Disease-modifying Therapies for Multiple Sclerosis: A guideline project protocol

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

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**DISCLOSURES**

Alexander Rae-Grant is a local PI for two multiple sclerosis (MS) treatment studies in progressive MS with Novartis and Biogen IDEC for which he does not receive any intellectual property or financial reimbursement; receives royalties from two textbooks he has published, one on neurology and one on MS; and organizes and receives honoraria for ground rounds and neurology review courses.

Alejandro Rabinstein currently serves as an associate editor for the *Neurocritical Care* journal; receives publishing royalties from Elsevier, Oxford, and UptoDate; and serves on the event
adjudication team for the PREVAIL trial and CAPS-2 registry, sponsored by Boston scientific, which both investigate left atrial appendicular closure device for stroke prevention. He served as an external safety monitor and received reimbursement from the NIH for the trial ALIAS which investigated albumin for acute ischemic stroke. His institution receives financial compensation from DJO Global for an investigator initiated study investigating the prevention of deep venous thrombosis in the upper extremities.

Bruce Cree has received compensation for consulting from Abbvie, Biogen IDEC, EMD Serono, MedImmune, Novartis, Genzyme/Sanoﬁ Aventis, and Teva Neurosciences; has received research support from Acorda, Avanir, Biogen IDEC, EMD Serono, Hoffman La Roche, MedImmune, and Teva Neurosciences; has given expert testimony and prepared an affidavit for medical malpractice cases (1 or 2 per year) within his area of expertise; and has acted as consultant in a legal proceeding for Biogen IDEC and Acorda.

Richard Dubinsky serves on a scientific advisory board for Allergan Pharmaceuticals; receives funding for travel from Allergan Pharmaceuticals, the Huntington Study Group, and the American Academy of Neurology (AAN); serves as an associate editor for Neurology®; has received honoraria from and served on a speakers bureau for Allergan Pharmaceuticals; and has received research support from Allergan Pharmaceuticals, the National Institutes of Health, and the Agency for Healthcare Research and Quality. His wife holds stock in Abbott Laboratories.

Gregory Day serves as the clinical director of the Anti-NMDA Receptor Encephalitis Foundation, Inc. Canada (the Foundation is supported by private donor contributions) but does not receive financial reimbursement for his appointment or service; receives funding from Washington University for an imaging study in which Avid Pharmaceuticals provides free radionucleotide tracer valued between $5,000 and $10,000, but does not receive any other compensation from the company; received the Future Leader in Dementia award in October 2013 (including travel support to a Canadian conference for dementia), sponsored by Pfizer, Canada; has received research support from the Weston Brain Foundation, as a recipient of the Eugene M Johnson Jr. Weston Brain Institute Postdoctoral Fellowship in Dementia Research; and holds stock in ANI Pharmaceuticals.

Michael Haboubi has received travel reimbursement and honoraria for grand rounds presentations in Madisonville, Kentucky.

June Halper has received consultant fees for a non-CME research activity from Biogen.

Jonathan P. Hosey has no relevant disclosures to report.

David E. Jones authored an MS Coalition consensus paper on disease-modifying therapies (DMTs) in MS and served as co-chair of the advocacy committee of the Consortium of Multiple Sclerosis Centers (CMSC), but did not receive financial compensation for either service; received institutional and personal compensation for consulting with Genzyme and Novartis Pharmaceuticals; receives institutional and personal compensation for consulting for Biogen IDEC, receives travel reimbursement from Biogen IDEC, Genzyme, CMSC, and Multiple Sclerosis Association of America (MSAA) for travel to meetings; has received honoraria for
projects with the CMSC and MSAA; is employed by the University of Virginia; and has given expert testimony on a malpractice case involving a patient with neurosarcoïdosis.

Annette Langer-Gould is involved in the National Multiple Sclerosis Society’s (NMSS) MS and Pregnancy Study, and the MS Prevalence Working Group, but does not receive financial compensation for her involvement; has received travel reimbursement from the Mayo Clinic, Arizona, where she spoke as an invited speaker; from the Institute of Medicine, Washington, DC, for participating on a study panel; and from the National Institute for Neurological Disorders and Stroke (NINDS), to participate in a study section; receives research support from Biogen IDEC for her service as a local PI for two clinical trials, from Hoffman LaRoche for her service as a local PI for a clinical trial, and from the NINDS as R01 grant funding.

Robert Lisak serves as the President of the CMSC and as a member of the Board of the DMC Foundation; has served on scientific advisory boards for Syntimmune and Mallinckrodt; has received funding for travel from the CMSC, the NMSS, the GBS/CIDP Foundation, and the International Syntimmune for travel to consultants meetings; has served as a journal editor for Clinical and Experimental Neuroimmunology and for Clinical Neuropharmacology; has received publishing royalties from Willey for International Neurology, A Clinical Approach; has received honoraria from Syntimmune, Mallinckrodt, and Teva Pharmaceuticals; has served on a speakers bureau for Teva Pharmaceuticals for non-drug-related talks; has received research support from Mallinckrodt for investigator-initiated wet bench studies, and from Teva, Biogen IDEC, Novartis, Avanir, and Acorda for serving as a site investigator in multicenter trials; has received financial compensation from the NMSS; has given expert testimony, prepared an affidavit, and acted as witness for Teva Pharmaceuticals; and has acted as a witness for Acorda.

Ruth Ann Marrie has served as site principal investigator for Sanofi-Aventis clinical trials; receives research grants from nonprofit organizations, including CIHR, NMSS, MS Society of Canada, MS Scientific Research Foundation, CMSC, Research Manitoba, and Rx & D Health Research Foundation; and serves on the editorial board of Neurology.

Daniel Pelletier has served on scientific advisory boards for Biogen-IDEC, Genzyme, Hoffman LaRoche, Acorda, Novartis, and EMD-Serono; has received research support for Biogen-IDEC, Genzyme, Hoffman LaRoche, and the NIH NINDS; and has received honoraria for providing consulting services at scientific advisory board meetings from Biogen-IDEC, Genzyme, Hoffman LaRoche, Acorda, Novartis, and EMD-Serono.

Sonja Potrebic receives travel reimbursement from the AAN for the RITE work group and Registry Committee meetings.

Rick Sommers reports no relevant disclosures.

Cynthia Sitcov reports no relevant disclosures.

Julie Stachowiak reports no relevant disclosures.
Thomas S.D. Getchius has received financial compensation for travel for speaking at the University of Louisville mTBI conference; has been serving as the vice-chair of the Council of Medical Specialty Societies Clinical Practice Guideline Component Group from November 2013 to present, and has received research support from the CDC as a grant for muscular dystrophy guideline development, dissemination, and implementation.

Shannon A. Merillat reports no relevant disclosures.

Tamara Pringsheim has received financial reimbursement for travel to attend the Movement Disorder Society Meeting from Allergan Canada, Teva Canada Innovation, and has received research support from Shire Canada Inc., and the Canadian Institute for Health Research.
GUIDELINE PROJECT PROTOCOL

Guideline project development plan

This proposed guideline project will be developed in accordance with the processes described in the AAN clinical practice guideline development process manual 2011 (as amended). The authors of this project will use the systematic review results to develop a practice advisory or guideline. The Guideline Development, Dissemination, and Implementation (GDDI) subcommittee will determine if the systematic review will inform an evidence-based guideline or a practice advisory. This protocol will be posted for public comment to solicit feedback from experts and non-experts. Patient representatives are included on the panel.

Guideline project timeline

The tentative timeline for development of the systematic review is as follows:

Protocol posted for public comment: July 13, 2015 to August 13, 2015

Review of abstracts: Completed by July 2015

Screening of full-text articles: Completed by August 2015

Review of full-text articles and data extraction: Completed by November 2015

Evidence tables: Completed by January 2016

First draft of systematic review: Completed and presented to the GDDI April 2016

Systematic review draft posted for public comment: May 2016

Composition of the Author Panel
In May 2015, a multidisciplinary panel consisting of 13 AAN physician members, 2 representative members from the Consortium of Multiple Sclerosis Centers (CMSC), 3 patient representative members was recruited to develop this systematic review, and 2 AAN staff representative members. The physicians include content experts (B.C., D.E.J., D.P., R.A.M., J.H.); a methodology expert (T.P.); Guideline Development, Dissemination, and Implementation Subcommittee (GDDI) members (A.R., A.R.G., G.D., S.P., R.D., A.L.G.); and CMSC representatives (J.H., R.L.). The patient representatives (J.S., R.S., C.S.) include 3 adults who have an MS diagnosis. The physicians and patient representatives were required to submit online conflict of interest (COI) forms and copies of their curriculum vitae (CV). The panel leadership, consisting of the lead author (A.R.-G.), the AAN methodologist (T.P.), and the AAN staff persons (T.G., S.M.), reviewed the COI forms and CVs for financial and intellectual COI. These documents were specifically screened to exclude both those individuals with a clear financial conflict and those whose profession and intellectual bias would diminish the credibility of the review in the eyes of the intended users. In accordance with AAN Policy, the lead author (A.R.-G.) has no COI. Four of the 20 authors were determined to have COI, but the COI were judged to be not significant enough to preclude them from authorship (D.E.J., B.C., D.P., R.L.). All authors determined to have COI will not be permitted to review or rate the evidence. These individuals will be used in an advisory capacity to help with the validation of the key questions, the scope of the literature search, and the identification of seminal articles to validate the literature search. Panel members with COI will be allowed to participate in the recommendation development process. The panel was recommended to the AAN GDDI leadership, who reviewed the author panel constitution and the panel leadership’s COI forms, and provided final approval.
This panel was solely responsible for the final decisions about the design, analysis, and reporting of the proposed systematic review, which was then submitted for approval to the AAN GDDI.

**Introduction to proposed guideline project topic**

Multiple sclerosis (MS) is the second most common cause of disability in young adults after trauma, and affects approximately 500,000 people in the United States and 2.5 million patients worldwide. Annual direct costs have been estimated at about $24,000 higher for the MS population than for the non-MS population. In most patients, MS is ultimately disabling, although the course varies markedly. Since 1993 12 disease-modifying therapies (DMTs) have been approved in the United States for relapsing forms of MS; most of these therapies are approved for use in other industrialized nations. Many additional medications have been used for disease modification of MS on the basis of evidence of varying quality. All have possible adverse effects which vary from cosmetic to life-threatening.

Controversies persist concerning who should receive these medications (type of MS, amount of disease activity, whether the patient has a clinically isolated syndrome of demyelination), when therapy should be initiated, and whether there are sufficient data to comment on the comparative efficacy of agents. In addition, changes in the diagnostic criteria for MS in 2010 as well as modification of classification scheme for multiple subtypes in 2014 may complicate the analysis and clinical application of efficacy data from clinical trials. Before recommending a specific therapy, the clinician must navigate these complexities, while carefully balancing the potential for therapeutic effects against drug- and individual-specific risk profiles and preferences. The recent proliferation of new DMTs (each with a different risk profile) has
advanced this discussion to the forefront of clinical care, increasing its relevance to clinicians and patients alike.

The prior AAN clinical practice guideline on DMTs in MS was published in 2002. At that time, fingolimod, teriflunomide, dimethyl fumarate, pegylated interferon beta-1a, glatiramer acetate 40 mg, natalizumab, and alemtuzumab were not commercially available. In addition, the 2002 guideline did not evaluate other medications that are either close to commercial approval now (e.g., daclizumab highyield process [DAC HYP], and ocreluzimab) or are widely used throughout the world (e.g., mycofenolate mofetil). In light of these therapeutic advances and persistent knowledge gaps, an updated systematic review and practice guideline was prioritized by the AAN GDDI and AAN leadership.

Rationale for this proposed guideline project

The guideline seeks to answer the following clinical questions:

Clinical Questions

1a. In people with MS, are DMTs superior to placebo as measured by annualized relapse rates?
1b. In people with MS, is any disease-modifying therapy (DMT) superior to another, as measured by a comparative effectiveness trial or network meta-analysis, in lowering the annualized relapse rate?
2a. In people with MS, are DMTs superior to placebo in reducing MRI new disease activity as measured by new T2 lesion burden, gadolinium-enhancing lesions, or atrophy measures?
2b. In people with MS, is any DMT superior to another, as measured by a comparative effectiveness trial or network meta-analysis, in reducing MRI new disease activity as measured by new T2 lesion burden, gadolinium-enhancing lesions, or atrophy measures?
3a. In people with MS, are DMTs superior to placebo in preventing disease progression as measured by in-study disease progression measures?

3b. In people with MS, is any DMT superior to another, as measured by a comparative effectiveness trial or network meta-analysis, in preventing disease progression as measured by in-study disease progression measures?

4. In people with MS, is any DMT superior to placebo in prolonging survival?

5a. In people with MS, are DMTs superior to placebo in preventing cognitive decline, as measured by tests of cognitive function?

5b. In people with MS, is any DMT superior to another, as measured by a comparative effectiveness trial or network meta-analysis, in preventing cognitive decline, as measured by tests of cognitive function?

6a. In people with MS, are DMTs superior to placebo in improving or maintaining health-related quality of life (HRQOL), as measured by general and disease-specific validated HRQOL measures?

6b. In people with MS, is any DMT superior to another, as measured by a comparative effectiveness trial or network meta-analysis, in improving or maintaining HRQOL, as measured by general and disease-specific validated HRQOL measures?

7a. In people with MS, are DMTs superior to placebo in validated measures of patient preferences?

7b. In people with MS, is any DMT superior to another, as measured by a comparative effectiveness trial or network meta-analysis, in validated measures of patient preferences?

8. In people with MS, is any DMT superior to placebo or other DMTs on measures of adherence to treatment?
9. In people with MS, is changing to a different DMT superior to continuing present DMT in terms of relapse rate and MRI T2 or gadolinium lesion activity?

10. In people with progressive MS without relapses, is continuing DMT superior to stopping DMT as measured by relapse rate or clinical disease progression?

11. What are the adverse effects of DMTs in patients with MS compared with placebo (e.g., depression, skin reactions, allergic reactions, progressive multifocal leukoencephalopathy, macular edema, symptomatic liver function abnormalities, infections, emergent autoimmune diseases, malignancy)?

12. What is the comparative cost effectiveness of using DMT vs not using DMT on direct and indirect costs of MS?

Possible supplementary materials (beyond systematic review data):

- Cost data for medications as available
- Recommendations for monitoring from package inserts
- Reference to related data such as MRI recommendations from the Consortium of Multiple Sclerosis Centers
- Stopping medication publication from the Agency for Healthcare Research and Quality in clinical context

All questions will be categorized and answered by MS disease subgroup -- relapsing-remitting MS, primary progressive MS, and secondary progressive MS with and without relapses. In addition, data on patients with clinically isolated syndromes of demyelination (either McDonald 2005 or 2011 criteria) will be included where applicable.
**Types of Participants**

Adults aged 18 years or older with relapsing-remitting MS, progressive MS with relapses, primary progressive MS, and secondary progressive MS. Definitions of MS have changed over time. Most recent studies use either 2005 or 2011 international diagnosis criteria for entry into clinical trials. In the 2011 version some patients previously diagnosed as having a clinically isolated syndrome would be rediagnosed as having MS. In addition, international classification of type of MS is usually based on 1999 or 2014 revision data.

**Types of Intervention**

DMTs are defined as medications that aim to impact the clinical course of MS by decreasing relapses and slowing the progression of the disease. We will limit our search to widely used medications that have been approved by one of the following organizations: the US Food and Drug Administration, Health Canada, or the European Medicines Agency. The following medications will be considered:

- Methotrexate
- Cyclophosphamide
- Azathioprine
- Corticosteroids for long-term disease modification only
- Interferon beta  
  (interferon beta-1a weekly IM, interferon beta-1a sq tiw, interferon beta-1b alt day, pegylated interferon beta-1a sq alt week)
- Glatiramer acetate
- Natalizumab
- Teriflunomide
- Mycophenolate mofetil
- Laquinimod
- Rituximab
- Daclizumab
- Mitoxantrone
- Alemtuzumab
- Fingolimod
- Dimethyl fumarate
- Ocrelizumab

**Comparison Group**
We will compare the effects of DMTs with placebo or with other DMTs.

**Types of Outcome Measures**

1. Clinical efficacy, as measured by the following outcomes: annualized relapse rate, new lesions on MRI, validated measures of disability and disease progression, cognition
2. Comparative efficacy
3. Adverse effects
4. Quality of life
5. Patient preferences
6. Adherence to treatment
7. Economic analysis

For each outcome measure, a minimally important clinical effect size will be determined a priori.

**Rationale for clinical questions**

Each of the questions above is geared toward gathering data on decision making which may improve care for people with MS. Decisions about starting and continuing DMT should incorporate POEMS (patient-oriented evidence that matters), personalized medicine (incorporating patient-specific health factors and risks as well as patient preferences and values), and risk management to reduce adverse events in chronically used medications.

In addition, there are data to suggest that some MS populations benefit more from DMTs than others, and this should be clarified so that those people with MS who are least likely to benefit from treatment are not subjected to treatment with medications which are not effective and for which there are known risks.
Adherence to treatment is a critical concern in the efficacy of long-term medication use. The subgroup felt that a systematic review of literature on DMT adherence may help guide clinicians with regard to which strategies may help optimize adherence in patients using DMTs.

**Study Screening and Selection Criteria**

Our search for relevant evidence will begin with evaluation of published systematic reviews in the Cochrane library on DMT in MS. We will evaluate all Cochrane reviews in duplicate using the AMSTAR tool, a rating instrument of systematic review quality. All published reviews will be updated by repeating the outlined search strategies from the date last searched in the review to the present. When there is a DMT for which no previous Cochrane review has been published, we will perform a de novo systematic review following the 2011 AAN guideline development process manual. To minimize publication bias, grey literature (including clinical trials and other sources of unpublished information about studies), review papers, meta-analyses, and case-reports will be considered and will inform conclusions and recommendations, and will be included in the formal evidence synthesis and weighting of recommendations.

**Inclusion Criteria**

- Medications licensed for use in Canada, the US, or Europe for disease modification in MS
• Study types to include: Randomized control trials, cohort studies, (n must be greater than 10)
• All languages

Exclusion Criteria
• Relapse management or symptomatic treatments
• Not relevant to the clinical questions
• Outside of study population
DISCLAIMER

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

CONFLICT OF INTEREST

The American Academy of Neurology is committed to producing independent, critical and truthful systematic reviews (SRs) and clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the conclusions of SRs and recommendations of CPGs. To the extent possible, the AAN keeps separate those who have a
financial stake in the success or failure of the products appraised in the SRs and CPGs and the developers of these documents. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. The AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, SR and CPG projects. Drafts of this protocol have been reviewed by at least one AAN committee. The AAN SR and CPG Author Conflict of Interest Policy can be viewed at www.aan.com. For complete information on this process, access the 2011 AAN process manual.
REFERENCES


