineers, drivers, students): 43% Heavy work (sailors, industrial workers, fishermen, craftsmen): 37%	Possible predictors all assessed at time of onset of MS (time of first symptoms) 1) Physical: Diagnostic category (definite MS vs. probable/possible MS); Clinical course (remittent vs. non-remittent) Brain stem symptoms (no vs. yes) Paresis (no vs. yes) Sensory disturbances (no vs. yes) 2) Mental: None 3) Laboratory: None 4) Radiographic: None 5) Other: Occupation (light work/ housewives vs. heavy	No direct measure of work capacity or ability Work status measured through self-report. Work status determined by receipt of disability pension. 1) Employed at last follow up, by disease subtype: 18/49 (37%) - Remittent MS 28/30 (93%) - Non-remittent MS 2) Employed at last follow up, by job type: 25/29 (86%) – Heavy work 21/50 (42%) – Light work 3) Employed at last follow up, by age: 26/50 (52%) ≤ age 30 20/29 (69%) > age 30 4) Univariate analyses of time to unemployment: Non-remittent MS vs. remittent ($p < 0.001$) Heavy vs. light work ($p < 0.01$) Male vs. female ($p < 0.05$) Age > 30 vs. ≤ 30 at onset ($p < 0.01$)	Possible misclassification of work exertion. Nurses were categorized as “light work,” but nursing ranks as one of the highest for musculoskeletal injuries in the US; similarly, working as a housewife was categorized as “light work,” though this may require significant physical exertion; Researchers relied on statistical testing to indicate differences between groups without calculating risk estimates, limiting ability to interpret findings; Sample size may be too small to detect true differences between groups in multivariate analyses. QUALITY ASSESSMENT: Study described as “population-based”?: Yes Follow up > 80%?: Yes Work outcomes assessed using a widely used scale?: Work status Work outcomes assessed in a blind fashion?: Unclear If subgroups with different work ability identified: a) was there adjustment for important prognostic factors?

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
				work) Age (≤ 30 vs. > 30) Sex (female vs. male) County of residence (Troms vs. Finnmark)	5) In multivariate analyses, only disease subtype was predictive of early unemployment ($p < 0.01$). 6) In multivariate analyses, when disease subtype was not considered, light work vs. heavy ($p < 0.01$) and age > 30 years ($p < 0.05$) were predictive of early unemployment.	Yes b) was there independent validation?: Yes
Gulick, Yam, and Touw, 1989	Inclusion: Previous diagnosis of MS; *not* a resident of a nursing home or long-term care facility; age ≤ 65; self-reported employment status one of following: "employed outside the home," "home-maker," "unemployed," or "retired" (of 8 possible responses) Exclusion: None specified	Cross-sectional study Location/recruitment: Subjects selected randomly from two local chapters of the National MS Society (n = 412) and recruited from a university-affiliated MS comprehensive care clinic (all in New Jersey) Data collection: All data collected by survey questionnaires, which included a personal data inventory, the ADL Self-Care MS Scale, and two open-ended questions about what conditions/situations make work or chores more difficult or easier to perform	N = 508 eligible respondents (response rate "approximately 90%") Age (mean ± SD): Employed outside home: 41.9 ± 8.9 Homemaker: 48.0 ± 9.2 Unemployed: 48.8 ± 9.9 Retired: 56.3 ± 7.0 Baseline measures of physical and mental functioning: Walking ability (subscale of ADL Self-Care MS Scale; mean ± SD): Employed outside home: 20.5 ± 6.9 Homemaker: 12.7 ± 9.0 Unemployed: 5.8 ± 7.5 Retired: 8.9 ± 8.4 Baseline work status: Employed outside home: 110 Homemaker: 209 Unemployed: 110 Retired: 79	1) Physical: Walking ability (subscale of ADL Self-Care MS Scale) 2) Mental: None 3) Laboratory: None 4) Radiographic: None 5) Other: Age Sex Marital status MS duration (since diagnosis) Education Investigators also reported responses to two open-ended questions about conditions/situations that make work or chores more difficult or easier to perform (responses to "easier to perform" questions not included in this	No direct measure of work capacity or ability Work status measured through self-report 1) 1-way ANOVA comparing work groups on selected characteristics (f Ratio): 39.5 ($p < 0.001$) - Present age 18.8 ($p < 0.001$) - MS duration 14.1 ($p < 0.001$) - Education 4.8 ($p < 0.001$) - Walking 2) Ranked comparison of conditions/ situations that impede work performance (selected physical functions among those employed outside the home [n = 104] and unemployed [n = 92]; data on homemakers and retired participants not described here): Fatigue: Employed: 50% Unemployed: 25% Walking: Employed: 12% Unemployed: 0 Standing:	Cross-sectional design - temporal relationship between exposure and outcome of employment status not assessed; No statistical comparison of responses across groups; Employment status at time of diagnosis was not considered; however, authors acknowledge that their method of categorizing study participants did not distinguish between "home makers who used to work" and "never employed workers who may be retired"; No information provided about how "unemployed" study participants were to answer this question. Not sure if their answers are based on prior employment experiences. QUALITY ASSESSMENT: Study described as "population-based"?: Yes Follow up > 80%?: NA Work outcomes assessed using a widely used scale?: Work status Work outcomes assessed in a blind fashion?: No If subgroups with different work ability identified: a) was there adjustment for important prognostic factors? Yes

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
				table)	Employed: 8% Unemployed: 12% Numbness: Employed: 8% Unemployed: 5% Tremors: Employed: o Unemployed: 10% Use of wheelchair: Employed: 0 Unemployed: 10% Restricted mobility: Employed: 0 Unemployed: 9% Stiffness: Employed: 5% Unemployed: 0	b) was there independent validation?: NA
Hammond, McLeod, Macaskill, et al., 1996	Inclusion: Clinically definite, probable, or possible MS Exclusion: None specified	Cross-sectional study Location/recruitment: Patients identified as part of epidemiological study of MS in New South Wales, Queensland, South Australia, Western Australia, and Tasmania Data collection: Survey/interview conducted by neurologists; included questions on age, sex, date of birth, occupation, marital	N = 2307, of which 2099 were of working age (15-64) and reported both DSS and employment data Age: NR Baseline measures of physical and mental functioning: NR Baseline work status: Men: 50% employed, 45% retired or receiving a pension Women: 27% employed, 30% retired or receiving a pension	1) Physical: Level of disability: Low (DSS 0-3) Moderate (DSS 4-6) Severe (DSS 7-9) 2) Mental: None 3) Laboratory: None 4) Radiographic: None 5) Other: Type of work (trade/farm vs. professional/clerical)	No direct measure of work capacity or ability Work status measured through self-report 1) Reported being “employed”: Men: 78% = DSS-low 27% = DSS-moderate 4% = DSS-severe Women: 40% = DSS-low 8% = DSS-moderate 1% = DSS-severe 2) Adjusting for age and sex, the relationship between DSS level and	Employment status prior to disease onset not considered; Cross-sectional design - temporal relationship between exposure and outcome of employment status not assessed; Sample size is a study strength, able to control for some possible confounders using multivariate analyses. QUALITY ASSESSMENT: Study described as “population-based”?: Yes Follow up > 80%?: NA Work outcomes assessed using a widely used scale?: Work status Work outcomes assessed in a blind fashion?: No If subgroups with different work ability

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
		status, and education; DSS score assessed for prevalence day (30 June 1981)			employment status was noted separately for men and women: Men – prevalence ratio (95% CI): Moderate vs. low DSS = 2.7 (2.1-3.6) Severe vs. low DSS = 17.6 (7.5-41.4) Women – prevalence ratio (95% CI): Moderate vs. low DSS = 4.0 (2.7-5.8) Severe vs. low DSS = 24.6 (8.0-76.1) Job type: Authors noted that trade and farm workers were less likely to be in paid employment than professional or clerical workers as their level of disability increased; however, no data were provided to support this statement.	identified: a) was there adjustment for important prognostic factors? Yes b) was there independent validation?: NA
Jacobs, Wende, Brown-scheidle, et al., 1999	Inclusion: Definite MS in the judgment of clinical site neurologists; entered into New York State MS Consortium registry Exclusion: None specified	Cross-sectional study Location/recruitment: Patients attended one of 12 MS centers comprising the New York State MS Consortium Data collection: Consortium registry/ study data collected using a 5-page form consisting of 2 sections: (a) 3 pages of demographic data and self-report assessments completed by patient (some mailed, some completed during office visit), and (b) 2 pages of clinical data	N = 3019 (55% relapsing-remitting, 31% secondary progressive, 9% primary progressive, 5% progressive relapsing) Age: Mean ± SD, 45.2 ± 11.2; median, 45.0 Baseline measures of physical and mental functioning: NR Baseline work status: NR	1) Physical: MS disease course (relapsing-remitting vs. progressive) 2) Mental: None 3) Laboratory: None 4) Radiographic: None 5) Other: None	No direct measure of work capacity or ability Work status measured through self-report 1) Employment status by disease course: Relapse-remitting: 55% employed Primary progressive: 21% employed 2) Disabled and under age 60: 44% with primary progressive 17% with relapsing-remitting 3) There were no group differences in patients who were homemakers, unemployed, or retired after 60 years of age (2-12%) in relapsing-remitting or progressive MS. 4) Interesting summary of type of insurance coverage by stage of	EDSS scores ascertained but not examined in conjunction with work status; Employment status prior to disease onset not considered; Cross-sectional design - temporal relationship between exposure and outcome of employment status not assessed; Multivariate analyses considering important known and suspected risk factors for both poor physical function and employment status were not conducted. QUALITY ASSESSMENT: Study described as “population-based”?: Yes Follow up > 80%?: NA Work outcomes assessed using a widely used scale?: Work status Work outcomes assessed in a blind fashion?: No

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
		completed by examining neurologist and/or study nurse (included physical exam findings, exacerbation history, MS type, EDSS score, and lab findings)			disease, which may be directly related to employment status. Participants with relapsing-remitting MS were more likely to be insured by HMOs and commercial carriers, and those with progressive MS were more likely to be covered by Medicare and Medicaid.	If subgroups with different work ability identified: a) was there adjustment for important prognostic factors? No b) was there independent validation?: No
Kornblith, La Rocca, and Baum, 1986	Inclusion: Interviewed as part of US National MS Survey Exclusion: Never worked; did not admit to having MS	Cross-sectional study; path analysis used to construct a causal model explaining variation in employment status Location/recruitment: Subjects were subset of patients interviewed for US National MS Survey; sampling and recruitment of this population not described in the current paper Data collection: Patient interviews designed to obtain disease history, employment history, and data on functional disability, utilization of medical services, costs incurred, and disruptions in the lives of patients and their families due to MS	N = 987 met inclusion/ exclusion criteria; 949 provided complete data for multivariate analysis Age: Mean, 48.3 Baseline measures of physical and mental functioning: Mobility dysfunction: No assistance needed: 31% Assistance needed half-time: 28% Assistance needed all the time: 41% Baseline work status: Employed: 20% Unemployed: 80%	1) Physical: Duration of illness Functional disability (Mobility Dysfunction Index) ADL and leisure disability (study-specific measure) 2) Mental: None 3) Laboratory: None 4) Radiographic: None 5) Other: Sex Age Marital status Education level Number of other adults in the home Number of children younger than 14	No direct measure of work capacity or ability Work status measured through self-report Proxy of physical function was assessed using the Mobility Dysfunction Index: a. No assistance needed indoor and outdoors b. Any combination of cane, walker, crutches, leg brace, use of person, for any amount of chair and wheel chair once in awhile c. Use of wheel chair more than half of the time indoors or outdoors. Data analyzed separately for males vs. females since sociocultural differences between sexes might affect employment in response to MS 1) Author's comment: Mobility was a major determinant of employment status in both males and females, while age and duration were minor. 2) Men: Each 1-point increase in the Mobility Dysfunction Index decreased the probability of males working by 24.3%.	Measurement of mobility is crude. The 3-point scale may not be sensitive enough to changes in physical function that are associated with inability to work; Stratified linear regression (by sex): Men: adjustment for age, education, and duration of illness; Women: adjustment for age, duration of illness, ADL, leisure activity, marital status; Authors indicate (p. 160) that occupational history over the life span was ascertained; however, these data are not included in the paper or considered in the analyses; Employment status prior to disease onset not considered. QUALITY ASSESSMENT: Study described as "population-based"?: Yes Follow up > 80%?: NA Work outcomes assessed using a widely used scale?: Work status Work outcomes assessed in a blind fashion?: No If subgroups with different work ability identified: a) was there adjustment for important prognostic factors? Yes b) was there independent validation?: No

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
					3) Women: Each 1-point increase in the Mobility Dysfunction Index decreased the likelihood of females working by 15.4%.	
LaRocca, Kalb, Kendall, et al., 1982	Inclusion: MS Exclusion: None specified	Cross-sectional study Location/recruitment: Patients recruited from an MS clinic in the Bronx, NY, and 3 (unspecified) voluntary agencies Data collection: Highly structured clinical interview, plus standard neurological exam with DSS assessment	N = 312 Age: Mean, 43; range, 18-72 Baseline measures of physical and mental functioning: Mean DSS, 4.6 Baseline work status: 77% unemployed; out of work for an average of 9 yr 96% employed at some time in the past	1) Physical: Duration of illness Symptoms Disability (measured by DSS scores) 2) Mental: None 3) Laboratory: None 4) Radiographic: None 5) Other: Age Sex Education Marital status Occupation Parenthood	No direct measure of work capacity or ability Work status measured through self-report 1) 76% of study sample were unemployed at assessment and out of work an average of 9 years; however, 96% had been employed at some time. 2) 1-point increase in DSS was associated with a 7% decrease in the likelihood of being employed 3) Being male increased the probability of being employed by 11%. 4) 86% of variability in employment status *un*explained by: Age Sex Education Marital status Occupation Parenthood However, variability in employment status was explained by factors such as premorbid personality, coping style, characteristics of the workplace, and social support systems. Authors suggest that these findings contribute to the probability of a patient with MS staying at work.	Cross-sectional design - temporal relationship between exposure and outcome of employment status not assessed; Reasons for leaving job not provided; No discussion section provided by authors where points about study bias and limitations were discussed; No tests of statistical significance. QUALITY ASSESSMENT: Study described as "population-based"?: Yes Follow up > 80%?: NA Work outcomes assessed using a widely used scale?: Work status Work outcomes assessed in a blind fashion?: Unclear If subgroups with different work ability identified: a) was there adjustment for important prognostic factors? Yes b) was there independent validation?: NA

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
Miller, Rudick, Cutter, et al., 2000	Inclusion: Clinically definite MS Exclusion: None specified	Cross-sectional study (validation of Multiple Sclerosis Functional Composite [MSFC], consisting of timed 25-ft walk, 9-Hole Peg Test [9-HPT], and Paced Auditory Serial Addition Test 3-min version [PASAT-3]) Location/recruitment: Patients with clinically definite MS recruited from 4 clinical sites in the US and Canada; stratified sampling plan by disease severity and sex; subjects selected to provide an even representation of mild (EDSS 0-3.0), moderate (EDSS 3.5-6.5), and severe (EDSS 7.0-8.5) neurological impairment Data collection: Following data collected (during clinic visits?): 1) MSFC 2) EDSS 3) Sickness Impact Profile (SIP) 4) SF-36 5) Fatigue Impact Scale (FIS) 6) Self-reported employment status 7) Social Support	N = 300 Age (mean ± SD): 44.7 ± 9.3 Baseline measures of physical and mental functioning: EDSS severity: Low (0-3.0): 38% Moderate (3.5-6.5): 44% High (7.0-8.5): 17% Baseline work status: Full-time: 24.2% Part-time: 13.1% Unemployed: 62.8%	1) Physical: EDSS scores MSFC scores 2) Mental: None 3) Laboratory: None 4) Radiographic: None 5) Other: None	No direct measure of work capacity or ability Work status measured through self-report 1) Employment status by EDSS score: EDSS (0-3.0): None – 37.5% Part-time – 20.5% Full-time – 42.0% EDSS (3.5-6.5): None – 74.6% Part-time – 10.0% Full-time – 15.4% EDSS (7.0-8.5): None – 85.7% Part-time – 5.4% Full-time – 8.9% 2) Employment status (0 = none; 1= part-time; 2 = full-time) correlated significantly with MSFC (Spearman coefficient = 0.43 [$p < 0.001$]), and correlation remained significant when EDSS controlled for (Spearman coefficient = 0.13 [$p < 0.05$]). No MSFC score is provided with regard to employment status. 3) When stratified by disease severity, Spearman correlations between MSFC and work status for: EDSS 0-3.0: 0.21 (p = NS) EDSS 3.5-5.5: 0.32 ($p < 0.001$) EDSS 7.0-8.5: 0.18 (p = NS)	The purpose of this study was to validate MSFC, and the authors state that employment status was included as a surrogate measure of health status impact. Researchers expected employment status to be moderately correlated with the MSFC. Authors cite low relative participant numbers in high EDSS severity subgroup (56/300) as explanation for lack of demonstrated statistical significance with respect to work status, although article also states selection process was designed to "provide an even representation" of EDSS severity QUALITY ASSESSMENT: Study described as "population-based"?: Yes Follow up > 80%?: NA Work outcomes assessed using a widely used scale?: Work status Work outcomes assessed in a blind fashion?: Unclear If subgroups with different work ability identified: Was there adjustment for important prognostic factors? No (except that overall sex ratio in study was said to reflect that of usual MS population) b) was there independent validation?: NA

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
		Survey-Tangible Support subscale				
Rao, Leo, Ellington, et al., 1991	Inclusion: MS Exclusion: None specified	Cross-sectional study Location/recruitment: Sample described as coming from a "large community-based sample of MS patients"; sampling/ recruitment not described in detail in this publication Data collection: Cognitive status (intact vs. impaired) determined on basis of performance on 31 cognitive test scores; patients then assessed using Minimal Record of Disability (includes EDSS, Kurtzke Functional Systems, Incapacity Status Scale, and Environmental Status Scale), a 2-hr occupational therapy evaluation, various self-report measures (Zung Depression Scale, State-Trait Anxiety Inventory, SIP), and relative/ friend ratings (Katz Adjustment Scale)	N = 100 MS patients (38 relapsing-remitting, 19 chronic-progressive, 43 chronic-stable); 100 non-MS controls used to determine cognitive impairment levels only Age: Mean, 45.9 Baseline measures of physical and mental functioning: EDSS (mean): 4.1 Baseline work status: NR ("Actual Work Status" scores reported only graphically [Figure 1])	1) Physical: None 2) Mental: Cognitive status (intact vs. impaired) 3) Laboratory: None 4) Radiographic: None 5) Other: None	No direct measure of work capacity or ability Work status measured through self-report Mean score on the Environmental Status Scale (range 0-4) for the "actual work status" item (1 of 7 items) was lower (approximately 1.8) for cognitively impaired versus cognitively intact (approximately 2.8) subjects ($p < 0.01$ [Figure 1.0])	Non-MS controls apparently used only in Katz Adjustment Scale determination; Cross sectional design - temporal relationship between exposure and outcome of employment status not assessed; Employment status prior to disease onset not considered. QUALITY ASSESSMENT: Study described as "population-based"?: Yes Follow up > 80%?: Yes Work outcomes assessed using a widely used scale?: Work status Work outcomes assessed in a blind fashion?: No If subgroups with different work ability identified: a) was there adjustment for important prognostic factors? No b) was there independent validation?: NA

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
Rozin, Schiff, Cooper, et al., 1982	Inclusion: Possible or probable MS by modified Allison and Miller criteria (diagnosis verified by research team); age 17-50; diagnosed during 1970-72 Exclusion: None specified	Cross-sectional study Location/recruitment: Study described below (Rozin, Schiff, Kahana, et al., 1975) updated with new series of patients contacted during 1974-78 Data collection: Interviews conducted by social workers in patients' homes; included questions on demographic data, family history, educational and occupational history, present economic status, usual daily schedule, and desire to work or be trained; neurological exam also performed and disability assessed using Hyllested scale. All patients classified according to functional groups as follows: A = completely handicapped, no rehabilitation potential; B = potential for vocational rehabilitation (including those who were working, but needed vocational rehabilitation services); and C = working, holding on to their	N = 117 eligible; 101 interviewed and classified according to functional group Age: Mean, 36 Baseline measures of physical and mental functioning: Disability: Mild (0-2): 57% Moderate (3-4): 36% Severe (5-6): 6% Functional groups (see under "Study Design" at left): A: 16% B: 24% C: 60% Baseline work status: Working: 60% (functional group C)	1) Physical: Neurological exam, content unspecified 2) Mental: None 3) Laboratory: None 4) Radiographic: None 5) Other: Disability assessed using Hyllested scale, graded 0-6 Years of education	Direct measure of work capacity or ability was conducted Work status measured through self-report Study participants initially grouped as follows (Series I and II combined; n = 299) n = 71 - Group A: Completely handicapped with no rehabilitation potential n = 53 - Group B: Potential for vocational rehabilitation, but unemployed or currently employed, but needs rehabilitation services for continuation of employment n = 175 - Group C: Currently working, holding previous jobs or changed jobs without intervention of rehabilitation services 1) Type of MS disability by Group (Series I and II combined): No disability: NR - Group A 3% - Group B 29% - Group C Physical MS: 59% - Group A 75% - Group B 61% - Group C Physical and mental MS: 30% - Group A 11% - Group B 6% - Group C Mental MS: 1% - Group A 2% - Group B	Evaluation of mental/cognitive function is unclear; Cross-sectional design - temporal relationship between exposure and outcome of employment status not assessed; Not clear whether process of classifying groups was independent of Hyllested scale grade (in terms of blinding), but probably was not. QUALITY ASSESSMENT: Study described as "population-based"?: Yes Follow up > 80%?: NA Work outcomes assessed using a widely used scale?: Work status, work ability Work outcomes assessed in a blind fashion?: No If subgroups with different work ability identified: a) was there adjustment for important prognostic factors? No b) was there independent validation?: NA

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
		previous jobs, or changed jobs without the intervention of rehabilitation services			1% - Group C Other causes: 7% - Group A 2% - Group B 1% - Group C MS and other: 3% - Group A 7% - Group B 2% - Group C “Comparison of Group A with Group C with mental disability due to MS (with or without physical disability) is higher in Group A than C – 31% vs. 7%, respectively – $p < 0.001$.” “Group A and Group C had similar percentages of subjects with physical disability due to MS. “ 2) Hyllested Criteria of Disability (Series I and II combined): Group A (n = 71): 15% - Mild (0-2) 38% - Moderate (3-4) 46% - Severe (5-6) Group B (n = 53): 36% - Mild (0-2) 51% - Moderate (3-4) 13% - Severe (5-6) Group C (n = 175): 74% - Mild (0-2) 25% - Moderate (3-4) 0.6% - Severe (5-6)	

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
Rozin, Schiff, Kahana, et al., 1975	Inclusion: MS; age 20-50 in 1971 Exclusion: None specified	Cross-sectional study Location/recruitment: Patient population derived from a survey of MS patients in Israel, updated in 1968 and including all MS patient living in Israel at the time (n = 490); those age 20-50 in 1971 included in present study Data collection: Interviews conducted by social workers in patients' homes; included questions on demographic data, family history, educational and occupational history, present economic status, usual daily schedule, and desire to work or be trained; neurological exam also performed and disability assessed using Hyllested scale; all patients classified according to functional groups as follows: A = completely handicapped, no rehabilitation potential; B = potential for vocational rehabilitation (including those who were working, but needed	N = 222 eligible; 159 interviewed; 172 classified according to functional group Age: 53% older than 40 Baseline measures of physical and mental functioning: Disability: Mild (0-2): 38% Moderate (3-4): 29% Severe (5-6): 33% Functional groups (see under "Study Design" at left): A: 24% B: 21% C: 55% Baseline work status: Not working: 76%	1) Physical: Neurological exam, content unspecified 2) Mental: None 3) Laboratory: None 4) Radiographic: None 5) Other: Disability assessed using Hyllested scale, graded 0-6	Direct measure of work capacity or ability was conducted Work status measured through self-report Study participants (n = 172) were initially grouped as follows: n = 41 - Group A: Completely handicapped with no rehabilitation potential n = 37 - Group B: Potential for vocational rehabilitation, but unemployed or currently employed, but needs rehabilitation services for continuation of employment n = 94 – Group C: Currently working, holding previous jobs or changed jobs without intervention of rehabilitation services 1) Type of MS disability by group: No disability: NR - Group A NR - Group B 50% - Group C Physical disability due to MS: 39% - Group A 81% - Group B 41% - Group C Physical and mental disability due to MS: 56% - Group A 19% - Group B 3% - Group C Mental disability due to MS: NR - Group A NR - Group B 1% - Group C	Evaluation of mental/cognitive function is unclear; Cross-sectional design - temporal relationship between exposure and outcome of employment status not assessed; Examines changes in work status across time period of disease. QUALITY ASSESSMENT: Study described as "population-based"?: Yes Follow up > 80%?: Yes Work outcomes assessed using a widely used scale?: Work status, work ability Work outcomes assessed in a blind fashion?: No If subgroups with different work ability identified: a) was there adjustment for important prognostic factors? No b) was there independent validation?: NA

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
		vocational rehabilitation services); and C = working, holding on to their previous jobs, or changed jobs without the intervention of rehabilitation services			Other causes of disability not connected with MS: 5% - Group A NR - Group B 5% - Group C 3) Hyllested Criteria of Disability: Group A (n = 41): 0% - Mild (0-2) 0% - Moderate (3-4) 100% - Severe (5-6) Group B (n = 37): 0% - Mild (0-2) 57% - Moderate (3-4) 43% - Severe (5-6) Group C (n = 94): 70% - Mild (0-2) 30% - Moderate (3-4) 0% - Severe (5-6) 4) Changes in work status from onset of MS to time study in 1971. Work type by work groups: Group A (n = 41): Unskilled labor: 18% - onset of MS 0% - at time of study Skilled, semiskilled, service: 27% - onset of MS 0% - at time of study Clerical, profession, student: 37% - onset of MS 0% - at time of study Housewives: 2% - onset of MS 0% - at time of study Not working: 6% - onset of MS 100% - at time of study	

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
					Group B (n = 37): Unskilled labor: 28% - onset of MS 3% - at time of study Skilled, semiskilled, service: 31% - onset of MS 3% - at time of study Clerical, profession, student: 31% - onset of MS 21% - at time of study Housewives: 5% - onset of MS 8% - at time of study Not working: 5% - onset of MS 65% - at time of study Group C (n = 94): Unskilled labor: 22% - onset of MS 8% - at time of study Skilled, semiskilled, service: 18% - onset of MS 17% - at time of study Clerical, profession, student: 40% - onset of MS 37% - at time of study Housewives: 12% - onset of MS 38% - at time of study Not working: 8% - onset of MS 0% - at time of study 4) Authors note that “of the 131 clients with working potential, only 18% stopped working because of MS” – supporting data not provided.	

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
Schein-berg, Holland, Larocca, et al., 1980	Inclusion: MS; patient at study clinic Exclusion: None specified	Cross-sectional study Location/recruitment: Sample of patients from a multidisciplinary MS clinic assembled by selecting alternate names from an alphabetic file Data collection: Structured interview containing 20 questions administered either by phone or in person; areas assessed included employment, education, household activities, and medical care	N = 401 selected; 257 (64%) completed interviews Age: 37% ≤ 39; 53% 40-59; 9% ≥ 60 Baseline measures of physical and mental functioning: NR Baseline work status: Employed: 19.5% Independent homemaker: 21.4% Semi-independent homemaker: 12.8% Employed in sheltered workshop: 1.2% Retired: 3.9% Student: 2.3% Unemployed: 38.5% Other: 0.4%	1) Physical: Self-report of physical limitations 2) Mental: None 3) Laboratory: None 4) Radiographic: None 5) Other: Job category	No direct measure of work capacity or ability Work status measured through self-report Among those having left employment, the most common reason for leaving among multiple reasons given by 182 subjects (categories not mutually exclusive): 52.7% - Physical difficulty 15.9% - Visual difficulty 12.1% - Transportation difficulty 9.3% - Fatigue 1.3% - Emotional difficulty 37.4% - Other (mainly marriage and/or pregnancy) Job category of currently employed subjects (n = 51): 35.3% - Clerical 23.5% - Professional 13.7% - Semi-Professional 13.7% - Skilled Labor 7.8% - Managerial 2.0% - Unskilled Labor 3.9% - Other Among the unemployed, 18.3% were seeking employment, training, or education, and 21.4% were able to care for their own home with little or no assistance.	Self-report of physical limitations without clinical measurement; Employment status prior to disease onset not considered; Cross-sectional design - temporal relationship between exposure and outcome of employment status not assessed; Sample size is too small to detect true differences between groups or to consider possible confounders in multivariate analysis; Descriptive study only. Authors' note indicates possible selection bias since sample was self-selected to come to the center where recruitment occurred. Sample may be more handicapped, more affluent, and better informed about availability of services than the general population with MS. Authors infer from findings that high unemployment rate among individuals with MS is partly due to current shortcomings of vocational rehabilitation agencies (note: study published in 1980, so rehabilitation services may have changed considerably since that time). QUALITY ASSESSMENT: Study described as "population-based"?: Yes (clinic) Follow up > 80%?: No Work outcomes assessed using a widely used scale?: Work status Work outcomes assessed in a blind fashion?: Unclear If subgroups with different work ability identified:

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
						a) was there adjustment for important prognostic factors? No b) was there independent validation?: NA
Verdier-Taillefer, Sazdovitch, Borgel, et al., 1995	Inclusion: Clinically or laboratory definite MS by Poser criteria; EDSS 3-7; age 20-50 Exclusion: None specified	Case-control study Location/recruitment: Subjects were consecutive patients at 4 neurology clinics in France between Jan and Dec 1991 Data collection: Study neurologist examined patients to determine type of MS, age at onset, and EDSS score. Neurologist then administered questionnaire asking about demographic characteristics and 14 specific items relating to the occupational environment of current (or past) job; subjects also asked (in open-ended way?) why they stopped working	N = 171 total = 77 cases (unemployed for < 5 yr at time of study) and 94 controls (still employed) Type of MS: Cases: 31% relapsing-remitting, 53% relapsing-progressive, 16% primary progressive Controls: 48% relapsing-remitting, 36% relapsing-progressive, 16% primary progressive Age (mean ± SD): Cases (unemployed): 39.0 ± 0.9 Controls (employed): 40.5 ± 0.7 Baseline measures of physical and mental functioning: EDSS (mean ± SD): Cases: 5.4 ± 0.1 Controls: 4.5 ± 0.1 Baseline work status: Cases (45% of total study population) unemployed Controls (55% of total study population) employed	1) Physical: EDSS See further under "Specific job characteristics," below 2) Mental: See under "Specific job characteristics," below 3) Laboratory: None 4) Radiographic: None 5) Other: Age Sex Marital status Job grade (high, medium, low) High school education (yes/no) Age at onset Type of MS Specific job characteristics: a) Public sector b) Desk job c) Sitting position d) Possibility of obtaining specific arrangements e) Travel time > 30 min/ day f) Daily working time > 8 hr	No direct measure of work capacity or ability Work status measured through self-report Work status (Yes/No) Cases = unemployed Controls = employed 1) Disease stage and work status (p = 0.01): Relapsing-remitting: Cases = 31% Controls = 48% Relapsing-progressive: Cases = 53% Controls = 36% Primary progressive: Cases = 16% Controls = 16% 2) EDSS (mean ± SD) and work status: Cases = 5.4 ± 0.1 Controls = 4.5 ± 0.1 p = 0.01 3) Work requirements and odds of unemployment (odds ratio [95% CI]): 0.9 (0.4-1.8) – close attention 0.7 (0.3 -1.5) – good memory 7.6 (3.2-18.2) – physical strength 3.1 (1.6 - 6.3) – manual precision	Retrospective design – EDSS not known at time cases ceased employment, but at time of study; Authors only indicate that cases were unemployed for less than 5 years at the time of the study, but do not indicate if they were employed at time of MS diagnosis. Since a high percentage indicated leaving work because of MS, it is assumed they were all employed at time of diagnosis; Cognitive function required for jobs (Table 3.0) may be biased by self-report by study subjects. QUALITY ASSESSMENT: Study described as "population-based"?: Yes Follow up > 80%?: NA Work outcomes assessed using a widely used scale?: Work status Work outcomes assessed in a blind fashion?: No If subgroups with different work ability identified: a) was there adjustment for important prognostic factors? Yes b) was there independent validation?: NA

Evidence Table 4. Association of clinical findings with work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Findings Considered	Results	Comments/Quality Scoring
				g) Accessibility problems h) Work requiring: - Close attention - Good memory - Physical strength - Manual precision - Rigid work schedule - Decision-making - Frequent moves	2.2 (1.1 - 4.6) – rigid work schedule 1.7 (0.7 - 3.4) – decision making 2.5 (1.3 - 4.9) – frequent moves 4) Job characteristics and odds of unemployment (odds ratio [95% CI]): 0.3 (0.1 - 0.5) – desk job 0.3 (0.1 - 0.7) – sitting position 0.4 (0.2, 0.8) – possibility of obtaining specific arrangements 1.7 (0.9-3.2) – travel time > 30 min 2.6 (1.2-5.7) – daily work hrs > 8 h 1.9 (0.9-4.0) – accessibility problems 5) Logistic regression of job characteristics significantly related to unemployment (odds ratio [p-value]): 0.4 ($p < 0.05$) – work in public sector 4.5 ($p < 0.01$) – work needing physical strength	

Evidence Table 5. Environmental factors and work ability

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Environmental Factors Considered	Results	Comments/Quality Scoring
Gulick, Yam, and Touw, 1989	Inclusion: Previous diagnosis of MS; *not* a resident of a nursing home or long-term care facility; age ≤ 65; self-reported employment status one of following: "employed outside the home," "home-maker," "unemployed," or "retired" (8 work status categories possible, but results were reported only for respondents in the above four categories because "too few subjects fit into categories of homebound employment, sheltered workshop, student, and volunteer for meaningful analysis") Exclusion: None specified	Cross-sectional study Location/recruitment: Subjects selected randomly from two local chapters of the National MS Society (n = 412) and recruited from a university-affiliated MS comprehensive care clinic (n = 96; all sites in New Jersey) Data collection: All data collected by survey questionnaires, which included a personal data inventory, the ADL Self-Care MS Scale, and two open-ended questions about what conditions/situations make work or chores more difficult or easier to perform	N = 508 eligible respondents (response rate "approximately 90%") Age (mean ± SD): Employed outside home: 41.9 ± 8.9 Homemaker: 48.0 ± 9.2 Unemployed: 48.8 ± 9.9 Retired: 56.3 ± 7.0 Sex: Respondents were comprised of 371 females and 137 males. No sex differences were noted among the work groups regarding education, duration of MS since diagnosis, or walking ability. Males working outside the home were older than their female counterparts (mean age 45.14 vs. 39.48; p = 0.001), but among the unemployed, males were younger (45.85 vs. 50.23; p = 0.047); the same was true in the retired group (males 54.31 vs. females 59.22; p = 0.002) (too few males in the homemaker group [n = 6] for sex difference analysis). Baseline measures of physical and mental	Rater-assigned responses to work-impeding categories of "heat/temperature intolerance" and work-enhancing category of cool temperature (Subject responses were to open-ended questions about conditions/situations that make it difficult [impeders] or easier [enhancers] to perform work or chores)	Work ability was not directly assessed. The only relevant work capacity variable was self-reported work status. Responses to open-ended questions regarding impediments to and enhancers of work performance were grouped into condition/situation categories by two independent raters. Inter-rater agreement coefficients ranged from 0.84 to 0.98 for four work-impeding categories and from 0.82 to 1.0 for five work-enhancing categories (particular categories tested for inter-rater agreement were not specified). 22 conditions that impede work performance were identified by 5% or more of participants. Among those employed outside the home, 7% included high temperature as a condition/situation that impeded work performance, along with 11 other work-impeding items such as fatigue (50%), walking (12%), vision (12%), balance (10%), standing (8%), writing (8%), numbness (8%), insufficient time (7%), pain (6%), lifting (5%), and stiffness (5%). However, none of those employed outside the home included cool temperature as a work-enhancer. High temperature was also cited as a work-impeding item by 6% of homemakers (along with 8 other items including fatigue, balance, weakness, walking, vision, pain, fine motor skills, and bending); and 8% of homemakers cited cool temperature as a work-enhancer.	Authors acknowledge that methods would not distinguish between lifelong homemakers versus homemakers who previously worked outside the home, and that some respondents who were never employed might never consider themselves to be retired. Authors suggest that intergroup differences in unassessed factors such as activity level or absence of air conditioners may have contributed to apparent differences in reports of "heat/temperature intolerance" as a work impediment among work status groups. Significant differences existed between work status groups with respect to self-reported age, MS duration, education, and walking ability. Several of these factors might conceivably be associated negatively or positively with temperature tolerance. Work status at time of MS diagnosis was not assessed. Only descriptive statistics were provided regarding temperature intolerance. No statistical comparisons were reported of this or other specific work-impeding or enhancing factors between work status groups; such statistical comparisons may not have been warranted or may not have been within the scope of the study. The concept and meaning of "work" in these questionnaire responses is necessarily general, subject to

Evidence Table 5. Environmental factors and work ability (continued)

Study	Selected Inclusion/ Exclusion Criteria	Study Design	Patients	Environmental Factors Considered	Results	Comments/Quality Scoring
			functioning: Walking ability (subscale of ADL Self-Care MS Scale; mean ± SD): Employed outside home: 20.5 ± 6.9 Homemaker: 12.7 ± 9.0 Unemployed: 5.8 ± 7.5 Retired: 8.9 ± 8.4 Baseline work status ("work category/group"): Employed outside home: 110 Homemaker: 209 Unemployed: 110 Retired: 79		By contrast, high temperature was not among the 13 work-impeding items cited by the unemployed, nor among the 11 work-impeding items cited by the retired group; although 6% of the retired listed cool temperature as a work-enhancer.	interpretation, and probably varies considerably between work group domains. For instance, the nature of work demands probably differs considerably for retired respondents versus those working outside the home. Study comprised solely of direct reporting and content analysis of questionnaire responses QUALITY ASSESSMENT: Study described as "population-based"?: Yes Follow up > 80%?: Yes – "approximately 90%" Work outcomes assessed using a widely used scale?: Yes Work outcomes assessed in a blind fashion?: NA If subgroups with different work ability identified: Was there adjustment for important prognostic factors – No, although via inter-group differences in age, years since diagnosis, education and walking ability were reported b) was there independent validation?: No

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Acronyms/Abbreviations Used in the Evidence Tables

4-AP	4-aminopyridine
9-HPT	9-Hole Peg Test
ACTH	adrenocorticotropic hormone
ADL	activities of daily living
AE	adverse event
AI	Ambulation Index
ANOVA	analysis of variance
APOE	apolipoprotein E
ASQ	Anxiety Scale Questionnaire
AUC	area under curve
AZA	azathioprine
BAEP	brainstem auditory evoked potential
BBT	Box-and-Block Test
BDI	Beck Depression Inventory
B/l	baseline
BMS	benign MS
BTX	botulinum toxin
CBT	cognitive-behavioral therapy
CDQ	Clinical Depression Questionnaire
CHF	congestive heart failure
CI	confidence interval
CNA	certified nursing assistant
CNS	central nervous system
Cop1	copolymer 1 = glatiramer acetate
CPMS	chronic progressive MS
CSF	cerebrospinal fluid
CT	computed tomography
CYCLO	cyclophosphamide
DBP	diastolic blood pressure
DEX	Dysexecutive Syndrome Questionnaire
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*
DSS	Disability Status Scale
DTR	deep tendon reflex
EADL	Extended Activities of Daily Living Scale
EDSS	Expanded Disability Status Scale
EEG	electroencephalogram
EMG	electromyogram
EMQ	Everyday Memory Questionnaire
ENS	electrical neuromuscular stimulation
FIM	Functional Independence Measure
FIS	Fatigue Impact Scale
FLAIR	fluid-attenuated inversion recovery
FSS	Fatigue Severity Scale
GA	glatiramer acetate = copolymer 1

GEMS	Global Evaluation-MS
GHQ-28	General Health Questionnaire-28
GI	gastrointestinal
GNDS	Guy's Neurological Disability Scale
GP	general practitioner
HIV	human immunodeficiency virus
HPLP-II	Health Promoting Lifestyle Profile II
HMO	health maintenance organization
hr	hour(s)
HRSD	Hamilton Rating Scale for Depression
IECS	Internal-External Control Scale
IFNβ-1a	interferon beta-1a
IFNβ-1b	interferon beta-1b
IgG	immunoglobulin-G
IgM	immunoglobulin-M
IL-2	interleukin-2
IM	intramuscular
IQR	interquartile range
ISS	Incapacity Status Scale
ITMS	intrathecal IgM synthesis
ITT	intention-to-treat
IV	intravenous
LHS	London Handicap Scale
MAQ	Memory Aids Questionnaire
MEP	motor evoked potential
MFIS	Modified Fatigue Impact Scale
MIU	million International Units
MMPI	Minnesota Multiphasic Personality Inventory
MMSE	Mini Mental State Examination
mo	month(s)
MP	methylprednisolone
MRD	Minimal Record of Disability
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
MS-FS	MS-Specific Fatigue Scale
MSIS	MS-Impairment Scale
MSQLI	MS Quality of Life Inventory
MTX	mitoxantrone
NA	not applicable
nIFNβ	natural interferon beta
NPV	negative predictive value
NR	not reported
NRS	Neurologic Rating Scale
NS	not statistically significant
NSAID	non-steroidal anti-inflammatory drug

PAIS-SR	Psychological Adjustment to Illness Scale – Self-Report
PASAT	Paced Auditory Serial Addition Test
PEX	plasma exchange
PFC	Problem-Focused Coping score from Ways of Coping Checklist
PO	per os (by mouth)
POMS	Profile of Mood States
PPMS	primary progressive MS
PPV	positive predictive value
PRQ	Personal Resources Questionnaire
QOL	quality of life
RCT	randomized controlled trial
ROM	range of motion
RR	risk ratio
RRMS	relapsing-remitting MS
SBP	systolic blood pressure
SC	subcutaneous
SCI	spinal cord injury
SD	standard deviation
SDDR	Standard Day Dependency Record
SDDRE	Standard Day Dependency Record-Essential Subscale
SDDRO	Standard Day Dependency Record-Occasions Subscale
SDMT	Symbol Digit Modalities Test
SE	standard error
SEAB	Self-Efficacy for Adjustment Behaviors Scale
SEG	supportive-expressive group therapy
SEP	somatosensory evoked potential
SES	Self-Esteem Scale
SET	Tempelaar Social Experience Checklist
SF-36	Medical Outcomes Study 36-Item Short-Form Health Survey
SIP	Sickness Impact Profile
SN	sensitivity
SNRS	Scripps Neurological Rating Scale
SP	specificity
SPMS	secondary progressive MS
SSDI	Social Security Disability Insurance
SSI	Supplemental Security Income
STAI	State-Trait Anxiety Inventory
STAI-S	State-Trait Anxiety Inventory-State
STAI-T	State-Trait Anxiety Inventory-Trait
STAXI	State-Trait Anger Expression Inventory
THC	tetrahydrocannabinol
UTI	urinary tract infection
VAMC	Veterans Affairs Medical Center
VAS	visual analog scale
VEP	visual evoked potential
VFS	Visual Faces Scale

WBC	white blood cell
wk	week(s)
WMS VR	Wechsler Memory Scale Visual Reproduction
yr	year(s)