Practice guideline: Disease-modifying therapies for adults with multiple sclerosis

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

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Acknowledgment

The authors acknowledge the North American Research Committee on Multiple Sclerosis (NARCOMS) Registry for its assistance in administering an outcomes survey, the results of which were included in this practice guideline. NARCOMS is supported in part by the Consortium of Multiple Sclerosis Centers (CMSC) and the Foundation of the CMSC.

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Approved by the Guideline Development, Dissemination, and Implementation Subcommittee on October 9, 2017; by the Practice Committee on October 21, 2017; and by the AAN Institute Board of Directors on March 6, 2018.

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STUDY FUNDING

This practice guideline was developed with financial support from the American Academy of Neurology (AAN). Authors who serve as AAN subcommittee members or as methodologists (A.R.-G., G.S.D., A.R., G.S.G., M.H., S.P., T.P.), or who are or were AAN staff members (T.S.D.G., S.A.M.), were reimbursed by the AAN for expenses related to travel to subcommittee meetings where drafts of manuscripts were reviewed. All authors on the panel were reimbursed by the AAN for expenses related to travel to 2 in-person meetings.

DISCLOSURE

A. Rae-Grant receives royalties from 2 textbooks he has published, 1 on neurology and 1 on multiple sclerosis (MS); organizes and receives honoraria for ground rounds and neurology review courses; and is local primary investigator for a clinical trial with MedDay Pharmaceuticals, for which he receives no personal compensation.

A. Rabinstein has no relevant disclosures to report.

B. Cree has received compensation for consulting from Abbvie, Biogen, EMD Serono, GeNeuro, Genzyme/Sanofi Aventis, Novartis, and Shire; 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 Acorda and Biogen.

G. Gronseth serves as associate editor (level of evidence review) for *Neurology*; serves on the editorial advisory board for *Neurology Now*; and is compensated by the American Academy of Neurology (AAN) for methodologic activities.

G. Day holds stock in ANI Pharmaceuticals.

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

J. Halper has no relevant disclosures to report.

J. Hosey has no relevant disclosures to report.

D. Jones has received personal compensation for consulting from Biogen and Genzyme; has received honoraria from the Consortium of Multiple Sclerosis Centers (CMSC), the Multiple Sclerosis Association of America (MSAA), and the Pharmacy Quality Alliance (PQA); has received institutional research support from Biogen and the National MS Society (NMSS); has received salary support from the CMSC; and has received travel reimbursement from Biogen and Genzyme and from the AAN, Can Do MS, the CMSC, and the MSAA.

R. Lisak served as the President of the CMSC and serves as a member of the Board of the DMC Foundation; has served on scientific advisory boards for Mallinckrodt, Syntimmune, Celegene, and Alexion; serves as chair of the adjudication committee of a clinical trial (PAREXEL); has

received funding for travel from the CMSC, the GBS/CIDP Foundation, the NMSS, and Syntimmune for travel to consultants meetings; has served as a journal editor for *Clinical and Experimental Neuroimmunology* and *Clinical Neuropharmacology*; has received publishing royalties from Willey for *International Neurology, A Clinical Approach*; has received honoraria from Mallinckrodt, Syntimmune, and Teva Pharmaceuticals, and from the consulting agencies AlphaSights, ClearView Healthcare Partners, GLC, and Insights Consulting; has served on a speakers bureau for Teva Pharmaceuticals for talks unrelated to pharmaceuticals; has received research support from Mallinckrodt for investigator-initiated wet bench studies, and from Acorda, Avanir, Biogen, Chugai, Genentech, MedImmune, Novartis, and Teva Pharmaceuticals for serving as a site investigator in multicenter trials; has given expert testimony, prepared an affidavit, and acted as witness for Teva Pharmaceuticals; and has acted as an expert on a patent case for Acorda. Wayne State University has received financial compensation from the NMSS for his salary as principle investigator for a research grant.

R.A. Marrie receives research grants from nonprofit organizations, including Canadian Institutes of Health Research (CIHR), the CMSC, Crohn's and Colitis Canada, the NMSS, the Multiple Sclerosis Society of Canada, the Multiple Sclerosis Scientific Research Foundation, and Research Manitoba; and serves on the editorial board of *Neurology*.

D. Pelletier has served on scientific advisory boards for Biogen, EMD Serono, Genzyme/Sanofi Aventis, Hoffman LaRoche, and Novartis; has received research support for Biogen, Genzyme, Hoffman LaRoche, and the National Institute of Neurological Disorders and Stroke (NINDS) of the NIH; and has received honoraria for providing consulting services at scientific advisory board meetings from Biogen, EMD Serono, Genzyme/Sanofi Aventis, Hoffman LaRoche, and Novartis.

S. Potrebic S receives travel reimbursement from the AAN for attending AAN Residency In-Service Training Examination Work Group meetings, AAN Axon Registry Committee meetings, AAN Guideline Development, Dissemination, and Implementation Subcommittee meetings, and the Guidelines International Network North America E-GAPPS (Evidence-based Guidelines Affecting Policy, Practice, and Stakeholders) conference.

R. Sommers reports no relevant disclosures.

C. Sitcov reports no relevant disclosures.

J. Stachowiak reports no relevant disclosures.

T. Getchius is a former AAN employee and reports no relevant disclosures.

S. Merillat reports no relevant disclosures.

T. Pringsheim has received research support from the CIHR and Shire Canada Inc.

ABBREVIATIONS

AAN: American Academy of Neurology
AEs: adverse effects
ALT: alanine aminotransferase
ARRs: annualized relapse rates
AST: aspartate aminotransferase
CIS: clinically isolated syndrome
CMSC: Consortium of Multiple Sclerosis Centers"
COI: conflict of interest
CV: curriculum vitae
DMTs: disease-modifying therapies
EDSS: Expanded Disability Status Scale
FDA: US Food and Drug Administration
GDDI: Guideline Development, Dissemination, and Implementation Subcommittee
IOM: Institute of Medicine
mIUs: milli-international units
MS: multiple sclerosis
NARCOMS: North American Research Committee on Multiple Sclerosis
PML: Progressive multifocal leukoencephalopathy
PPMS: primary progressive MS
RCTs: randomized controlled trials
RD: risk difference
REMS: risk evaluation and mitigation strategies
RMD: raw mean difference
RR: risk ratio
RRMS: relaxing−remitting MS
SAEs: serious adverse effects
SMD: standardized mean difference
SPMS: secondary progressive MS

ABSTRACT

Objective: To review evidence on starting, switching, and stopping disease-modifying therapies (DMTs) for multiple sclerosis (MS) in people with clinically isolated syndrome (CIS), relapsing–remitting MS (RRMS), and progressive forms of MS; and to develop recommendations for starting, switching, and stopping DMTs.

Methods: The guideline panel followed the American Academy of Neurology (AAN) 2011 guideline development process, as amended. Relevant, peer-reviewed research articles, systematic reviews, and abstracts were identified using a literature search of MEDLINE, CENTRAL, and EMBASE published from database inception to November 2016. Studies were rated (Class I–IV) using the AAN therapeutic classification of evidence scheme. The systematic review also used prior published Cochrane reviews on DMT for MS. Recommendations were developed using the AAN process, including a modified Delphi process. People with MS were involved throughout the guideline development process, and 2 public review periods were held.

Results: Twenty Cochrane reviews and an additional 73 full-text articles were selected for data extraction through an updated systematic review, completed in November 2016. In people with RRMS, many DMTs are superior to placebo as measured by annualized relapses rates (ARRs), new disease activity as measured by new MRI T2 lesion burden, and in-study disease progression (see summary and full-text publications). For people with RRMS who experienced a relapse while using interferon beta or glatiramer acetate, alemtuzumab is more effective than interferon beta-1a 44 micrograms subcutaneous 3 times per week in reducing the ARR. For people with primary progressive MS, ocrelizumab is probably more effective than placebo as measured by in-study disease progression. DMT for MS have varying adverse effects. In people with CIS, glatiramer acetate and interferon beta-1a subcutaneous 3 times per week are more effective than placebo in decreasing the risk of conversion to MS. Cladribine, immunoglobulins, interferon beta-1a 30 micrograms intramuscular weekly, interferon beta-1b subcutaneous alternate day, and teriflunomide are probably more effective than placebo in decreasing the risk of conversion to MS.

Recommendations: The guideline panelists made 17 starting, 10 switching, and 3 stopping recommendations, each supported by structured rationales. These recommendations included patient engagement strategies and individualization of treatment, a focus on monitoring of adherence, and assessment of disease comorbidities. The panelists also included recommendations for who should start a DMT, including people with RRMS and people with a single clinical demyelinating event and 2 or more brain lesions characteristic of MS who decide they want to take DMTs. The panelists included recommendations for switching where breakthrough disease occurs. They also discussed DMT risks, including counseling about progressive multifocal leukoencephalopathy risk in people with MS taking natalizumab, fingolimod, rituximab, ocrelizumab, and dimethyl fumarate. The panelists made suggestions for

future research, including higher potency treatment initially vs standard stepped-care protocols, longer term studies, studies focused on patient-centered outcomes, comparative effectiveness studies, better definitions of *highly active MS,* and studies of various switching strategies.

INTRODUCTION

Multiple sclerosis (MS) affects more than 400,000 people in the United States, and more than 2.3 million people have MS worldwide.[e1] In the United States, annual direct (health-related) costs are estimated to be $24,000 or more for people living with MS than for those without MS.[e2]

MS is considered an immune-mediated demyelinating disease of the CNS, characterized on histopathology by focal perivenular infiltrates of leukocytes (primarily macrophages and lymphocytes) and plaque formation.[e3,e4] In acute plaques, oligodendroglial cells are injured, with relative axonal sparing, although many axons are also transected. In these plaques, macrophages stain positively for myelin antigens, indicating active scavenging of myelin debris. Chronic plaques show astrogliosis, with fewer inflammatory cells seen compared with acute plaques. In people with progressive MS, widespread microglial activation is seen in addition to focal plaques. Cortical plaques are common in early and late MS. These cortical plaques are not associated with venules and are likely caused by direct pial infiltration by inflammatory cells. Wallerian degeneration[e5] and mitochondrial dysfunction[e6] are thought to contribute to gradual worsening of function and to brain and spinal cord volume loss. Ectopic meningeal, perivascular, and intraparenchymal lymphoid follicle–like structures of B cells have been found.[e7] In some cases, meningeal lymphoid follicle–like structures are associated with underlying cortical plaques, suggesting that secreted factors from follicles may contribute to demyelination.

Extensive immunologic studies of peripheral blood show differences in immune regulation between persons with MS and unaffected controls. These differences include alterations in the proportions of regulatory T cells and different patterns of cytokine expression. Many CNS autoimmune diseases, such as neuromyelitis optica or *N*-methyl-D-aspartate receptor encephalitis, are associated with pathologic antibodies directed against a specific target.[e8] However, in MS, all attempts at identifying antigen-specific targets have been unsuccessful, including logical potential candidates such as myelin proteins (e.g., myelin basic protein, myelin oligodendrocyte glycoprotein, and proteolipid protein).[e9] Analysis of oligoclonal bands has also failed to reveal a consistent antibody pattern across people with MS.[e10] Cloned antibodies from CSF oligoclonal bands have not revealed a common antigenic target.[e11] Thus, intrathecal synthesis of gamma globulins, the immunochemical hallmark of MS, does not appear to be associated with specific CNS targets.[e12,e13]

Despite an inability to conclusively determine an autoimmune target in people with MS, the success of clinical trials evaluating a wide variety of immune-modulating or immune-

suppressing treatments strongly supports immune-mediated mechanisms of disease propagation.[e14] Since 1993, multiple disease-modifying therapies (DMTs) have been approved in the United States for the treatment of relapsing forms of MS; most of these therapies are approved for use in other countries. In addition, many other medications have been used off label for disease modification of MS. Effective medications share several features: (1) All effective medicines modify measures of disease activity such as relapse rates, the emergence of new or enhancing lesions on MRI, disability, or other parameters. (2) None of these medications is curative. (3) All these medications may have adverse effects (AEs), which may vary from bothersome to life-threatening.

Although the disease course is known to vary widely, life expectancy may be shortened by about 6 to 7 years in persons with MS.[e15] In addition, in many people with MS, progression of the disease ultimately leads to severe disability.[e16] Early studies suggested that most individuals with relapsing−remitting MS (RRMS) make the transition to secondary progressive MS (SPMS) if observed for long enough intervals.[e17] These statistics challenge clinicians to manage and control disease activity in the interest of helping persons with MS maintain a vibrant and meaningful life.

The 2002 American Academy of Neurology (AAN) clinical practice guideline on DMTs in MS[e18] systematically reviewed injectable medications then approved for use in people with MS, including interferon beta-1b (interferon beta-1b subcutaneous alternate day: BETASERON), interferon beta-1a IM (interferon beta-1a IM weekly: AVONEX), interferon beta-1a subcutaneous (interferon beta-1a subcutaneous 3 times per week [Rebif]) and glatiramer acetate (COPAXONE). Medications commonly prescribed off label for the treatment of MS were not reviewed (e.g., azathioprine, cyclophosphamide, mycophenolate mofetil).[e18] The treatment landscape has changed considerably since then, with more than 17 medications currently approved and widely prescribed for treating MS in the United States, and other agents nearing commercial approval. As a result, clinicians and people with MS may now choose from several medications, with differing mechanisms of action, risk profiles, and monitoring requirements. These additional options have increased interest in comparing different medications for which specific data may not be available.[e12,e19] In addition, changes in the diagnostic criteria for MS[e20] in 2010, and modification of the classification scheme for MS subtypes[e21] in 2014, have complicated the extension of efficacy data from clinical trials to particular subgroups of people with MS. Before recommending a specific therapy, the clinician must navigate these complexities while carefully balancing the potential for therapeutic benefits of a medication with patient preferences, monitoring recommendations, drug- and individual-specific risk factors, and concerns regarding the long-term risk of MS-related disability and morbidity.

Recognizing all of this, AAN members and leadership articulated a strong need for a practice guideline reflective of the current evidence landscape and specific to the prescribing of DMTs to people with MS. Because of these complexities, an up-to-date practice guideline focusing on these medications is essential to AAN members and other clinicians committed to the delivery of optimal care to people with MS.

This practice guideline reviews indications for the use of DMTs in people with MS; counseling before and during use of DMTs; patient preferences regarding DMT use; matters pertinent to switching or stopping DMTs; and indications for use in different MS types (RRMS, SPMS, primary progressive MS [PPMS]). Potential AEs related to DMT use are also reviewed, including AEs that may have an impact on medication tolerability, and uncommon events that may have serious, even irreversible, consequences for the patient. When available, data concerning patient preference and patient-prioritized outcomes for treatment were expressly analyzed (AAN guideline development process manual).[e22] Data from RCTs were preferred. When sufficient Class I and II evidence (appendix e-4) was not available, related evidence and practical axioms of care were used to develop recommendations, consistent with the guideline development process.[e22] In addition, the 5 members of the guideline panel (G.S.D, A.R.-G., M.J.A., T.P., R.A.M.) solicited opinions concerning outcome measures of importance from the other guideline panelists and people with MS (the latter consulted through the North American Research Committee on Multiple Sclerosis [NARCOMS] registry) using a formalized process. Perceived health benefits, AEs, and risks were formally considered in recommendation development. This methodology ensures that recommendations are evidence-driven and practicable but does not diminish the importance of interpreting recommendations on a patient-by-patient basis, accepting that systematic differences between people with MS enrolled in RCTs and those encountered in clinical practice (i.e., generalizability) may affect the translation of findings into practice.

The guideline panel developed clinical questions and disseminated them for public review in the guideline protocol before the initial systematic review. The initial public review indicated no need for substantive changes to the clinical questions. Adequate evidence was available to address the following questions:

1. In people with RRMS, are DMTs superior to placebo or other DMTs as measured by annualized relapse rates (ARRs)?

2. In people with RRMS, are DMTs superior to placebo or other DMTs in reducing MRI-detected new disease activity as measured by new T2 lesion burden or atrophy measures?

3. In people with RRMS, are DMTs superior to placebo or other DMTs in preventing disease progression as measured by in-study disease progression measures?

4. In people with RRMS who experience disease activity while using a DMT, is changing to a different DMT superior to continuing the present DMT in terms of relapse rate and MRI-detected T2 or gadolinium-enhanced lesion activity?

5. In people with progressive MS, are DMTs superior to placebo or other DMTs as measured by relapse rate or in-study disease progression?

6. What are the AEs of DMTs in people with MS compared with placebo (AE-related discontinuation and serious or life-threatening AEs)?

7. In people with clinically isolated syndromes (CIS), are DMTs superior to placebo in decreasing the risk of conversion to MS?

DESCRIPTION OF THE ANALYTIC PROCESS

In May 2015, the AAN Guideline Development, Dissemination, and Implementation Subcommittee (GDDI) recruited a multidisciplinary panel to develop this practice guideline. The panel consists of 12 AAN physician and nurse members, 2 representative members from the Consortium of Multiple Sclerosis Centers (CMSC), and 3 patient representatives (appendices e-1 and e-2). Two AAN staff representatives were also appointed to the panel. The physicians include content experts (R.A.M., B.A.C.C., J.H., D.E.J., D.P.); a methodology expert (T.P.); GDDI members (A.R.G., G.S.D., A.R., G.S.G., M.H., S.P.); and CMSC representatives (J.H., R.L.). The patient representatives (C.S., R.S., J.S.) are 3 adults with an MS diagnosis. They were involved as authors throughout the guideline development process and fully participated in development and refinement of the clinical questions, in identification of outcomes important to patients, and in the drafting of and voting on recommendations. All panel members 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.S.D.G., S.A.M.), reviewed the COI forms and CV for financial and intellectual COI. These documents were specifically screened to exclude not only individuals with a clear financial conflict but also those whose professional and intellectual biases might diminish the perceived credibility of the review. In accordance with AAN policy, the lead author (A.R.G.) has no COI. Four of the 20 authors were determined to have COI, which were judged to be not significant enough to preclude them from authorship (B.A.C.C., D.E.J., R.L., D.P.). All authors determined to have COI were not permitted to review or rate the evidence. These individuals were involved in an advisory capacity to help validate key questions, assess the scope of the literature search, identify seminal articles to validate the literature search, and participate in the recommendation development process. AAN GDDI leadership provided final approval of author panel composition. This panel was solely responsible for decisions concerning the design, analysis, and reporting of the proposed systematic review, which was then submitted for approval to the AAN GDDI.

This practice guideline follows the methodologies described in the 2011 edition of the AAN's guideline development process manual, as amended to include an updated classification scheme for therapeutic studies, a formalized prioritization process for guideline topic nominations, and a change in the order of steps for the external (peer) review process.[e22] The guideline panelists summarize the process here and provide a detailed description in the appendices referenced later. This process is compliant with Institute of Medicine (IOM) standards for guideline development; IOM standards were specifically reviewed and adhered to during the guideline development process.[e22] Over the course of guideline development, the public and experts had an opportunity to review the draft protocol during a 30-day public comment period, during which the document was posted on the AAN Web site. During this period, AAN staff sent invitations to review and comment on the guideline to key stakeholders, including all AAN section members, and

pertinent external physician and patient organizations, including the CMSC, the Multiple Sclerosis Association of America, the Multiple Sclerosis Coalition, and the National Multiple Sclerosis Society. All comments during public review were individually addressed by the panel and, where appropriate, led to modification of the draft guideline or recommendations, or informed the updated systematic review. The guideline was reviewed by the GDDI before and after the public comment period.

Panel members developed the clinical questions and the data extraction template. The guideline panel defined DMTs as medications that aim to affect the clinical course of MS by decreasing relapses or slowing disease progression or both. The guideline panelists limited the search for relevant literature to medications that have been approved by the US Food and Drug Administration (FDA), Health Canada, or the European Medicines Agency, or to medications historically used for disease modification in MS but which were not licensed for this purpose. When disputes arose concerning whether a medication should be included, the panel erred on the side of inclusion (e.g., corticosteroids for disease modification and cladribine). In addition, agents which potentially would receive licensure within the timeframe of the guideline process were included. For example, the FDA approved daclizumab May 2016 and ocrelizumab March 2017. After FDA approval was received, daclizumab (ZINBRYTA) was voluntarily removed from the market on March 2, 2018, by its manufacturers, Biogen and AbbVie, due to serious adverse events in relapsing MS.[e22a] Medications still in early phases of clinical testing were not included. With this strategy, 23 medications were identified and included in the initial and subsequent systematic reviews: methotrexate, cyclophosphamide, pulsed corticosteroids for disease modification, interferon beta (4 types: interferon beta-1b subcutaneous alternate day, interferon beta-1a intramuscular [IM] weekly, pegylated interferon subcutaneous every other week, interferon beta-1a subcutaneous 3 times per week), glatiramer acetate (proprietary form daily 20 mg subcutaneous form, proprietary form 3 days per week 40 mg subcutaneous form, generic form 20 mg subcutaneous daily form), natalizumab, azathioprine, teriflunomide, mycophenolate mofetil, rituximab, ocrelizumab, daclizumab, mitoxantrone, alemtuzumab, fingolimod, dimethyl fumarate, IV immunoglobulin for disease modification, and cladribine. To find relevant studies, the project methodologist (T.P.) searched the Cochrane Library for Cochrane Systematic Reviews, including any of the aforementioned medications for disease modification in individuals with MS. All Cochrane reviews were evaluated by a second reviewer and rated using A Measurement Tool to Assess Systematic Reviews, which is a rating instrument of systematic review quality.[e23] Cochrane reviews were updated by repeating the outlined search strategies in MEDLINE and CENTRAL or EMBASE (or both CENTRAL and EMBASE) from the date last searched in the review to November 2016. Appendix e-3 presents the complete search strategies. When there was a DMT for which no previous Cochrane review had been published, the author panel performed a de novo systematic review following the 2011 AAN guideline development process manual, as amended.[e22] The search was restricted to peer-reviewed English-language articles in humans. For efficacy outcomes, the panelists considered

data from randomized controlled trials (RCTs). For harms, the panel considered data from RCTs, cohort studies, case reports, or case series.

Two nonconflicted panel members rated the class of evidence for each article according to the AAN scheme for classification of therapeutic articles (see appendix e-4 for the rating scheme). A third panel member resolved any disagreements. Outcome data from included studies were extracted by the guideline methodologist and verified by a second panel member. Data for different disease types (RRMS, SPMS, PPMS) were analyzed separately where possible. Studies comparing different DMTs were included in this analysis. Before data analysis, the panel completed an anonymous survey on what would be considered a minimal clinically meaningful difference for various measures of DMT efficacy and AEs to use in the analytic portion of the guideline. For relapses, a relative risk reduction of 5% or less was considered clinically important, and a relative risk reduction of 2% or less was considered clinically unimportant. For disability progression, a relative risk reduction of 2% or more was considered clinically important, and a relative risk reduction of 1% or less was considered clinically unimportant. For AE-related discontinuation, a risk difference (RD) of 10% or more was considered clinically important, and an RD of 5% or less was considered clinically unimportant. For serious or life-threatening AEs, an RD of 0.1% or more was considered clinically important, and an RD of 0.01% or less was considered clinically unimportant. The evidence tables are presented in appendix e-5, published as a separate document at Neurology.org. A table of studies excluded from the guideline analysis is presented in appendix e-6.

A modified form of the Grading of Recommendations Assessment, Development and Evaluation process was used to develop conclusions.[e24] In this process, the evidence is analyzed on the basis of various parameters of risk of bias (multiple types), consistency, directness, precision, and publication bias. Appendix e-7 delineates the rules for determining the confidence in the evidence, and appendix e-8 presents the evidence synthesis tables. This process permits transparency in the upgrading or downgrading of evidence classification.[e24]

The panel formulated practice recommendations on the basis of the strength of evidence and other factors, including axiomatic principles of care, the magnitude of anticipated health benefits relative to harms, financial burden, availability of interventions, and patient preferences. The panel assigned levels of obligation (A, B, C, U) to the recommendations using a modified Delphi process. In some cases, the panel reviewed, revised, and revoted on recommendations on the basis of public commentary and other input during the guideline development process, reflecting the dynamic nature of this process. Appendix e-9 indicates the steps and rules for developing

recommendations, and appendix e-10 presents the rationale profile tables supporting the recommendations. Considerations for future research and recommendations for future studies were also developed during the guideline development process.

Supporting tables are included to assist the clinician. Table e-1 presents considerations/populations for which the guideline panel suggests caution regarding specific FDA-approved MS therapies. Table e-2 provides key risks of MS therapies and potential mitigation strategies. Table e-3 summarizes the medications reviewed, including their dosage, route, and frequency; MS type for which the medication received FDA approval; recommended monitoring where applicable; whether there is a risk evaluation and mitigation strategies (REMS) program; and FDA statements on pregnancy.

Throughout guideline development, an ongoing dissemination and implementation plan was developed and refined, reflecting the high visibility and wide scope of this guideline. This was performed in accordance with the updated GDDI process for dissemination and implementation.

This guideline will be reassessed over time for currency and the need for updating as indicated in the 2011 AAN guideline development process manual, as amended.[e22]

Physician and patient survey on desired outcomes

Although studies have independently considered how MS experts[e25,e26] and people with MS[e27–e32] weight factors in therapeutic decision making, few studies have investigated how closely aligned prescriber and patient priorities are throughout this process. Because AAN guidelines are developed primarily to improve the ability of neurologists and other physicians to meet patient needs, the panelists sought to compare how outcomes potentially affected by DMTs were rank-ordered by panel experts (N = 18) and people with MS (N = 2,156). Data from 5 outcomes of interest were consistently reported in high-quality (Class I or II) studies of medications for people with RRMS: relapse rate, disability progression, discontinuation of treatment because of AEs, neuroimaging changes, and serious adverse effects (SAEs; threatening life or organ). Three additional outcomes of interest were identified through review of studies focused on patient-specified outcome measures,[e27,e31,e32] including the effect of treatment on cognition, MS symptoms (e.g., fatigue, pain, urinary incontinence), and quality of life measures. On the basis of these data, 5 members of the DMTs for MS guideline panel developed a survey to be distributed

to MS experts and people with MS wherein they would rank all outcomes "in order of importance to you when choosing a MS treatment." The DMTs for MS guideline panel (referred to in the survey as "the AAN Multiple Sclerosis Guideline Development Panel") was electronically surveyed using Google Surveys (December 18, 2015, to January 11, 2016). Persons with MS participating in the NARCOMS registry were invited to participate by email. Responses from persons with MS were accrued over a 7-day period (January 5–11, 2016). Survey questions (appendix e-11) were developed in consultation with Multiple Sclerosis Guideline Development Panel leadership and NARCOMS executive committee members.

Survey results

The survey invitation was distributed to 9,126 NARCOMS participants, of whom 5,487 (65.5%) had completed the NARCOMS Fall 2015 Update. Nearly 24% (2,156) of those invited and all 18 members of the DMT for MS guideline development panel (100%) responded to the survey request. The percentage of respondents designating an outcome as first-, second-, or third-highest priority is shown in figure e-1. Specific outcomes were identified as priorities in therapeutic decision making by similar proportions of guideline panelists and persons with MS. The majority of respondents from each group identified as priority outcomes the ability of DMT for MS to reduce disability progression and the potential for SAEs associated with the treatment. Guideline panelists tended to be more likely than persons with MS to prioritize a reduction in relapse rate when choosing a DMT for MS (Fisher exact test, 2-tailed: $p = 0.055$). No significant differences were observed between respondents concerning other outcomes (Fisher exact test, 2-tailed: $p > 0.05$). Forty-seven percent of persons with MS and 33.3% of guideline panelists identified the selection of therapies most likely to lead to improvements in QOL, MS symptoms, or preservation of cognition as priority outcomes in DMT selection ($p = 0.34$). Reporting concerning these outcome measures was limited (figure e-2), with data concerning 1 or more of these measures included in 11 of 58 (19%) of clinical trials reviewed.

ANALYSIS OF EVIDENCE

A total of 20 Cochrane systematic reviews were identified and used in the evidence review process. These systematic reviews included 70 RCTs, which were included in the panel's evidence synthesis. For the update of the Cochrane reviews and de novo systematic reviews, the combined searches yielded 4,301 abstracts. Each abstract was reviewed for relevance by at least 2 panel members, who deemed 284 as relevant. Full text of these articles was reviewed by 2 panelists working independently of each other. An additional 73 articles were identified for data extraction.

All trials included individuals with MS aged 18 years or older. The maximum age of participants varied across trials, but it was generally from 50 to 60 years. Most studies were 2 years in length (range between 6 months and 3 years). Trials occurred in multiple countries worldwide.

Clinical question 1: In people with RRMS, are DMTs superior to placebo or other DMTs as measured by ARRs?

The efficacy of DMTs for preventing relapses was assessed in most trials by measuring the proportion of people with MS with relapses compared with placebo over 2 years. Annualized relapse rates were derived from this information. Results are reported by medication (medications alphabetized).

Alemtuzumab

One Class I study[e33] and 1 Class II study[e34] (Class II owing to unclear allocation concealment) evaluated the proportion of people with RRMS with at least 1 relapse at 2 years with alemtuzumab treatment compared with interferon beta-1a subcutaneously 3 times per week. Meta-analysis of data from 914 participants revealed a risk ratio (RR) of 0.43 (95% CI, 0.29–0.61), favoring alemtuzumab. Meta-analysis of data from the same 2 studies revealed a raw mean difference (RMD) in the ARR of 0.26 (95% CI, 0.22–0.29), favoring alemtuzumab.

Conclusions

For individuals with RRMS, alemtuzumab is more effective than interferon beta-1a subcutaneously 3 times per week in reducing the risk of relapse at 2 years (high confidence in the evidence, 1 Class 1 study, 1 Class II study; confidence upgraded owing to magnitude of effect). For individuals with RRMS, alemtuzumab is more effective than interferon beta-1a subcutaneously 3 times per week in reducing the ARR (high confidence in the evidence, 1 Class I study, 1 Class II study; confidence upgraded owing to magnitude of effect).

Azathioprine

One Class II study[e35] (Class II owing to unclear allocation concealment) evaluated the proportion of individuals with at least 1 relapse at 2 years with azathioprine vs placebo in 59 people with MS. This study found an RR of 0.74 (95% CI, 0.50–1.07), favoring treatment. The same study reported the mean number of relapses during the second year of treatment; the RMD was 0.49 (95% CI, 0.07–0.91), favoring treatment.

There are 2 Class II studies[e36,e37] comparing azathioprine to beta interferons in 244 individuals with RRMS in terms of the ARR. Massacesi et al[e36] (Class II owing to less than 80% completion) and Etemadifar et al[e37] (Class II owing to unclear allocation concealment, more than 2 primary outcomes) studies allowed any of the interferon beta preparations for MS disease management. Meta-analysis of data from these studies shows a rate ratio of 0.64 (95% CI, 0.44–0.92), favoring azathioprine. One of these Class II studies[e37] also evaluated the proportion of individuals with RRMS with relapses at 1 year. The RR was 0.75 (95% CI, 0.55–0.99), favoring azathioprine.

Conclusions

For individuals with RRMS, there is insufficient evidence to determine the efficacy of azathioprine compared with placebo in reducing the risk of relapse over 24 months (very low confidence in the evidence, 1 Class II study; confidence downgraded because of imprecision). Azathioprine is probably more effective than placebo in reducing the mean number of relapses during the second year of treatment (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect). Azathioprine is more effective than beta interferons in reducing the ARR (high confidence in the evidence, 2 Class II studies; confidence upgraded owing to magnitude of effect). Azathioprine is probably more effective than beta interferon in reducing the risk of relapse over 12 months (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect).

Cladribine

Two Class II studies[e38,e39] evaluated cladribine vs placebo in 1,376 individuals with RRMS (Romine et al[e38] Class II owing to unclear allocation concealment, Giovannoni[e39] Class II owing to unclear allocation concealment and baseline characteristics). One study[e39] evaluated 2 different doses of oral cladribine, and the other[e38] evaluated subcutaneous cladribine. The RMD in the ARR was 0.19 (95% CI, 0.14–0.24). The proportion of people with MS with at least 1

relapse at 2 years was studied in 1 Class II study of 1,326 individuals treated with oral cladribine 3.5 mg/kg or 5.2 mg/kg.[e39] The RR was 0.53 (95% CI, 0.45–0.63) in individuals treated with either dose of cladribine relative to placebo.

Conclusions

For individuals with RRMS, cladribine is more effective than placebo in reducing the ARR (high confidence in the evidence, 2 Class II studies; confidence upgraded owing to magnitude of effect). Cladribine is probably more effective than placebo in reducing the risk of relapse over 2 years (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect).

Corticosteroids

One Class IV study of 81 individuals with RRMS[e40] evaluated the effect of methylprednisone 1 g/d for 5 days every 4 months vs placebo on the risk of relapse at 2 years and on the ARR (Class IV for clinical measures owing to lack of blinding, included because of blinded MRI measures [Class II]). The RR for at least 1 relapse at 2 years was 1.16 (95% CI, 0.851–1.591); the RMD in the ARR was 0.0 (95% CI, -0.238 to 0.238).

Two Class II studies[e41,e42] evaluated monthly pulsed methylprednisolone added to beta interferon treatment compared with placebo added to beta interferon treatment in 471 individuals with RRMS (Sorensen et al[e41] study used interferon beta-1a 44 micrograms subcutaneous 3 times weekly; Ravnborg et al[e42] study used interferon beta-1a 30 micrograms IM weekly). Both studies were Class II owing to less than 80% completion. The RR for at least 1 relapse at 2 years was 0.33 (95% CI, 0.20–0.54) on the basis of data from the Sorensen[e41] study, and the RR for at least 1 relapse at 3 years was 0.78 (95% CI, 0.62–0.98) on the basis of data from the Ravnborg[e42] study. The RMD in the ARR based on data from both studies was 0.24 (95% CI, 0.02–0.47).

Conclusions

For individuals with RRMS, there is insufficient evidence to determine the efficacy of pulsed corticosteroids alone compared with placebo in reducing the risk of relapse over 2 years or the

ARR (very low confidence in the evidence, 1 Class IV study). Treatment with monthly pulsed corticosteroids added to interferon beta-1a is probably more effective than placebo added to interferon beta-1a in reducing the risk of relapse over 2 years and 3 years (moderate confidence in the evidence, 1 Class II study, confidence upgraded owing to magnitude of effect). Treatment with monthly pulsed corticosteroids added to interferon beta-1a is probably more effective than placebo added to interferon beta-1a in reducing the ARR (moderate confidence in the evidence, 2 Class II studies).

Cyclophosphamide

One Class III study[e43] evaluated cyclophosphamide vs placebo in 14 individuals with RRMS (Class III owing to randomization, lack of blinding, lack of defined primary outcome, study group differed at baseline). The RR for at least 1 relapse at 1 year was 0.67 (95% CI, 0.25–1.44). The RMD between cyclophosphamide and placebo for the ARR was 1.80 (95% CI, 0.56–3.04).

Conclusions

For individuals with RRMS, there is insufficient evidence to determine the efficacy of cyclophosphamide compared with placebo in reducing the risk of relapse over 12 months (very low confidence in the evidence, 1 Class III study). Cyclophosphamide is possibly more effective than placebo in reducing the ARR (low confidence in the evidence, 1 Class III study; confidence upgraded owing to magnitude of effect).

Daclizumab high-yield process

One Class I study[e44] evaluated the effect of daclizumab high-yield process (HYP) vs placebo in 397 individuals with RRMS. The RR for relapse at 1 year was 0.54 (95% CI, 0.38–0.75), and the RMD in the ARR was 0.25 (95% CI, 0.13–0.37). One Class II study[e45] compared daclizumab HYP with interferon beta-1a 30 micrograms IM weekly in 1,841 individuals with RRMS over 3 years (Class II owing to less than 80% completion). The RR for at least 1 relapse at 3 years was 0.67 (95% CI, 0.60–0.75), and the RMD in the ARR was 0.17 (95% CI, 0.12–0.22), favoring daclizumab HYP.

Safety note

After FDA approval was received, daclizumab (ZINBRYTA) was voluntarily removed from the market on March 2, 2018, by its manufacturers, Biogen and AbbVie, due to serious adverse events in relapsing MS.[e22a]

Conclusions

For individuals with RRMS, daclizumab HYP is more effective than placebo in decreasing the risk of at least 1 relapse at 1 year (high confidence in the evidence, 1 Class I study, confidence upgraded owing to magnitude of effect). Daclizumab HYP is more effective than placebo in decreasing the ARR (high confidence in the evidence, 1 Class I study, confidence upgraded owing to magnitude of effect). Daclizumab HYP is probably more effective than interferon beta-1a 30 micrograms IM weekly in decreasing the risk of at least 1 relapse at 3 years (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect). Daclizumab HYP is probably more effective than interferon beta-1a 30 micrograms IM weekly in decreasing the ARR at 3 years (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect).

Dimethyl fumarate

One Class I study[e46] and 1 Class II study[e47] evaluated the efficacy of dimethyl fumarate vs placebo on relapses in 1,540 individuals with RRMS (Gold et al[e47] Class II owing to less than 80% completion). The RR for the proportion of individuals with at least 1 relapse at 2 years with dimethyl fumarate compared with placebo was 0.64 (95% CI, 0.54–0.77), and the RMD in the ARR was 0.19 (95% CI, 0.13–0.25). Note that glatiramer acetate was included to provide a reference arm in this study, and the study was not powered for noninferiority or superiority, which is required for approval by a regulatory agency.[e46]

Conclusions

In individuals with RRMS, dimethyl fumarate is more effective than placebo in decreasing the risk of at least 1 relapse at 2 years (high confidence in the evidence, 1 Class I study and 1 Class II study; confidence upgraded owing to magnitude of effect). Dimethyl fumarate is more effective than placebo in decreasing the ARR (high confidence in the evidence, 1 Class I study and 1 Class II study; confidence upgraded owing to magnitude of effect).

Fingolimod

One Class I study[e48] and 1 Class II study[e49] compared fingolimod with placebo for the risk of relapse at 2 years in 1,556 individuals with RRMS (Calabresi et al[e49] Class II owing to less than 80% completion, allocation concealment unclear). The RR for the proportion of individuals with at least 1 relapse at 2 years was 0.57 (95% CI, 0.50–0.65), favoring fingolimod. Two Class I studies[e48,e50] and 1 Class II study[e49] compared fingolimod with placebo for the ARR in 1,670 individuals with RRMS (Calabresi et al[e49] Class II owing to less than 80% completion, unclear allocation concealment). The raw mean difference between fingolimod and placebo was 0.21 (95% CI, 0.16–0.26), favoring fingolimod. One Class I study[e51] compared fingolimod with interferon beta-1a 30 micrograms IM weekly in 860 individuals with RRMS. The RR for at least 1 relapse at 12 months was 0.58 (95% CI, 0.46–0.75), and the RMD in the ARR was 0.17 (95% CI, 0.08–0.26), favoring fingolimod.

Conclusions

For individuals with RRMS, fingolimod is more effective than placebo in reducing the risk of relapse over 2 years (high confidence in the evidence, 1 Class I study and 1 Class II study; confidence upgraded owing to magnitude of effect). Fingolimod is more effective than placebo in reducing the ARR (high confidence in the evidence, 2 Class I studies and 1 Class II study). Fingolimod is more effective than interferon beta-1a in reducing the risk of relapse at 1 year (high confidence in the evidence, 1 Class I study; confidence upgraded owing to magnitude of effect). Fingolimod is more effective than interferon beta-1a 30 micrograms IM weekly in reducing the ARR (high confidence in the evidence, 1 Class I study; confidence upgraded owing to magnitude of effect).

Glatiramer acetate

Two Class I studies[e46,e52] and 1 Class II study[e53] evaluated the ARR with glatiramer acetate compared with placebo in 2,368 individuals with RRMS (Johnson et al[e53] Class II owing to unclear allocation concealment). The RMD was 0.18 (95% CI, 0.09–0.28), favoring glatiramer acetate. There is 1 Class I study[e46] and 2 Class II studies[e53,e54] in 1,012 individuals with RRMS evaluating the proportion of individuals with at least 1 relapse at 2 years (Bornstein et al[e54] study Class II owing to unclear allocation concealment). The RR was 0.82 (95% CI, 0.69–0.97), favoring glatiramer acetate. One Class II study[e55] compared glatiramer acetate with interferon beta-1a 44 micrograms subcutaneous 3 times per week in 764 individuals with RRMS (Class II owing to unclear allocation concealment). No difference was seen between the proportion of people with MS with at least 1 relapse at 2 years, with an RR of 0.93 (95% CI, 0.77–1.14). Two

Class II studies[e56,e57] compared glatiramer acetate with interferon beta-1b subcutaneous alternate day (250 micrograms) in 1,420 individuals with RRMS (both studies Class II owing to unclear allocation concealment). There was no difference between the proportion of people with MS with at least 1 relapse at 2 years, with an RR of 1.19 (95% CI, 0.75–1.90). There is 1 Class I study[e58] comparing glatiramer acetate with interferon beta-1a 30 micrograms IM once per week in 509 individuals with RRMS. There was no difference between treatments in the proportion of individuals with at least 1 relapse over 3 years, with an RR of 1.27 (95% CI, 0.93–1.74). There is 1 Class I study[e59] comparing a complex nonbiologic generic form of glatiramer acetate (Glatopa) with a proprietary form of glatiramer acetate (Copaxone) in 794 individuals with RRMS. No difference was seen between groups in the proportion of individuals who had a confirmed relapse at 9 months, with an RR of 0.79 (95% CI, 0.61–1.04).

Conclusions

For individuals with RRMS, glatiramer acetate is more effective than placebo in reducing the ARR (high confidence in the evidence, 2 Class I studies and 1 Class II study). Glatiramer acetate is probably more effective than placebo in reducing the risk of relapse at 2 years (moderate confidence in the evidence, 1 Class I and 2 Class II studies). Interferon beta-1a 44 micrograms subcutaneous 3 times per week is possibly no more effective than glatiramer acetate in reducing the risk of at least 1 relapse at 2 years (low confidence in the evidence, 1 Class II study). Interferon beta-1b 250 micrograms subcutaneous alternate day is possibly no more effective than glatiramer acetate in reducing the risk of at least 1 relapse at 2 years (low confidence in the evidence, 2 Class II studies; confidence downgraded owing to imprecision). Interferon beta-1a 30 micrograms IM once per week is possibly no more effective than glatiramer acetate in decreasing the risk of relapse at 3 years (low confidence in the evidence, 1 Class I study; confidence downgraded owing to imprecision). Complex nonbiologic glatiramer acetate is possibly no more effective than Copaxone in reducing the risk of relapse at 9 months (low confidence in the evidence, 1 Class I study, confidence downgraded owing to imprecision).

Immunoglobulins

Two Class I studies[e60,e61] and 2 Class II studies[e62,e63] compared immunoglobulins with placebo in 460 individuals with RRMS (Achiron et al[e62] Class II owing to more than 2 primary outcomes, Lewanska et al[e63] Class II owing to unclear allocation concealment). Meta-analysis of study results revealed no difference between treatments, with an RMD of 0.37 (95% CI, -0.21 to 0.94) in the ARR. One Class I study[e60] and 1 Class II study[e62] compared IV immunoglobulin with placebo infusions and reported the proportion of 190 individuals with at least 1 relapse at 2 years

(Achiron Class II owing to unclear allocation concealment). The RR was 0.74 (95% CI, 0.61–0.87), favoring immunoglobulins.

Conclusions

For individuals with RRMS, there is insufficient evidence to determine the efficacy of immunoglobulins compared with placebo in reducing the ARR (very low confidence in the evidence, 2 Class I and 2 Class II studies; confidence downgraded owing to imprecision). Immunoglobulins are more effective than placebo in reducing the risk of at least 1 relapse over 2 years (high confidence in the evidence, 1 Class I study and 1 Class II study; confidence upgraded owing to magnitude of effect).

Interferon beta-1a 30 micrograms IM weekly

One Class I study[e64] and 1 Class II study[e65] evaluated the proportion of individuals with RRMS with at least 1 relapse at 2 years compared with placebo (Jacobs et al[e65] Class II owing to unclear allocation concealment). Meta-analysis of data from 1,198 individuals revealed an RR of 0.79 (95% CI, 0.68–0.92), favoring treatment. One Class I study[e64] found that interferon beta-1a 30 micrograms IM weekly was more effective than placebo in reducing the ARR, with an RMD of 0.08 (95% CI, 0.01–0.15).

Conclusions

For individuals with RRMS, interferon beta-1a 30 micrograms IM weekly is more effective than placebo in reducing the risk of relapse over 24 months (high confidence in the evidence, 1 Class I study, 1 Class II study; confidence upgraded owing to magnitude of effect). Interferon beta-1a 30 micrograms IM weekly is probably more effective than placebo in reducing the ARR (moderate confidence in the evidence, 1 Class I study).

Interferon beta-1a 44 micrograms subcutaneous 3 times per week

One Class I study[e66] compared interferon beta-1a 44 micrograms subcutaneous 3 times per week with placebo in 560 individuals with RRMS. The risk of relapse at 2 years was significantly lower with interferon beta-1a 44 micrograms subcutaneous 3 times per week, with an RR of 0.84

(95% CI, 0.77–0.92). One Class II study[e67] compared interferon beta-1a 44 micrograms subcutaneous 3 times per week with interferon beta-1a 30 micrograms IM weekly in 677 individuals with RRMS (Class II owing to less than 80% completion). The risk of relapse at 1 year was significantly lower with interferon beta-1a 44 micrograms subcutaneous 3 times per week compared with interferon beta-1a 30 micrograms IM weekly, with an RR of 0.84 (95% CI, 0.72–0.99).

Conclusions

For individuals with RRMS, interferon beta-1a 44 micrograms subcutaneous 3 times per week is more effective than placebo in reducing the risk of relapse at 2 years (high confidence in the evidence, 1 Class I study; confidence upgraded owing to magnitude of effect). Interferon beta-1a 44 micrograms subcutaneous 3 times per week is probably more effective than interferon beta-1a 30 micrograms IM weekly in reducing the risk of relapse at 1 year (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect).

Interferon beta-1b subcutaneous alternate day

One Class II study[e68] including 227 individuals with RRMS evaluated the effect of interferon beta-1b 8 milli-international units (mIUs) subcutaneous alternate day vs placebo on relapses (Class II owing to unclear allocation concealment). This study found an RR of 0.82 (95% CI, 0.70–0.95) for the proportion of individuals with at least 1 relapse at 2 years and an RMD of 0.43 (95% CI, 0.24–0.62) in the relapse rate over 2 years.

Conclusions

For individuals with RRMS, interferon beta-1b 8 mIUs subcutaneous alternate day is probably more effective than placebo in reducing the risk of relapse over 2 years (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect). Interferon beta-1b 8 mIUs subcutaneous alternate day is probably more effective than placebo in reducing the relapse rate over 2 years (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect).

Methotrexate

One Class III study[e69] compared methotrexate with placebo in 20 individuals with RRMS (Class III because relevant baseline characteristics not presented). There was no significant difference in the risk of relapse over 18 months, with an RR of 0.35 (95% CI, 0.10–1.04). One Class III study[e70] compared methotrexate with interferon beta-1a 30 micrograms IM weekly in 80 individuals with RRMS (Class III owing to unclear allocation concealment, noninferiority/equivalence trial methodology not followed as described in risk of bias, and no primary outcome specified). The standardized mean difference (SMD) between interferon and methotrexate for the number of relapses over 12 months was 0.497 (95% CI, 0.052–0.942), favoring interferon beta-1a 30 micrograms IM weekly over methotrexate.

Conclusions

In individuals with RRMS, there is insufficient evidence to determine the efficacy of methotrexate compared with placebo in decreasing the proportion of people with MS who relapsed over 18 months (very low confidence in the evidence, 1 Class III study). Methotrexate is possibly less effective than interferon beta-1a 30 micrograms IM weekly in decreasing the number of relapses over 12 months (low confidence in the evidence, 1 Class III study; confidence in evidence upgraded due to magnitude of effect).

Mitoxantrone

One Class I study[e71] compared mitoxantrone with placebo in 51 individuals with RRMS. The RR for the proportion of individuals with a relapse over 24 months was 0.47 (95% CI, 0.27–0.77), favoring mitoxantrone.

Conclusion

For individuals with RRMS, mitoxantrone is more effective than placebo in decreasing the risk of relapse at 2 years (high confidence in the evidence, 1 Class I study; confidence upgraded owing to magnitude of effect).

Mycophenolate mofetil

Two Class II studies[e72,e73] compared mycophenolate mofetil plus interferon beta-1a 30 micrograms IM weekly with placebo plus interferon beta-1a 30 micrograms IM weekly in 50 individuals with RRMS (both Class II owing to unclear allocation concealment). No significant difference was observed between treatments in the risk of relapse at 1 year, with an RR of 0.63 (95% CI, 0.18–2.23). One Class II study[e74] compared mycophenolate mofetil to interferon beta-1a 30 micrograms IM weekly in 35 individuals with RRMS (Class II owing to unclear allocation concealment). There was no significant difference in the risk of relapse at 6 months, with an RR of 1.18 (95% CI, 0.22–6.16).

Conclusions

For individuals with RRMS, mycophenolate plus interferon beta-1a 30 micrograms IM weekly is possibly no more effective than placebo plus interferon beta-1a 30 micrograms IM weekly in decreasing the risk of relapse at 1 year (low confidence, 2 Class II studies; confidence in evidence downgraded owing to imprecision). There is insufficient evidence to determine the efficacy of mycophenolate mofetil compared with interferon beta-1a 30 micrograms IM weekly in decreasing the risk of relapse at 6 months (very low confidence in the evidence, 1 Class III study).

Natalizumab

One Class I study[e75] compared natalizumab with placebo in 942 individuals with RRMS. The risk of at least 1 relapse at 2 years was significantly lower with natalizumab than with placebo, with an RR of 0.56 (95% CI, 0.49–0.64). The ARR was significantly lower with natalizumab, with an RMD of 0.41 (95% CI, 0.31–0.51).

Conclusion

For individuals with RRMS, natalizumab is more effective than placebo in reducing the risk of relapse at 2 years and reducing the ARR (high confidence in the evidence, 1 Class I study; confidence upgraded owing to magnitude of effect).

Ocrelizumab

Two Class I studies[e76] compared ocrelizumab 600 mg IV every 24 weeks to interferon beta-1a 44 micrograms subcutaneous 3 times per week in 1,656 individuals with RRMS. The RMD in the ARR was 0.130 (95% CI, 0.078–0.182), favoring ocrelizumab.

Conclusion

For individuals with RRMS, ocrelizumab is more effective than interferon beta-1a 44 micrograms subcutaneous 3 times per week in reducing the ARR (high confidence in the evidence, 2 Class I studies).

Pegylated interferon

One Class I study[e77] compared pegylated interferon 125 micrograms every 2 weeks with placebo in 1,012 individuals with RRMS. The risk of at least 1 relapse at 1 year was significantly lower with pegylated interferon, with an RR of 0.62 (95% CI, 0.49–0.78). The ARR was significantly lower with pegylated interferon 125 micrograms every 2 weeks, with an RMD of 0.11 (95% CI, 0.01–0.21).

Conclusion

For individuals with RRMS, pegylated interferon 125 micrograms every 2 weeks is more effective than placebo in reducing the risk of relapse and the ARR at 1 year (high confidence in the evidence, 1 Class I study; confidence upgraded owing to magnitude of effect).

Rituximab

One Class II study compared rituximab with placebo in 104 individuals with RRMS[e78] (Class II owing to unclear allocation concealment). The risk of relapse was significantly lower with rituximab compared with placebo, with an RR of 0.51 (95% CI, 0.28–0.94). The ARR at 1 year was not significantly different between treatments, with an RMD 0.30 (95% CI, -0.07 to 0.67).

Conclusions

For individuals with RRMS, rituximab is probably more effective than placebo in decreasing the risk of relapse at 1 year (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect). There is insufficient evidence to determine the efficacy of rituximab compared with placebo in decreasing the ARR at 1 year (very low confidence in the evidence, 1 Class II study; confidence downgraded owing to imprecision).

Teriflunomide

One Class II study[e79] compared teriflunomide with placebo in 1,088 individuals with RRMS (Class II owing to less than 80% completion). The risk of at least one relapse at 2 years was significantly lower with teriflunomide, with an RR of 0.88 (95% CI, 0.79–0.98). Three Class II studies[e79–e81] compared teriflunomide with placebo in 1,597 individuals with RRMS (O'Connor et al[e80] Class II owing to unclear allocation concealment; Confavreux et al[e81] Class II owing to less than 80% completion). The ARR was significantly lower with teriflunomide compared with placebo, with an RMD of 0.18 (95% CI, 0.11–0.25).

Conclusions

For individuals with RRMS, teriflunomide is probably more effective than placebo in decreasing the risk of relapse at 2 years (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect). Teriflunomide is more effective than placebo in decreasing the ARR (high confidence in the evidence, 3 Class II studies; confidence upgraded owing to magnitude of effect).

Clinical question 2: In people with RRMS, are DMTs superior to placebo or other DMTs in reducing MRI new disease activity as measured by new T2 lesion burden or atrophy measures?

Various measures of the effect of DMTs on MRI disease activity were performed, including mean differences in volume or number of T2 lesions, the proportion of people with MS with new or enlarging T2 lesions, or changes in whole brain volume compared with baseline.

Alemtuzumab

One Class I study[e33] in 563 people with RRMS whose MS relapsed compared alemtuzumab with interferon beta-1a 44 micrograms subcutaneous 3 times per week and reported a decrease in T2 lesion volume from baseline to 2 years, with an SMD of 0.18 (95% CI, 0.01–0.36). The same study reported a lower proportion of people with MS with new or enlarging T2 lesions at 2 years in those treated with alemtuzumab compared with interferon beta-1a 44 micrograms subcutaneous 3 times per week, with an RR of 0.84 (95% CI, 0.71–0.99). One Class II study[e34] found no difference between alemtuzumab and interferon beta-1a 44 micrograms subcutaneous 3 times per week concerning the T2 lesion load from baseline to 3 years, with an SMD 0.10 (95% CI, -0.20 to 0.39). The same Class II study[e34] found a smaller decrease in brain volume on T1 from baseline to 3 years with alemtuzumab compared with interferon beta-1a 44 micrograms subcutaneous 3 times per week, with an SMD of 0.37 (95% CI, 0.07–0.67).

Conclusions

For individuals with RRMS, alemtuzumab is probably more effective than interferon beta-1a 44 micrograms subcutaneous 3 times per week in decreasing the volume of T2 lesions from baseline to 2 years (moderate confidence in the evidence, 1 Class I study). Alemtuzumab is probably more effective than interferon beta-1a 44 micrograms subcutaneous 3 times per week in reducing the risk of new or enlarging T2 lesions at 2 years (moderate confidence in the evidence, 1 Class I study). There is insufficient evidence to determine the efficacy of alemtuzumab compared with interferon beta-1a 44 micrograms subcutaneous 3 times per week in decreasing the T2 lesion load from baseline to 3 years (very low confidence in the evidence, 1 Class II study; confidence downgraded owing to imprecision). Alemtuzumab is probably more effective than interferon beta-1a 44 micrograms subcutaneous 3 times per week in decreasing reduction in brain volume on T1 from baseline to 3 years (moderate confidence in the evidence, 1 Class II study, confidence upgraded owing to magnitude of effect).

Azathioprine

One Class II study[e36] comparing azathioprine with beta interferons (various preparations) evaluated the proportion of individuals with RRMS with no new T2 lesions at 2 years. There was no significant difference between treatments, with an RR of 1.21 (95% CI, 0.81–1.82).

Conclusion

For individuals with RRMS, there is insufficient evidence to determine the efficacy of azathioprine compared with beta interferons in reducing the risk of new T2 lesions at 2 years (very low confidence in the evidence, 1 Class II study; confidence downgraded owing to imprecision).

Cladribine

One Class II study[e39] evaluated the effect of 2 different doses of oral cladribine (3.5 mg vs 5.25 mg) in 1,326 individuals with RRMS on the proportion of people with MS with at least 1 active T2 lesion at 2 years. This study demonstrated an RR of 0.529 (95% CI, 0.478–0.587) with either dose of cladribine compared with placebo.

Conclusion

For people with RRMS, cladribine is probably more effective than placebo in reducing the risk of at least 1 active T2 lesion at 2 years (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect).

Corticosteroids

One Class II study[e40] compared pulsed corticosteroids with placebo in 81 individuals with RRMS on MRI T2 lesion volume and brain parenchymal volume at 5 years (Class II for MRI outcome owing to blinded MRI reading). This study demonstrated an SMD of 0.203 (95% CI, -0.234 to 0.640) for T2 lesion volume and an SMD of 0.622 (95% CI, 0.175–1.068) for brain parenchymal volume at 5 years.

Conclusions

For people with RRMS, there is insufficient evidence to determine the efficacy of pulsed corticosteroids compared with placebo in reducing T2 lesion volume at 5 years (very low confidence in the evidence, 1 Class II study, confidence downgraded owing to imprecision). Pulsed corticosteroids are probably more effective than placebo in reducing the loss of parenchymal volume at 5 years (moderate confidence in the evidence, 1 Class II study, confidence upgraded owing to magnitude of effect).

Daclizumab HYP

One Class I study[e44] evaluated the effect of daclizumab HYP vs placebo on the mean number of new or newly enlarging lesions at 1 year in 397 individuals with RRMS. This study found an SMD of 0.94 (95% CI, 0.74–1.15) favoring daclizumab HYP. One Class II study[e45] compared daclizumab HYP with interferon beta-1a 30 micrograms IM weekly in 1,841 individuals with RRMS. The SMD in the mean number of new or newly enlarging T2 hyperintense lesions over 2 years was 0.42 (95% CI, 0.33–0.52), favoring daclizumab HYP.

Conclusions

For individuals with RRMS, daclizumab HYP is more effective than placebo in preventing new or newly enlarging T2 lesions at 1 year (high confidence in the evidence, 1 Class I study; confidence upgraded owing to magnitude of effect). Daclizumab HYP is probably more effective than interferon beta-1a 30 micrograms IM weekly in preventing new or newly enlarging T2 lesions at 2 years (moderate confidence in the evidence, 1 Class II study, confidence upgraded owing to magnitude of effect). See safety note on page 35.

Dimethyl fumarate

One Class I study[e46] and 1 Class II study[e47] compared the effect of dimethyl fumarate with placebo on the mean number of new or enlarging T2 lesions at 2 years in 1,097 individuals with RRMS. The SMD was 0.49 (95% CI, 0.29–0.69), favoring dimethyl fumarate.

Conclusion

In individuals with RRMS, dimethyl fumarate is more effective than placebo in decreasing the number of new or enlarging T2 lesions at 2 years (high confidence in the evidence, 1 Class I study and 1 Class II study; confidence upgraded owing to magnitude of effect).

Fingolimod

One Class I study[e48] and 1 Class II study[e49] compared the proportion of individuals with new or enlarging T2 lesions at 2 years with fingolimod vs placebo in 1,224 persons with RRMS. The RR was 0.65 (95% CI, 0.59–0.71), favoring fingolimod. One Class I study[e51] in 733 individuals with RRMS compared fingolimod with interferon beta-1a 30 micrograms IM. The RR for the proportion of individuals with new or enlarged T2 lesions at 12 months was 0.83 (95% CI, 0.72–0.96).

Conclusions

In individuals with RRMS, fingolimod is more effective than placebo in reducing the risk of new or enlarging T2 lesions at 2 years (high confidence in the evidence, 1 Class I study and 1 Class II study; confidence upgraded owing to magnitude of effect). Fingolimod is probably more effective than interferon beta-1a 30 micrograms IM weekly in reducing the risk of new or enlarging T2 lesions over 1 year (moderate confidence in the evidence, 1 Class I study).

Glatiramer acetate

One Class I study[e46] compared the number of new or enlarging T2 lesions at 2 years in 292 individuals with RRMS receiving glatiramer acetate vs placebo. The SMD between treatments was 0.46 (95% CI, 0.23–0.69), favoring glatiramer acetate. One Class II study[e55] compared the proportion of people with MS with active T2 lesions at 2 years with glatiramer acetate vs interferon beta-1a 44 micrograms subcutaneous 3 times per week in 460 individuals with RRMS. There was no difference between treatments, with an RR of 0.95 (95% CI, 0.82–1.11).

Conclusions

For individuals with RRMS, glatiramer acetate is more effective than placebo in decreasing the number of new or enlarging T2 lesions at 2 years (high confidence in the evidence, 1 Class I study; confidence upgraded owing to magnitude of effect). Interferon beta-1a 44 micrograms subcutaneous 3 times per week is possibly no more effective than glatiramer acetate in decreasing the risk of active T2 lesions at 2 years (low confidence in the evidence, 1 Class II study).

Interferon beta-1a IM weekly

One Class I study[e64] evaluated the mean change in brain volume from baseline to 2 years and the cumulative number of new or enlarged T2 lesions at months 12 and 24 with interferon beta-1a 30 micrograms IM weekly compared with placebo. No significant difference in brain volume was detected (SMD 0.003 [95% CI, -0.128 to 0.134]); however, the cumulative number of new or enlarged T2 lesions was lower in the group receiving interferon beta-1a 30 micrograms IM weekly (SMD 0.37 [95% CI, 0.23–0.50]).

Conclusions

For individuals with RRMS, there is insufficient evidence to determine the efficacy of interferon beta-1a 30 micrograms IM weekly compared with placebo in reducing loss of in brain parenchymal volume at 2 years (very low confidence in the evidence, 1 Class I study; confidence downgraded owing to imprecision). Interferon beta-1a 30 micrograms IM weekly is more effective than placebo in reducing the cumulative number of new or enlarged T2 lesions at months 12 and 24 (high confidence in the evidence, 1 Class 1 study; confidence upgraded owing to magnitude of effect).

Interferon beta-1a 44 micrograms subcutaneous 3 times per week

One Class I study[e66] evaluated new T2 activity over 2 years in 366 individuals with RRMS treated with interferon beta-1a 44 micrograms subcutaneous 3 times per week compared with placebo. The RR for new T2 activity was 0.75 (95% CI, 0.67–0.83), favoring interferon beta-1a 44 micrograms subcutaneous 3 times per week. One Class II study[e67] compared interferon beta-1a 44 micrograms subcutaneous 3 times per week with interferon beta-1a IM weekly in 677 individuals with RRMS. The proportion of individuals with new or enlarging T2 lesions at 1 year was significantly lower with interferon beta-1a subcutaneous 3 times per week, with an RR of 0.67 (95% CI, 0.58–0.78).

Conclusions

For individuals with RRMS, interferon beta-1a 44 micrograms subcutaneous 3 times per week is more effective than placebo in reducing the risk of new or enlarging T2 lesions at 2 years (high confidence in the evidence, 1 Class I study; confidence upgraded owing to magnitude of effect). Interferon beta-1a 44 micrograms subcutaneous 3 times per week is probably more effective than interferon beta-1a IM weekly in reducing the risk of new or enlarging T2 lesions at 1 year

(moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect).

Mitoxantrone

One Class I study[e71] of mitoxantrone vs placebo evaluated the number of new lesions on T2 from baseline to 2 years in 42 individuals with RRMS. The SMD between treatments was 0.64 (95% CI, 0.02–1.26), favoring mitoxantrone.

Conclusion

In individuals with RRMS, mitoxantrone is more effective than placebo in decreasing the number of new lesions on T2 at 2 years (high confidence in the evidence, 1 Class I study; confidence upgraded owing to magnitude of effect).

Mycophenolate mofetil

One Class II study[e73] compared mycophenolate mofetil plus interferon beta-1a 30 micrograms IM weekly with placebo plus interferon beta-1a 30 micrograms IM weekly in 24 individuals with RRMS. There was no significant difference in T2 lesion volume percent change or brain volume percent change at 1 year between treatments. The SMD for T2 lesion volume percent change was 0.52 (95% CI, -0.29 to 1.34) and for brain volume percent change was 0.72 (95% CI, -0.11 to 1.55). One Class II study[e74] compared mycophenolate mofetil to interferon beta-1a 30 micrograms IM weekly in the mean number of new T2 lesions at 6 months in 35 individuals with RRMS. There was no significant difference between treatments, with an SMD of 0.38 (95% CI, -0.29 to 1.06).

Conclusions

In individuals with RRMS, there is insufficient evidence to determine the efficacy of mycophenolate mofetil plus interferon beta-1a 30 micrograms IM weekly compared with placebo plus interferon beta-1a in decreasing the percentage of T2 lesion volume change or brain volume change at 1 year (very low confidence in the evidence, 1 Class II study; confidence downgraded owing to imprecision). There is insufficient evidence to determine the efficacy of

mycophenolate mofetil compared with interferon beta-1a 30 micrograms IM weekly in decreasing the mean number of new T2 lesions at 6 months (very low confidence in the evidence, 1 Class II study; confidence downgraded owing to imprecision).

Natalizumab

One Class I study[e75] compared natalizumab with placebo in 942 individuals with RRMS. The risk of having at least 1 new or enlarging T2 lesion at 1 year was significantly lower with natalizumab than placebo, with an RR of 0.49 (95% CI, 0.43–0.57). The MRI T2 lesion load at 2 years was significantly less with natalizumab than with placebo, with an SMD of 0.28 (95% CI, 0.14–.42); individuals treated with natalizumab had a mean decrease in lesion load, and individuals treated with placebo had a mean increase in lesion load.

Conclusion

In individuals with RRMS, natalizumab is more effective than placebo in reducing the risk of at least 1 new or enlarging T2 lesion at 1 year and in reducing the MRI T2 lesion load at 2 years (high confidence in the evidence, 1 Class I study; confidence upgraded owing to magnitude of effect).

Ocrelizumab

Two Class I studies[e76] compared ocrelizumab 600 mg IV every 24 weeks to interferon beta-1a 44 micrograms subcutaneous 3 times per week in 1,656 individuals with RRMS. The proportion of individuals with new or newly enlarged lesions on T2 MRI was significantly lower with ocrelizumab, with an RR of 0.63 (95% CI, 0.57–0.70). Individuals treated with ocrelizumab also had smaller decreases in brain volume from week 24 to 96 compared with interferon beta-1a, with an SMD of 0.148 (95% CI, 0.051–0.244).

Conclusions

In individuals with RRMS, ocrelizumab is more effective than interferon beta-1a 44 micrograms subcutaneous 3 times per week in decreasing the proportion of individuals with new or newly enlarged lesions on T2 MRI (high confidence in the evidence, 2 Class I studies). Ocrelizumab is

more effective than interferon beta-1a 44 micrograms subcutaneous 3 times per week in decreasing the mean percentage brain volume change from week 24 to 96 (high confidence in the evidence, 2 Class I studies).

Pegylated interferon

One Class I study[e77] compared pegylated interferon 125 micrograms every 2 weeks with placebo in 933 individuals with RRMS. The number of new or newly enlarging T2 lesions at 1 year was significantly reduced with pegylated interferon, with an SMD of 0.60 (95% CI, 0.46–0.73).

Conclusion

For individuals with RRMS, pegylated interferon is more effective than placebo in reducing the number of new or newly enlarging T2 lesions at 1 year (high confidence in the evidence, 1 Class I study, confidence upgraded owing to magnitude of effect).

Rituximab

One Class II study[e78] compared rituximab with placebo in 104 individuals with RRMS. The mean decrease in volume of lesions on T2 MRI from baseline to week 36 was significantly greater with rituximab compared with placebo, with an SMD of 0.48 (95% CI, 0.07–0.90).

Conclusion

For individuals with RRMS, rituximab is probably more effective than placebo in decreasing the volume of T2 lesions from baseline to week 36 (moderate confidence in the evidence, 1 Class II study, confidence upgraded owing to magnitude of effect).

Teriflunomide

One Class II study[e79] compared teriflunomide 14 mg with placebo in 721 individuals with RRMS. Teriflunomide was more effective than placebo in decreasing the volume of MRI T2 lesions at 2 years than placebo, with an SMD of 0.19 (95% CI, 0.05–0.34).

Conclusion

For individuals with RRMS, teriflunomide is probably more effective than placebo in decreasing the volume of MRI T2 lesions at 2 years (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect).

Clinical question 3: In people with RRMS, are DMTs superior to placebo or other DMTs in preventing disease progression as measured by in-study disease progression measures?

The most consistently reported measure for in-study disability progression was the proportion of people with MS with disability progression. This measure was defined as an increase in the Expanded Disability Status Scale (EDSS) of 1 point in those with a baseline EDSS less than or equal to 5.0, or an increase of 0.5 points in those with a baseline EDSS 5.5 or greater, sustained for 3 or 6 months, which was detected over a 2-year study period.

Alemtuzumab

One Class I study[e33] and 1 Class II study[e34] evaluated the proportion of people with MS with disability progression sustained for 6 months over 2 years with alemtuzumab compared with interferon beta-1a 44 micrograms subcutaneous 3 times per week, including a total of 914 people with MS. Meta-analysis of data demonstrated an RR of 0.44 (95% CI, 0.28–0.70), favoring alemtuzumab. One Class 1 study[e33,e82] comparing alemtuzumab with interferon beta-1a in 628 individuals with RRMS evaluated the proportion of people with MS with confirmed disability improvement on the EDSS of at least 0.5 points from baseline to 24 months. The RR was 1.55 (95% CI, 1.23–1.98), favoring alemtuzumab.

Conclusions

For individuals with RRMS, alemtuzumab is more effective than interferon beta-1a 44 micrograms subcutaneous 3 times per week in reducing the risk of disability progression over 2

years (high confidence in the evidence, 1 Class I study and 1 Class II study; confidence upgraded owing to magnitude of effect). Alemtuzumab is more effective than interferon beta-1a in increasing the proportion of individuals with confirmed disability improvement on the EDSS over 2 years (high confidence in the evidence, 1 Class I study; confidence upgraded owing to magnitude of effect).

Azathioprine

One Class II study[e35] evaluated the proportion of individuals with disability progression sustained for at least 24 months with azathioprine vs placebo, reporting an RR of 0.58 (95% CI, 0.23–1.46), favoring azathioprine.

Conclusion

For individuals with RRMS, there is insufficient evidence to determine the efficacy of azathioprine compared with placebo in reducing the risk of disability progression over 24 months (very low confidence in the evidence, 1 Class II study; confidence downgraded owing to imprecision).

Cladribine

One Class II study[e39] evaluated the proportion of people with MS with a 3-month sustained change in EDSS at 2 years with 2 doses of oral cladribine in 1,326 individuals with RRMS. Compared with placebo, the RR for either dose of cladribine was 0.72 (95% CI, 0.56–0.91), favoring cladribine.

Conclusion

For individuals with RRMS, cladribine is probably more effective than placebo in reducing the risk of disability progression over 2 years (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect).

Corticosteroids

One Class IV study[e40] compared every 4 months pulsed IV corticosteroids (methylprednisolone 1 g for 5 days with oral prednisone taper) with placebo for disability progression (sustained changed in EDSS for 4 months) at 2 years in 81 individuals with RRMS. The RR was 0.14 (95% CI, 0.04–0.49), favoring pulsed corticosteroids. One Class II study[e42] evaluated the proportion of people with MS with disability progression sustained for 6 months with pulsed corticosteroid added to interferon beta-1a 30 micrograms IM weekly compared with placebo added to interferon in 341 individuals with RRMS over 3 years. The RR was 0.93 (95% CI, 0.66–1.33), favoring pulsed corticosteroids.

Conclusions

For individuals with RRMS, pulsed corticosteroids are possibly more effective than placebo in reducing the risk of disability progression at 2 years (low confidence in the evidence, 1 Class IV study; confidence upgraded owing to magnitude of effect). Pulsed corticosteroids added to interferon beta-1a 30 micrograms IM weekly are possibly no more effective than placebo added to interferon beta-1a 30 micrograms IM weekly in reducing the risk of disability progression over 3 years (low confidence in the evidence, 1 Class II study).

Daclizumab HYP

One Class I study[e44] evaluated the proportion of individuals with disease progression sustained for 3 months with daclizumab HYP compared with placebo after 1 year in 397 individuals with RRMS. The RR was 0.43 (95% CI, 0.22–0.84), favoring daclizumab HYP. One Class II study[e45] compared daclizumab HYP to interferon beta-1a 30 micrograms IM weekly in 1,841 individuals with RRMS. The RR for disability progression sustained for 3 months over 3 years was 0.80 (95% CI, 0.66–0.98), favoring daclizumab HYP.

Conclusions

In individuals with RRMS, daclizumab HYP is more effective than placebo in decreasing the risk of disability progression at 1 year (high confidence in the evidence, 1 Class I study; confidence upgraded owing to magnitude of effect). Daclizumab HYP is probably more effective than interferon beta-1a 30 micrograms IM weekly in decreasing the risk of disability progression

at 3 years (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect). See safety note on page 35.

Dimethyl fumarate

One Class I study[e46] and 1 Class II study[e47] evaluated dimethyl fumarate vs placebo in 1,539 individuals with RRMS. The RR for disability progression sustained for 3 months over 2 years was 0.65 (95% CI, 0.53–0.81), favoring dimethyl fumarate.

Conclusion

In individuals with RRMS, dimethyl fumarate is more effective than placebo in decreasing the risk of disability progression over 2 years (high confidence in the evidence, 1 Class I study and 1 Class II study; confidence upgraded owing to magnitude of effect).

Fingolimod

One Class I study[e48] and 1 Class II study[e49] compared fingolimod with placebo in 1,556 individuals with RRMS. The RR for disability progression sustained for 3 months over 2 years was 0.81 (95% CI, 0.68–0.96), favoring fingolimod. One Class I study[e51] compared fingolimod with interferon beta-1a 30 micrograms IM weekly in 860 individuals with RRMS. The RR for disability progression sustained for 3 months over 1 year was 0.74 (95% CI, 0.45–1.21).

Conclusions

In individuals with RRMS, fingolimod is more effective than placebo in reducing the risk of disability progression over 2 years (high confidence in the evidence, 1 Class I study and 1 Class II study; confidence upgraded owing to magnitude of effect). Fingolimod is possibly no more effective than interferon beta-1a 30 micrograms IM weekly in reducing the risk of disability progression over 1 year (low confidence in the evidence, 1 Class I study; confidence downgraded owing to imprecision).

Glatiramer acetate

One Class I[e46] and 2 Class II studies[e53,e54] compared glatiramer acetate with placebo in 1,024 individuals with RRMS. The RR for the proportion of individuals with disease progression sustained for at least 3 months over 2 years was 0.76 (95% CI, 0.53–1.08). One Class II study[e57] compared glatiramer acetate with interferon beta-1b subcutaneous alternate day (250 mg) in 1,345 individuals with RRMS. A greater proportion of individuals taking interferon beta-1b subcutaneous alternate day had confirmed disease progression compared with those taking glatiramer acetate, with an RR of 1.32 (95% CI, 1.08–1.64). One Class I study[e58] compared glatiramer acetate with interferon beta-1a 30 micrograms IM once per week in 487 individuals with RRMS. There was no difference in the proportion of individuals with EDSS progression over 3 years, with an RR of 0.87 (95% CI, 0.63–1.20).

Conclusions

For individuals with RRMS, glatiramer acetate is possibly no more effective than placebo in reducing the risk of disability progression over 2 years (low confidence in the evidence, 1 Class I and 2 Class II studies; confidence downgraded owing to imprecision). Interferon beta-1b 250 mg subcutaneous alternate day is probably less effective than glatiramer acetate in decreasing the risk of disease progression over 2 years (moderate confidence in the evidence, 1 Class II study; confidence in evidence upgraded owing to magnitude of effect). Interferon beta-1a 30 micrograms IM once weekly is possibly no more effective than glatiramer acetate in decreasing the risk of EDSS progression over 3 years (low confidence in the evidence, 1 Class I study; confidence downgraded owing to imprecision).

Immunoglobulins

One Class I study[e60] and 1 Class II study[e62] compared immunoglobulins with placebo, measuring the risk of disability progression over 2 years in 190 people with RRMS. There was no difference between immunoglobulins and placebo, with an RR of 0.70 (95% CI, 0.39–1.24).

Conclusion

For individuals with RRMS, there is insufficient evidence to determine the efficacy of immunoglobulins compared with placebo in reducing the risk of disability progression at 2 years

(very low confidence in the evidence, 1 Class I study and 1 Class II study; confidence downgraded owing to imprecision).

Interferon beta-1a IM weekly

One Class I study[e64] and 1 Class II study[e65] evaluated the proportion of individuals with disability progression sustained for 3 or 6 months over the 2-year study period and included a total of 1,198 people with MS. Meta-analysis of data demonstrated an RR of 0.71 (95% CI, 0.52–0.97), favoring interferon beta-1a 30 micrograms IM weekly.

Conclusion

For individuals with RRMS, interferon beta-1a 30 micrograms IM weekly is more effective than placebo in reducing the risk of disability progression over 24 months (high confidence in the evidence, 1 Class I study and 1 Class II study; confidence upgraded owing to magnitude of effect).

Interferon beta-1b subcutaneous alternate day

One Class III study[e68] evaluated the proportion of individuals with RRMS with disability progression sustained for 3 months in a 3-year study of interferon beta-1b 8 mIUs subcutaneous alternate day vs placebo. This study demonstrated an RR of 0.73 (95% CI, 0.47–1.14).

Conclusion

For individuals with RRMS, there is insufficient evidence to determine the efficacy of interferon beta-1b 8 mIUs subcutaneous alternate day compared with placebo in reducing the risk of disability progression over 36 months (very low confidence in the evidence, 1 Class III study; confidence downgraded owing to imprecision).

Interferon beta-1a subcutaneous 3 times per week

One Class I study[e66] compared interferon beta-1a 44 micrograms subcutaneous 3 times per week with placebo in 560 individuals with RRMS. The proportion of individuals with disability progression sustained for 3 months was significantly lower with interferon beta-1a 44 micrograms subcutaneous 3 times per week compared with placebo, with an RR of 0.77 (95% CI, 0.61–0.96).

Conclusion

For people with RRMS, interferon beta-1a 44 micrograms subcutaneous 3 times per week is more effective than placebo in reducing the risk of disability progression over 2 years (high confidence in the evidence, 1 Class I study; confidence upgraded owing to magnitude of effect).

Methotrexate

One Class III study[e69] compared methotrexate with placebo in 20 individuals with RRMS. There was no significant difference between treatments in the risk of disability progression over 18 months, with an RR of 0.73 (95% CI, 0.24–2.00). One Class III study[e70] compared methotrexate with placebo in 80 individuals with RRMS. There was no significant difference between treatments in the EDSS score at 12 months, with an RMD of 0.39 (95% CI, -0.01 to 0.79).

Conclusions

There is insufficient evidence to determine the efficacy of methotrexate compared with placebo in the risk of disability progression over 18 months (very low confidence in the evidence, 1 Class III study). There is insufficient evidence to determine the efficacy of methotrexate compared with interferon beta-1a in decreasing the EDSS at 12 months (very low confidence in the evidence, 1 Class III study).

Mitoxantrone

One Class I study[e71] compared mitoxantrone with placebo in 51 individuals with RRMS. The RR for disability progression from baseline to endpoint at 2 years was 0.20 (95% CI, 0.05−0.73), favoring mitoxantrone.

Conclusion

For people with RRMS, mitoxantrone is more effective than placebo in decreasing the risk of disability progression at 2 years (high confidence in the evidence, 1 Class I study, confidence upgraded owing to magnitude of effect).

Natalizumab

One Class I study[e75] compared natalizumab with placebo in 942 individuals with RRMS. The risk of disability progression sustained for 12 weeks over 2 years was significantly lower with natalizumab, with an RR of 0.64 (95% CI 0.52–0.80).

Conclusion

For people with RRMS, natalizumab is more effective than placebo in decreasing the risk of disability progression at 2 years (high confidence in the evidence, 1 Class I study, confidence upgraded owing to magnitude of effect).

Ocrelizumab

There are 2 Class I studies[e76] comparing ocrelizumab 600 mg IV every 24 weeks to interferon beta-1a 44 micrograms subcutaneous 3 times per week in 1,656 individuals with RRMS. The RR for disability progression sustained for 3 months over 2 years was 0.67 (95% CI, 0.51–0.88), and the RR for disability progression confirmed for 6 months over 2 years was 0.67 (95% CI, 0.50–0.89), both favoring ocrelizumab. The proportion of individuals with disability improvement confirmed at 3 months over 2 years was 1.33 (95% CI, 0.95–1.88).

Conclusions

For individuals with RRMS, ocrelizumab is more effective than interferon beta-1a 44 micrograms subcutaneous 3 times per week in decreasing the risk of in-study disability progression confirmed at 3 and 6 months over 2 years (high confidence in the evidence, 2 Class I

studies). Ocrelizumab is possibly no more effective than interferon beta-1a 44 micrograms subcutaneous 3 times per week in increasing the proportion of individuals with disability improvement confirmed at 3 months (low confidence in the evidence, 2 Class I studies, confidence downgraded owing to imprecision).

Pegylated interferon

One Class I study[e77] compared pegylated interferon 250 micrograms every 2 weeks with placebo in 1,012 individuals with RRMS. The RR for disease progression sustained for 3 months over 1 year was 0.61 (95% CI, 0.40–0.93).

Conclusion

For people with RRMS, pegylated interferon is more effective than placebo in decreasing the risk of disability progression at 1 year (high confidence in the evidence, 1 Class I study, confidence upgraded owing to magnitude of effect).

Teriflunomide

Two Class II studies[e79,e81] compared teriflunomide 14 mg to placebo in 1,479 individuals with RRMS. Teriflunomide was associated with a lower risk of disability progression sustained for 12 weeks than placebo, with an RR of 0.76 (95% CI, 0.62–0.93).

Conclusion

In individuals with RRMS, teriflunomide 14 mg is more effective than placebo in reducing the risk of disability progression over 2 years (high confidence in the evidence, 2 Class II studies; confidence upgraded owing to magnitude of effect).

Clinical question 4: In people with RRMS who experience disease activity while on a DMT, is changing to a different DMT superior to continuing the present DMT in terms of relapse rate and MRI T2 activity?

Alemtuzumab

One Class I study[e33] compared alemtuzumab with interferon beta-1a 44 micrograms subcutaneous 3 times per week in individuals with RRMS who experienced a relapse in the preceding year while taking interferon (any formulation) or glatiramer acetate. Alemtuzumab was more effective than interferon beta-1a 44 micrograms subcutaneous 3 times per week in reducing the risk of relapse at 2 years, with an RR of 0.59 (95% CI, 0.51–0.69), reducing the ARR with an RMD of 0.26 (95% CI, 0.13–0.39), reducing the proportion of people with MS with disability progression over 2 years, with an RR of 0.38 (95% CI, 0.28–0.50), and decreasing the proportion of individuals with new or enlarging T2 hyperintense lesions at 24 months, with an RR of 0.68 (95% CI, 0.58–0.78).

Conclusion

For individuals with RRMS who experienced a relapse on interferon beta or glatiramer acetate, alemtuzumab is more effective than interferon beta-1a 44 micrograms subcutaneous 3 times per week in reducing the ARR, the risk of relapse, disability progression, and risk of new or enlarging T2 lesions over 2 years (high confidence in the evidence, 1 Class I study; confidence upgraded owing to magnitude of effect).

Natalizumab

One Class I study[e83] compared interferon beta-1a 30 micrograms IM weekly plus natalizumab ("natalizumab add-on therapy") to interferon beta-1a 30 micrograms IM weekly plus placebo in 1,171 individuals with RRMS who experienced at least one relapse in the past 12 months on interferon. Natalizumab add-on therapy was more effective than adding placebo for all clinical outcome measures, with an RR for relapse at 2 years of 0.62 (95% CI, 0.55–0.70), an RMD in ARR of 0.41 (95% CI, 0.36–0.59), and an RR of 0.80 (95% CI, 0.69–0.93) for disability progression sustained for 12 weeks over 2 years. Natalizumab add-on therapy was also more effective than adding placebo for all MRI outcomes, including the risk of having at least 1 new or enlarging T2 lesion at 1 year, with an RR of 0.51 (95% CI, 0.44–0.59).

One Class II study[e84] compared glatiramer acetate plus natalizumab with glatiramer acetate plus placebo in 110 individuals with RRMS who relapsed at least once in the past 12 months on glatiramer acetate (Class II owing to unclear allocation concealment). There was no difference between natalizumab add-on therapy and placebo in the number of individuals who relapsed over

6 months, with an RR of 0.80 (95% CI, 0.42–1.52). Natalizumab add-on therapy was more effective than placebo in decreasing the mean number of new or enlarging T2 lesions at 6 months, with an SMD of 0.48 (95% CI, 0.10–0.86).

Conclusions

In individuals with RRMS who experienced 1 or more relapses in the preceding 12 months on interferon, adding natalizumab is more effective than adding placebo in decreasing the risk of relapse over 2 years, the ARR, the risk of disability progression over 2 years, and the risk of new or enlarging T2 lesions at 1 year (high confidence in the evidence, 1 Class I study; confidence upgraded owing to magnitude of effect). In individuals with RRMS who experienced 1 or more relapses in the preceding 12 months on glatiramer acetate, there is insufficient evidence to determine the efficacy of natalizumab added to glatiramer acetate compared with placebo added to glatiramer acetate in decreasing the risk of relapse at 6 months (very low confidence in the evidence, 1 Class II study; confidence downgraded owing to imprecision). Natalizumab added to glatiramer acetate is probably more effective than placebo added to glatiramer acetate in decreasing the cumulative number of new or enlarging T2 lesions at 6 months (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect).

Clinical context

Natalizumab is not presently utilized as an add-on therapy to other DMTs because of safety concerns of combination therapy with this medicine.

Clinical question 5: In people with progressive MS, are DMTs superior to placebo or other DMTs as measured by relapse rate or in-study disease progression?

Clinical context

In older studies, different forms of progressive MS may have been included together (SPMS and primary progressive MS). This is reflected in the description of the results.

Azathioprine

One Class II study[e85] compared azathioprine with placebo in 64 people with progressive forms of MS (Class II owing to allocation concealment unclear, baseline characteristics). This study demonstrated an RR of 0.53 (95% CI, 0.25–1.10) for relapses at 2 years, and an RMD of 0.31 (95% CI, 0.01–0.61) in the number of relapses at 2 years. The study also evaluated the proportion of individuals with disability progression from baseline to endpoint over 3 years and demonstrated an RR of 0.64 (95% CI, 0.32–1.25), favoring azathioprine.

Conclusions

For people with progressive forms of MS, there is insufficient evidence to determine the efficacy of azathioprine compared with placebo in reducing the risk of relapse over 2 years (very low confidence in the evidence, 1 Class II study; confidence downgraded owing to imprecision). Azathioprine is probably more effective than placebo in reducing the mean number of relapses over 2 years (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect). There is insufficient evidence to determine the efficacy of azathioprine compared with placebo in reducing the risk of disability progression over 3 years (very low confidence in the evidence, 1 Class II study; confidence downgraded owing to imprecision).

Cladribine

One Class II study[e86] evaluated the proportion of people with MS with disability progression at 1 year in 111 individuals with SPMS treated with subcutaneous cladribine compared with placebo (Class II owing to unclear allocation concealment). The RR was 0.78 (95% CI, 0.44–1.42).

Conclusion

For individuals with SPMS, subcutaneous cladribine is possibly no more effective than placebo in reducing the risk of disability progression at 1 year (low confidence in the evidence, 1 Class II study).

Corticosteroids

One Class II study[e87] compared high-dose corticosteroids (bimonthly pulses of 500 mg IV for 3 days) to low-dose corticosteroids (bimonthly pulses of 10 mg IV for 3 days) in 108 individuals

with SPMS (Class II owing to allocation concealment unclear, baseline characteristics). The RR for the proportion of individuals with relapses at 2 years was 0.33 (95% CI, 0.08–1.44). The RR for the proportion of people with MS with worsening of disability from baseline to endpoint was 1.50 (95% CI, 0.29–7.54). One Class II study[e88] compared corticosteroids added to mitoxantrone with placebo added to mitoxantrone in 71 individuals with SPMS (Class II owing to allocation concealment unclear, no primary outcome specified). There was no difference in the EDSS at the end of the 6-month treatment period, with an RMD of 0.03 (95% CI, -0.91 to 0.97).

Conclusions

In individuals with SPMS, there is insufficient evidence to determine the efficacy of high-dose pulsed steroids compared with low-dose pulsed corticosteroids in reducing the proportion of individuals with relapses at 2 years and the proportion of individuals with disability progression at 2 years (very low confidence in the evidence, 1 Class II study; confidence in evidence downgraded due to imprecision). There is insufficient evidence to determine the efficacy of corticosteroids added to mitoxantrone compared with placebo added to mitoxantrone in decreasing the EDSS at 6 months (very low confidence in the evidence, 1 Class II study; confidence downgraded owing to imprecision).

Cyclophosphamide

Two Class II studies[e89,e90] evaluated the proportion of 97 individuals with progressive forms of MS with disability progression over 2 years (both Class II owing to unclear allocation concealment). The RR for disability progression was 1.37 (95% CI, 0.88−2.13).

Conclusion

For individuals with progressive forms of MS, there is insufficient evidence to determine the efficacy of cyclophosphamide compared with placebo in reducing the risk of disability progression over 2 years (very low confidence in the evidence, 2 Class II studies; confidence downgraded owing to imprecision).

Glatiramer acetate

One Class II study[e91] compared glatiramer acetate with placebo in 106 individuals with progressive forms of MS (Class II owing to allocation concealment unclear). The RR for the proportion of individuals with confirmed disability progression sustained for 3 months over 2 years was 0.69 (95% CI, 0.33–1.46). One Class II study[e92] compared glatiramer acetate with placebo in 943 individuals with PPMS (allocation concealment unclear, less than 80% completion). The RR for confirmed disability progression sustained for 3 months over 2 years was 0.87 (95% CI, 0.75–1.02).

Conclusions

For people with progressive forms of MS, glatiramer acetate is possibly no more effective than placebo in reducing the risk of disability progression over 2 years (low confidence in the evidence, 1 Class II study). For people with PPMS, glatiramer acetate is possibly no more effective than placebo in reducing the risk of disability progression over 2 years (low confidence in the evidence, 1 Class II study).

Fingolimod

There is 1 Class II study[e93] comparing fingolimod 0.5 mg with placebo in 823 individuals with PPMS (Class II because less than 80% completed the study). The proportion of individuals with confirmed disability progression at 3 months was not different between individuals treated with fingolimod vs placebo, with an RR of 1.00 (95% CI, 0.91–1.09). More individuals treated with fingolimod compared with placebo were free of new or newly enlarging T2 lesions on MRI, with an RR of 1.32 (95% CI, 1.20–1.46).

Conclusions

In individuals with PPMS, fingolimod is possibly no more effective than placebo in decreasing the proportion of individuals with confirmed disability progression at 3 months (low confidence in the evidence, 1 Class II study). Fingolimod is probably more effective than placebo in increasing the proportion of individuals with no new or newly enlarging T2 lesions (moderate confidence in the evidence, 1 Class II study, confidence upgraded owing to magnitude of effect).

Immunoglobulins

There are 2 Class II studies[e94,e95] comparing immunoglobulins with placebo in 515 individuals with progressive MS (Hommes et al,[e94] Class II owing to unclear allocation concealment; Pohlau et al,[e95] Class II owing to allocation concealment unclear, less than 80% completion). There was no difference between immunoglobulins and placebo in the risk of at least 1 relapse at 2 years, with an RR of 0.96 (95% CI, 0.79–1.16), or in the risk of disability progression over 2 years, with an RR of 0.96 (95% CI, 0.74–1.25).

Conclusion

For individuals with progressive MS, there is insufficient evidence to determine the efficacy of immunoglobulins compared with placebo in reducing the risk of relapse or disability progression over 2 years (very low confidence in the evidence, 2 Class II studies; confidence downgraded due to imprecision).

Interferon beta-1a IM weekly

One Class II study[e96] evaluated the efficacy of interferon beta-1a 60 micrograms IM weekly for relapse prevention and clinical disease progression in 436 individuals with SPMS (Class II owing to unclear allocation concealment). Individuals treated with interferon beta-1a 30 micrograms IM weekly had a lower risk of relapse at 2 years, with an RR of 0.72 (95% CI, 0.54–0.95). The proportion of individuals with disability progression sustained for 3 months was not different between interferon beta-1a 60 micrograms IM weekly and placebo, with an RR of 0.85 (95% CI, 0.64–1.12). One Class I study[e97] in 50 individuals with PPMS found that the proportion of individuals with disability progression sustained for 3 months was not different between interferon beta-1a 30 micrograms IM weekly and placebo, with an RR of 1.19 (95% CI, 0.78–1.21).

Conclusions

For individuals with SPMS, interferon beta-1a 60 micrograms IM weekly is probably more effective than placebo in reducing the risk of relapse over 2 years (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect). For individuals with SPMS, interferon beta-1a 30 micrograms IM weekly is possibly no more effective than placebo in reducing the risk of disability progression over 24 months (low confidence in the evidence, 1 Class II study). For individuals with PPMS, interferon beta-1a 30 micrograms IM weekly is possibly no more effective than placebo in reducing the risk of disability progression

over 2 years (low confidence in the evidence, 1 Class I study; confidence downgraded due to imprecision).

Interferon beta-1a subcutaneous 3 times per week

There is 1 Class I study[e98] comparing interferon beta-1a subcutaneous 22 micrograms or 44 micrograms 3 times per week with placebo in 618 individuals with SPMS. Both doses of interferon beta-1a subcutaneous 3 times per week were more effective than placebo in decreasing the mean number of exacerbations per year. The RMD between interferon beta-1a subcutaneous 3 times per week of 22 micrograms and placebo was 0.21 (95% CI, 0.14–0.28), and the RMD between interferon beta-1a subcutaneous 3 times per week of 44 micrograms and placebo was 0.21 (95% CI, 0.15–0.27), favoring interferon beta-1a subcutaneous 3 times per week. The same study also evaluated the risk of disability progression sustained for 3 months over 2 years. There was no difference between either dose of interferon beta-1a subcutaneous 3 times per week and placebo, with an RR of 0.93 (95% CI, 0.79–1.10).

Conclusions

In individuals with SPMS, interferon beta-1a subcutaneous 3 times per week is more effective than placebo in decreasing the mean number of exacerbations per year (high confidence in the evidence, 1 Class I study; confidence upgraded owing to magnitude of effect). Interferon beta-1a subcutaneous 3 times per week is possibly no more effective than placebo in reducing the risk of disability progression over 2 years (low confidence in the evidence, 1 Class I study; confidence downgraded owing to imprecision).

Interferon beta-1b subcutaneous alternate day

Two Class II studies[e99,e100] evaluated the efficacy of interferon beta-1b 8 mIUs subcutaneous alternate day compared with placebo on relapse risk, ARR, and disability progression in 1,333 individuals with SPMS (both Class II owing to less than 80% completion). The RR for at least 1 relapse over 3 years was 0.84 (95% CI, 0.75–0.93), and the RMD in ARR was 0.16 (95% CI, 0.02–0.29), favoring interferon beta-1b 8 mIUs subcutaneous alternate day. The RR for the proportion of people with MS with disability progression over 3 years was 0.85 (95% CI, 0.71–1.02), favoring interferon beta-1b 8 mIUs subcutaneous alternate day. One Class II study[e101] compared interferon beta-1b 8 mIUs subcutaneous alternate day vs placebo in 73 individuals with PPMS (Class II owing to unclear allocation concealment). The RR for the proportion of

people with MS with disability progression sustained for 3 months over a 2-year period was 0.71 (95% CI, 0.35–1.42).

Conclusions

For people with SPMS, interferon beta-1b 8 mIUs subcutaneous alternate day is more effective than placebo in reducing the risk of relapse over 3 years (high confidence in the evidence, 2 Class II studies; confidence upgraded owing to magnitude of effect). Interferon beta-1b 8 mIUs subcutaneous alternate day is more effective than placebo in reducing the ARR (high confidence in the evidence, 2 Class II studies, confidence upgraded owing to magnitude of effect). Interferon beta-1b 8 mIUs subcutaneous alternate day is possibly no more effective than placebo in reducing the risk of disability progression over 36 months (low confidence in the evidence, 2 Class II studies; confidence downgraded owing to imprecision). For people with PPMS, interferon beta-1b 8 mIUs subcutaneous alternate day is possibly no more effective than placebo in reducing the risk of disability progression over 2 years (low confidence in the evidence, 1 Class II study).

Methotrexate

There is 1 Class II study[e102] comparing methotrexate with placebo in 60 individuals with chronic progressive MS (Class II owing to unclear allocation concealment [chronic progressive MS in now referred to as primary progressive MS]). The risk of relapse over 2 years was not significant between treatments, with an RR of 0.75 (95% CI, 0.24–2.36). The risk of disability progression sustained for 2 months over 2 years was not significant between treatments, with an RR of 0.69 (95% CI, 0.38–1.22).

Conclusion

For individuals with chronic progressive MS, there is insufficient evidence to determine the efficacy of methotrexate compared with placebo in reducing the risk of relapse or disability progression over 2 years (very low confidence in the evidence, 1 Class II study; confidence downgraded owing to imprecision).

Mitoxantrone

There is 1 Class II study[e103] comparing mitoxantrone (12 mg/m^2 and 5 mg/m^2) with placebo in 124 individuals with worsening RRMS and SPMS (Class II owing to unclear allocation concealment). The risk of relapse over 2 years was lower with mitoxantrone, with an RR of 0.68 (95% CI, 0.48–0.94). The RR for disability progression from baseline to endpoint over 2 years was 0.33 (95% CI, 0.13–0.82), also favoring mitoxantrone. Note that results were not stratified for disease subgroup.

Conclusion

For individuals with worsening RRMS and SPMS, mitoxantrone is probably more effective than placebo in decreasing the risk of relapse and disability progression over 2 years (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect).

Ocrelizumab

There is 1 Class II study[e104] of ocrelizumab 600 mg every 24 weeks compared with placebo in 731 individuals with PPMS (Class II owing to less than 80% completing trial). The proportion of individuals with confirmed disability progression at 3 months was lower in individuals treated with ocrelizumab than placebo, with a hazard ratio of 0.76 (95% CI, 0.59–0.98). The proportion of individuals with confirmed disability progression at 6 months was lower with ocrelizumab than with placebo, with a hazard ratio of 0.75 (95% CI, 0.58–0.98).

Conclusion

In individuals with PPMS, ocrelizumab is probably more effective than placebo in decreasing the hazard of disability progression at 3 and 6 months (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect).

Rituximab

There is 1 Class II study[e105] of rituximab vs placebo in 439 individuals with PPMS (Class II owing to unclear allocation concealment). There was no difference between treatments in the proportion of individuals with confirmed disease progression sustained for 3 months after 2 years of treatment, with an RR of 0.78 (95% CI, 0.60–1.02).

Conclusion

In individuals with PPMS, rituximab is possibly no more effective than placebo in decreasing the risk of disease progression over 2 years (low confidence in the evidence, 1 Class II study).

Clinical question 6: What are the AEs of DMTs in people with MS compared with placebo (AE-related discontinuation, and serious or life-threatening AEs)?

Clinical context

Safety data in this analysis are derived from comparisons available in the randomized trials obtained in the systematic review. A fuller accounting of AEs and risks is provided in the product manufacturer package insert. For each agent, common and expected AEs and rare but clinically important risks are noted in a clinical context section. Pregnancy-related information is included in table e-3.

Alemtuzumab

Meta-analysis of the 2 Class I studies[e33,e34] and 1 Class II study[e106] found an RD of -4.4% (95% CI, -7.0 to -1.8) for AE-related discontinuation, with more individuals in the group receiving interferon beta-1a 44 micrograms subcutaneous 3 weekly injections discontinuing because of AEs than in the group receiving alemtuzumab. There was no significant difference in the risk of cancer, death, liver toxicity, serious infection, or immune thrombocytopenic purpura between treated groups across 24-month follow-up. There was a higher risk of "thyroid-associated" events (e.g., hyperthyroidism, hypothyroidism, thyroiditis, goiter, and thyroid cyst) in individuals treated with alemtuzumab compared with those treated with interferon beta-1a, with an RD of 13.9% (95% CI, 9.3–18.6).

Conclusions

Alemtuzumab has a possibly important lower risk than interferon beta-1a of AE-related discontinuation at 24 months (low confidence in the evidence, 2 Class I studies and 1 Class II

study, confidence in evidence downgraded owing to imprecision). There is insufficient evidence to determine the difference between alemtuzumab and interferon beta-1a in the risk of cancer, death, liver toxicity, serious infection, and immune thrombocytopenic purpura (very low confidence in the evidence, 2 Class I studies and 1 Class II study; confidence downgraded owing to imprecision). Alemtuzumab has a higher risk than interferon beta-1a of a thyroid-associated event (high confidence in the evidence, 2 Class I studies and 1 Class II study).

Clinical context

Key safety issues with alemtuzumab include infusion reactions, hyperthyroidism, immune thrombocytopenia, antiglomerular basement membrane disease, and rare serious and life-threatening infection. REMS program activities include prophylaxis for infusion reactions, ongoing laboratory monitoring for medication safety, and baseline and yearly skin examinations. Alemtuzumab may increase the risk of malignancies, including thyroid cancer, melanoma, and lymphoproliferative disorders.

Azathioprine

One Class II study[e35] of 52 individuals with RRMS found an RD of 16.69% (95% CI, -2.26 to 34.69) between azathioprine and placebo for the proportion of individuals with AE-related discontinuation.

Conclusions

For individuals with RRMS, there is insufficient evidence to determine the RD between azathioprine and placebo for AE-related discontinuation at 24 months (very low confidence in the evidence, 1 Class II study; confidence downgraded owing to imprecision).

Clinical context

Azathioprine has a variety of known AEs and risks that are reviewed in the package insert. Thiopurine methyltransferase genotyping or phenotyping may assist in identifying people with MS at risk of developing severe or life-threatening myelotoxicity on this medication. Risks of malignancy include lymphoma. Azathioprine has mutagenic potential in men and women. The

following can occur related to azathioprine: gastrointestinal hypersensitivity reaction, cytopenias, infections, hepatotoxicity, and other risks noted in the package insert.

Cladribine

One Class II study[e39] of 1,326 individuals with RRMS found an RD of 3.68% (95% CI, 1.42%–5.66%) between cladribine and placebo for the proportion of individuals who discontinued because of AEs at 2 years. The same study found an RD of 1.13% (95% CI, 0.12%–2.07%) for neoplasms and an RD of 24.86% (95% CI, 21.55%–28.00%) for lymphocytopenia. Neoplasms in the cladribine group included uterine leiomyomas, melanoma, cervical carcinoma, carcinoma of pancreas, and ovarian carcinoma; no tumors were seen in the placebo group.

Conclusions

For individuals with RRMS, there is insufficient evidence to determine whether cladribine is importantly different from placebo in the risk of AE-related discontinuation at 2 years (very low confidence in the evidence, 1 Class II study, confidence downgraded owing to imprecision). Cladribine possibly has a higher risk of neoplasms than placebo (low confidence in the evidence, 1 Class II study). Cladribine probably has a higher risk of lymphocytopenia than placebo (moderate confidence in the evidence, 1 Class II study, confidence upgraded owing to large effect size).

Clinical context

Various AEs and risks have been seen with cladribine, more commonly with high-dose infusions. Bone marrow suppression, fever, neuropathy (with high-dose infusion), and serious infection have occurred with use for various indications.

Corticosteroids

One Class II study[e41] evaluated the number of individuals with RRMS discontinuing treatment because of AEs with pulsed corticosteroids plus interferon vs placebo plus interferon over 2 years. The RD was 24.15% (95% CI, 12.18%–36.13%), with more individuals receiving corticosteroids discontinuing treatment because of AEs. Data from the same study found an RD

between pulsed corticosteroid plus interferon and placebo plus interferon of 14.82% (95% CI, 1.39%–27.74%) for psychiatric symptoms. Data from 2 Class II studies[e41,e42] found an RD of 21.9% (95% CI, 15.5%–28.3%) for sleep disturbances with corticosteroids plus interferon vs placebo plus interferon.

Conclusions

For individuals with RRMS, pulsed corticosteroids plus interferon probably importantly increases the risk of AE-related discontinuation at 2 years compared with placebo plus interferon (moderate confidence in the evidence, 1 Class II study, confidence upgraded owing to magnitude of effect). Pulsed corticosteroids plus interferon possibly importantly increases the risk of psychiatric symptoms compared with placebo plus interferon (low confidence in the evidence, 1 Class II study). Pulsed corticosteroids plus interferon has a higher risk of sleep disturbances compared with placebo plus interferon (high confidence in the evidence, 2 Class II studies; confidence upgraded owing to magnitude of effect).

Clinical context

Corticosteroids have multiple well-known short- and long-term risks. The package insert provides more detailed information. Steroids are usually used intermittently for MS. Risks primarily include acute psychotic reaction or insomnia, weight gain, and stimulation of hyperglycemia. Long-term risks with intermittent steroid use include avascular necrosis of femoral or humeral head, osteoporosis, and cataracts.

Cyclophosphamide

One Class III study[e43] of cyclophosphamide vs placebo evaluated the risk of AE-related discontinuation at 1 year in 14 people with RRMS. The RD was -12.5% (95% CI, -47.09% to 27.86%).

Conclusion

For individuals with RRMS, there is insufficient evidence to determine the RD between cyclophosphamide and placebo for AE-related discontinuation at 1 year (very low confidence in the evidence, 1 Class III study).

Clinical context

Cyclophosphamide is a potent alkylating agent with major potential toxicities. These include myelosuppression and bone marrow failure, urinary tract and renal toxicity, cardiotoxicity, pulmonary toxicity, secondary malignancies, and venoocclusive liver disease.

Daclizumab HYP

One Class I study[e44] of daclizumab HYP vs placebo evaluated the RD in serious infections over 1 year. The RD was 2.88% (95% CI, 0.47%–6.15%), with more individuals with daclizumab HYP experiencing serious infections. The same study evaluated the RD for elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) beyond 5 times the normal upper limit and found an RD of 3.84% (95% CI, 0.82%–7.55%) with daclizumab HYP. One Class II study[e45] compared daclizumab HYP with interferon beta-1a over 3 years. The RD for AE-related discontinuation was 3.3% (95% CI, 0.001%–6.46%), with more individuals in daclizumab HYP than interferon discontinuing treatment.

Conclusions

For individuals with RRMS, daclizumab HYP has a higher risk of serious infection and pronounced AST/ALT elevation than placebo (high confidence in the evidence, 1 Class I study; confidence upgraded owing to magnitude of effect). Daclizumab HYP possibly importantly increases the risk of AE-related discontinuation compared with interferon (low confidence in the evidence, 1 Class II study). See safety note on page 35.

Clinical context

Daclizumab can cause hepatic injury, including autoimmune hepatitis; immune-mediated disorders such as skin reactions; lymphadenopathy; noninfectious colitis; and other immune-mediated disorders. See safety note on page 35.

Dimethyl fumarate

One Class I study[e46] and 1 Class II study[e47] evaluated the number of people with MS who discontinued dimethyl fumarate vs placebo because of AEs (excluding relapses) at 2 years in 1,540 individuals with RRMS. The RD was 6.5% (95% CI, 2.0%–10.9%). Data from the same 2 studies found an RD for serious infections at 2 years of 0.8% (95% CI, -0.7% to 2.2%).

Conclusion

For individuals with RRMS, dimethyl fumarate possibly importantly increases the risk of AE-related discontinuation compared with placebo (low confidence in the evidence, 1 Class I study and 1 Class II study; confidence downgraded owing to imprecision). There is insufficient evidence to determine the RD between dimethyl fumarate and placebo for serious infections (very low confidence in the evidence, 1 Class I study and 1 Class II study; confidence downgraded owing to imprecision).

Clinical context

Common but manageable AEs include flushing, abdominal pain, and diarrhea. Occasional persistent lymphopenia occurs. Rarer risks include angioedema and anaphylaxis. Progressive multifocal leukoencephalopathy (PML) has occurred with dimethyl fumarate and compounded forms of fumarate, most cases of which occur with persistent lymphopenia with lymphocyte counts less than $0.5x10^9$/L persisting for more than 6 months.

Fingolimod

There are 1 Class I study[e48] and 1 Class II study[e49] comparing fingolimod with placebo in 1,556 individuals with RRMS. The RD for AE-related discontinuation at 2 years was 3.6% (95% CI, -4.4% to 11.5%). The RD for lower respiratory tract or lung infection was 3.0% (95% CI, 0.2%–5.9%), and the RD for having an ALT 5 times the normal level was 1.1% (95% CI, 0.94%–3.33%). The RD for death was -0.4% (95% CI, -1.73% to 0.48%) and neoplasms was 1.23% (95% CI, -1.23% to 4.1%). There is 1 Class I study[e51] comparing fingolimod with interferon beta-1a in 860 individuals with RRMS. The RD for AE-related discontinuation at 1 year was 1.88% (95% CI, -0.99% to 4.84%), and the RD for neoplasms was 1.63% (95% CI, 0.22%–

3.41%). In individuals with PPMS, there is 1 Class II study comparing fingolimod with placebo. The RD for AE-related discontinuation was 8.08% (95% CI, 3.70%–12.79%).

Conclusions

In individuals with RRMS, fingolimod is possibly no different from placebo in the risk of AE-related discontinuation at 2 years (low confidence in the evidence, 1 Class I study and 1 Class II study; confidence downgraded owing to imprecision). Fingolimod increases the risk of lower respiratory tract or lung infection compared with placebo (high confidence in the evidence, 1 Class I study and 1 Class II study; confidence upgraded owing to magnitude of effect). Fingolimod possibly importantly increases the risk of having an ALT 5 times the normal level compared with placebo (low confidence in the evidence, 1 Class II study). There is insufficient evidence to determine the RD between fingolimod and placebo for death and neoplasms (very low confidence in the evidence, 1 Class II study; confidence downgraded owing to imprecision). Fingolimod is probably not different from interferon beta-1a in the risk of AE-related discontinuation at 1 year (moderate confidence in the evidence, 1 Class I study). Fingolimod has a higher risk than interferon beta-1a of neoplasm (high confidence in the evidence, 1 Class I study; confidence in evidence upgraded owing to magnitude of effect). In individuals with PPMS, fingolimod possibly importantly increases the risk of AE-related discontinuation (low confidence in the evidence, 1 Class II study).

Clinical context

More common AEs include headache, liver transaminase elevation (at times 6 to 9 months after initiation), diarrhea, cough, influenza, sinusitis, back and abdominal pain, and pain in extremities. Rare but important risks include infections, such as herpes zoster, that may be disseminated; testing for varicella zoster antibodies and immunization if low is recommended before initiating fingolimod. Other risks include macular edema, posterior reversible encephalopathy syndrome, liver injury, increased risk of cryptococcal infection, and basal cell carcinoma. Rare cases of PML have occurred with fingolimod.

Glatiramer acetate

One Class I study[e46] and 2 Class II studies[e53,e54] compared glatiramer acetate with placebo for AE-related discontinuation over 2 years in 1,015 individuals with RRMS. The difference in treatment discontinuation was not significant, with an RD of 2.2% (95% CI, -1.4 to 5.8). There is

1 Class II study[e55] of 756 individuals with RRMS comparing AE-related discontinuation rates of glatiramer acetate and interferon beta-1a subcutaneous 3 times per week. There was no significant difference in discontinuation rates between the treatments, with an RD of 0.97% (95% CI, -2.39 to 4.35). One Class II study[e57] of 1,333 individuals with RRMS compared injection site reactions and influenza-like illness from glatiramer acetate with those from interferon beta-1b subcutaneous alternate day (250 micrograms). The risk of injection site reactions was higher with glatiramer acetate than with interferon beta-1b subcutaneous alternate day, with an RD of 10.12% (95% CI, 4.44% to 15.67%). The risk of influenza-like illness was higher with interferon beta-1b subcutaneous alternate day than glatiramer acetate, with an RD of 34.81% (95% CI, 30.74%–38.53%). There is 1 Class I study comparing a complex nonbiologic generic glatiramer acetate (Glatopa) with Copaxone in 794 individuals with RRMS. The rate of AE-related treatment discontinuation was higher in the group receiving the complex nonbiologic generic glatiramer acetate (Glatopa), with an RD of 2.28% (95% CI, 0.03–4.82%).

Conclusions

For individuals with RRMS, glatiramer acetate is probably not different from placebo in the risk of AE-related discontinuation at 2 years (moderate confidence in the evidence, 1 Class I and 2 Class II studies). Glatiramer acetate is possibly not different from interferon beta-1a subcutaneous 3 times per week in the risk of AE-related discontinuation (low confidence in the evidence, 1 Class II study). Interferon beta-1b subcutaneous alternate day possibly importantly has a lower risk of injection site reactions than glatiramer acetate (low confidence in the evidence, 1 Class II study). Interferon beta-1b subcutaneous alternate day probably has a higher risk of influenza-like illness than glatiramer acetate (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect). Complex nonbiologic generic glatiramer acetate (Glatopa) possibly importantly increases the risk of AE-related discontinuation relative to Copaxone (low confidence in the evidence, 1 Class I study; confidence downgraded owing to small magnitude of effect).

Clinical context

Common AEs include lipoatrophy and skin necrosis. Postinjection reaction consisting of flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, or urticaria may occur and is generally transient and self-limiting.

Immunoglobulins

There is 1 Class I study[e60] evaluating the risk of AE-related discontinuation at 24 months with immunoglobulin vs placebo in 150 individuals with RRMS. The RD was 2.67% (95% CI, -3.74% to 9.86%).

Conclusion

In individuals with RRMS, immunoglobulins are probably no different from placebo in the risk of AE-related discontinuation at 2 years (moderate confidence in the evidence, 1 Class I study).

Clinical context

Immunoglobulins may cause thrombosis and should be avoided in people with MS with increased thrombotic risk. Renal dysfunction, acute renal failure, or osmotic nephrosis may occur with immunoglobulins. Anaphylaxis may occur. In people with MS using immunoglobulins that are not immunoglobulin A depleted, an immunoglobulin A level should be obtained before initiating therapy.

Interferon beta-1a IM weekly

Meta-analysis of 1 Class I study[e64] and 1 Class II study[e65] found that interferon beta-1a IM weekly was not associated with a higher risk of AE-related discontinuation than placebo at 2 years, with an RD difference of 3.0% (95% CI, -1.4% to 7.4%).

Conclusion

For individuals with RRMS, interferon beta-1a IM weekly is probably not different from placebo in the risk of AE-related discontinuation (moderate confidence in the evidence, 1 Class I study and 1 Class II study).

Clinical context

Interferon betas as a class cause postinjection flulike symptoms, including chills, fever, myalgia, and asthenia. People with MS should be advised to report any symptoms of depression, suicidal ideation, or psychosis. Other AEs of interferon betas include hepatic injury, anaphylaxis, decreased peripheral blood counts, thrombotic microangiopathy, and emergent autoimmune disorders. Subcutaneous forms of interferon beta may cause injection site reactions. Interferon beta-1b may cause skin necrosis.

Interferon beta-1a subcutaneous 3 times per week

There is 1 Class I study[e66] comparing interferon beta-1a subcutaneous 3 times per week with placebo in 560 individuals with RRMS. The RD in AE-related discontinuation at 2 years was 2.95% (95% CI, -0.21% to 5.58%). There is 1 Class I study[e98] comparing interferon beta-1a subcutaneous 3 times per week with placebo in 619 individuals with SPMS. The RD in AE-related discontinuation over 3 years was 5.79% (95% CI, 1.73–9.28%). There is 1 Class II study[e67] comparing interferon beta-1a subcutaneous 3 times per week with interferon beta-1a IM weekly in 677 individuals with RRMS. The RD in AE-related discontinuation over 1 year was 0.28% (95% CI, -3.27% to 3.83%).

Conclusions

In people with RRMS, interferon beta-1a subcutaneous 3 times per week is possibly no different from placebo in the risk of AE-related discontinuation at 2 years (low confidence in the evidence, 1 Class I study; confidence downgraded owing to imprecision). In people with SPMS, interferon beta-1a subcutaneous 3 times per week possibly importantly increases the risk of AE-related discontinuation over 3 years (low confidence in the evidence, 1 Class I study, confidence downgraded owing to imprecision). In people with RRMS, interferon beta-1a subcutaneous 3 times per week is possibly no different from interferon beta-1a IM weekly in the risk of AE-related discontinuation at 1 year (low confidence in the evidence, 1 Class II study).

Clinical context

See the preceding clinical context section for interferon betas for a description of related AEs.

Interferon beta-1b subcutaneous alternate day

One Class II study[e68] of 227 individuals with RRMS found a risk difference of 7.25% (95% CI, 2.11%–13.43%) between interferon beta-1b subcutaneous alternate day and placebo for the proportion of individuals with AE-related discontinuation. One Class II study[e99] of 718 individuals with SPMS found an RD of 8.42% (95% CI, 4.47%–12.56%) between interferon beta-1b subcutaneous alternate day and placebo for the proportion of individuals with AE-related discontinuation. The risk of injection site reactions was higher in all studies of individuals with RRMS, SPMS, and PPMS, with an RD of 63.66% (95% CI, 53.41%–71.64%), 38.09% (95% CI, 31.1%–44.52%), and 77.78% (95% CI, 59.34%–88.28%), respectively.

Conclusions

In people with RRMS and SPMS, interferon beta-1b subcutaneous alternate day possibly importantly increases the risk of AE-related discontinuation (low confidence in the evidence, 1 Class II study for each MS subtype). In people with RRMS, SPMS, and PPMS, interferon beta-1b subcutaneous alternate day probably has a higher risk of injection site reactions than placebo (moderate confidence in the evidence, 1 Class II study for each MS subtype; confidence upgraded owing to magnitude of effect).

Clinical context

See the preceding clinical context section for interferon betas for a description of related AEs.

Mitoxantrone

There is 1 Class II study[e103] assessing the risk of AEs with mitoxantrone compared with placebo over 2 years in 126 individuals with relapsing progressive MS. Mitoxantrone use was associated with a higher risk of amenorrhea (RD 28.00% [95% CI, 10.40%–47.58%]), nausea and vomiting (RD 55.49% [95% CI, 38.97%–67.52%]), alopecia (RD 30.04% [95% CI, 12.65%–45.01%]), urinary tract infections (RD 19.76% [95% CI, 5.21%–33.52%]), and leukopenia (RD 19.35% [95% CI, 9.62%–30.85%]).

Conclusions

In individuals with relapsing progressive MS, mitoxantrone probably importantly increases the risk of amenorrhea, nausea and vomiting, and alopecia (moderate confidence in the evidence, 1 Class II study, confidence upgraded owing to magnitude of effect). Mitoxantrone possibly importantly increases the risk of urinary tract infections and leukopenia (low confidence in the evidence, 1 Class II study).

Clinical context

Mitoxantrone is a potent cytotoxic chemotherapeutic agent. Congestive heart failure may occur during or after treatment. Risk increases with cumulative mitoxantrone dose. Cumulative lifetime dosing of mitoxantrone should not exceed 140 mg/m^2. Treatment-related acute leukemia has been reported in people with MS treated with mitoxantrone.

Natalizumab

There is 1 Class I study[e75] comparing natalizumab with placebo in 942 individuals with RRMS. There was no difference between natalizumab and placebo in the risk of AE-related discontinuation, with an RD of 3.2% (95% CI, -0.6% to 6.5%). No significant risk difference was reported in neoplasms (RD 0.5% [95% CI, -1.1% to 1.6%]) or death (RD 0.3% [95% CI, -0.9% to 1.2%]).

Conclusions

In individuals with RRMS, natalizumab is possibly no different from placebo in the risk of AE-related discontinuation over 2 years (low confidence in the evidence, 1 Class I study, confidence in evidence downgraded owing to imprecision). There is insufficient evidence to determine the difference between natalizumab and placebo in the risk of neoplasm or death (very low confidence in the evidence, 1 Class I study; confidence downgraded owing to imprecision).

Clinical context

Natalizumab may cause anaphylaxis; anaphylaxis should prompt discontinuation of natalizumab. Natalizumab increases the risk of PML. Risk factors for this include longer duration of use, prior use of immunosuppressants, and presence of anti–John Cunningham virus (JCV) antibodies.

Other risks include rare opportunistic infections such as herpes encephalitis or meningitis, hepatotoxicity, and other infections. Risk stratification is an important component of care for people with MS using natalizumab. Assessing baseline risk for starting natalizumab, including the previously mentioned risks, is important. In addition, checking anti-JCV antibodies every 6 months enables early identification of transition to JCV antibody-positive status. Recent updated risk estimates show that the risk of developing PML is small at antibody index values of 0.9 or less, and increases with index values greater than 1.5 in individuals with MS who have been treated with natalizumab for more than 2 years.[e107]

Natalizumab discontinuation

There is 1 Class II study[e108] comparing natalizumab discontinuation−fingolimod initiation strategies in 142 individuals with RRMS who had received natalizumab for at least 6 months and wanted to discontinue treatment (Class II owing to less than 80% completion rate). Individuals were randomized to (1) 8-week washout following last natalizumab infusion, followed by oral fingolimod 0.5 mg; (2) 12-week washout following last natalizumab infusion, followed by oral fingolimod 0.5 mg; or (3) 16-week washout following last natalizumab infusion, followed by oral fingolimod 0.5 mg. The proportion of individuals with no active T2 lesions on MRI after 8 weeks of fingolimod treatment was significantly higher in the 8-week washout group compared with the 16-week washout group, with an RR of 1.90 (95% CI, 1.22–3.08), and was significantly higher in the 12-week washout group compared with the 16-week washout group, with an RR of 1.92 (95% CI, 1.19–3.13).

There is 1 Class II study[e109] comparing natalizumab continuation with natalizumab discontinuation in 87 individuals with RRMS who had been treated with natalizumab for at least 12 months and had no relapses during the previous 12 months (Class II for baseline characteristics not equivalent and no primary outcome defined). Compared with placebo, the RR for MRI disease recurrence at 6 months was 0.05 (95% CI, 0.01–0.27), favoring natalizumab continuation. There was no difference in the proportion of individuals with relapse at 6 months between the natalizumab continuation and placebo groups, with an RR of 0.26 (95% CI, 0.06–1.07).

There is 1 Class II study[e110] comparing tapered discontinuation of natalizumab with immediate discontinuation of natalizumab in 50 individuals with RRMS who had taken natalizumab for 2 years or longer (Class II for baseline characteristics not equivalent and no primary outcomes specified). The change in MRI T2 lesion volume from baseline to 12 months post-natalizumab

discontinuation was significantly greater in the immediate discontinuation group compared with the tapered discontinuation group, with an SMD of 0.92 (95% CI, 0.34–1.51).

Conclusions

For individuals with RRMS, 8-week natalizumab washout followed by fingolimod 0.5 mg is probably more effective than 16-week natalizumab washout followed by fingolimod 0.5 mg in increasing the proportion of individuals with no active T2 lesions (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect). For individuals with RRMS, 12-week natalizumab washout followed by fingolimod 0.5 mg is probably more effective than 16-week natalizumab washout followed by fingolimod 0.5 mg in increasing the proportion of individuals with no active T2 lesions (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect). Natalizumab continuation is probably more effective than natalizumab discontinuation in decreasing the proportion of individuals with MRI disease recurrence at 6 months (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect). Natalizumab continuation is possibly no more effective than natalizumab discontinuation in decreasing the proportion of individuals with clinical relapses at 6 months (low confidence in the evidence, 1 Class II study). Tapered discontinuation of natalizumab is probably more effective than immediate discontinuation of natalizumab in lowering the change in volume of T2 lesions at 12 months (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect).

Ocrelizumab

There are 2 Class I studies[e76] comparing ocrelizumab 600 mg IV every 24 weeks with interferon beta-1a 44 micrograms subcutaneous 3 times per week in 1,656 individuals with RRMS. The RD in AE-related discontinuation was -2.50% (95% CI, -4.20% to -0.07%), with more individuals who were receiving interferon beta-1a discontinuing because of AEs than those taking ocrelizumab. The RD in serious infections or infestations was -1.6% (95% CI, -3.1% to -0.1%), with more individuals taking interferon beta-1a experiencing a serious infection or infestation. There was no difference in the risk of neoplasm (RD 0% [95% CI, -1.1% to 1.2%]) or death (RD -0.2% [95% CI, -1.12% to 1.12%]) between the 2 treatments. There is 1 Class II study[e104] comparing ocrelizumab 600 mg IV every 24 weeks with placebo in 725 individuals with PPMS. There was no difference in the risk of AE-related discontinuation, serious infections, neoplasms, or death between ocrelizumab and placebo.

Conclusions

In people with RRMS, ocrelizumab probably importantly decreases the risk of AE-related discontinuation at 2 years compared with interferon beta-1a (moderate confidence in the evidence, 2 Class I studies; confidence downgraded owing to magnitude of effect). Ocrelizumab decreases the risk of serious infections or infestation compared with interferon beta-1a (high confidence in the evidence, 2 Class I studies). There is insufficient evidence to determine the risk of neoplasm or death with ocrelizumab compared with interferon beta-1a (very low confidence in the evidence, 2 Class I studies; confidence downgraded owing to imprecision). In individuals with PPMS, there is insufficient evidence to determine the risk of AE-related discontinuation, serious infections, neoplasms, or death with ocrelizumab compared with placebo (very low confidence in the evidence, 1 Class II study; confidence downgraded owing to imprecision).

Pegylated interferon

There is 1 Class I study[e77] comparing pegylated interferon 125 micrograms every 2 weeks with placebo in 1,012 individuals with RRMS. The RD in AE-related discontinuation at 1 year was 3.48% (95% CI, 1.35%–5.82%). The RD for severe AEs, defined as symptoms that cause severe discomfort, incapacitation, or a significant effect on daily life, was 6.98% (95% CI, 2.69%–11.25%).

Conclusions

In people with RRMS, pegylated interferon possibly importantly increases the risk of AE-related discontinuation at 1 year (low confidence in the evidence, 1 Class I study; downgraded owing to imprecision). In people with RRMS, pegylated interferon importantly increases the risk of severe AEs (high confidence in the evidence, 1 Class I study; confidence upgraded owing to magnitude of effect).

Clinical context

See the preceding clinical context section for interferon betas for a description of related AEs.

Rituximab

There is 1 Class II study[e78] comparing rituximab with placebo in 104 individuals with RRMS. The RD in AE-related discontinuation from the study was -1.37% (95% CI, -14.57% to 7.35%) and in an infection-associated SAE was 2.82% (95% CI, -15.88% to 5.37%).

Conclusion

In individuals with RRMS, there is insufficient evidence to determine the RD between rituximab and placebo for AE-related withdrawal and infection-associated SAEs (very low confidence in the evidence, 1 Class II study; confidence downgraded owing to imprecision).

Clinical context

Fatal infusion reactions may occur within 24 hours of rituximab infusion. Severe mucocutaneous reactions, reactivation of hepatitis B, and PML have occurred. Rituximab may increase the risk of infections, cardiac arrhythmias, bowel obstruction or perforation, and cytopenias.

Teriflunomide

There is 1 Class II study[e79] comparing teriflunomide with placebo in 1,088 individuals with RRMS for AE-related discontinuation. The RD in AE-related discontinuation over 2 years was 2.36% (95% CI, -1.47% to 5.75%). There is 1 Class II study[e81] comparing teriflunomide with placebo in 1,165 individuals with RRMS for serious infections. The RD for serious infections was 0.35% (95% CI, -2.07% to 2.29%).

Conclusions

For individuals with RRMS, teriflunomide is possibly no different from placebo in the risk of AE-related discontinuation (low confidence in the evidence, 1 Class II study). There is insufficient evidence that teriflunomide is different from placebo in the risk of serious infections (very low confidence in the evidence, 1 Class II study; confidence downgraded owing to imprecision).

Clinical context

Common AEs may include increased blood pressure, alopecia, headache, diarrhea, nausea, and increase in liver functions. Animal data suggest teriflunomide may cause major birth defects if used during pregnancy. Severe liver injury, including fatal liver failure, has been reported in people with MS on leflunomide, and a similar risk is possible for teriflunomide.

Clinical question 7: In people with CIS, are DMTs superior to placebo in decreasing the risk of conversion to MS?

Cladribine

There is 1 Class II study[e111] comparing oral cladribine 5.25 mg/kg with placebo in 410 individuals with CIS. This study was rated Class II owing to less than 80% completing the study. The risk of conversion to MS over 2 years was significantly lower with cladribine, with an RR of 0.43 (95% CI, 0.29–0.62).

Conclusion

For individuals with CIS, cladribine is probably more effective than placebo in reducing the proportion of people converting to MS over 3 years (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect).

Glatiramer acetate

There is 1 Class I study[e112] comparing glatiramer acetate with placebo in 481 individuals with CIS. The risk of conversion to MS over 3 years was significantly lower with glatiramer acetate, with an RR of 0.58 (95% CI, 0.44–0.75).

Conclusion

For individuals with CIS, glatiramer acetate is more effective than placebo in reducing the proportion of people converting to CDMS over 3 years (high confidence in the evidence, 1 Class I study; confidence upgraded owing to magnitude of effect).

Immunoglobulins

There is 1 Class II study[e113] comparing IV immunoglobulin with placebo in 90 individuals with CIS. This study was Class II owing to lack of allocation concealment. The risk of conversion to MS over 1 year was significantly lower with IV immunoglobulin, with an RR of 0.50 (95% CI, 0.28–0.88).

Conclusion

For individuals with CIS, IV immunoglobulin is probably more effective than placebo in reducing the proportion of people converting to MS over 1 year (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect).

Interferon beta-1a IM weekly

There is 1 Class II study[e114] comparing interferon beta-1a IM weekly with placebo in 383 individuals with CIS. This study was Class II owing to lack of allocation concealment. The risk of conversion to MS over 3 years was significantly lower with interferon beta-1a IM weekly, with an RR of 0.71 (95% CI, 0.56–0.89%).

Conclusion

For individuals with CIS, interferon beta-1a IM weekly is probably more effective than placebo in reducing the proportion of people converting to MS over 3 years (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect).

Interferon beta-1a subcutaneous 3 times per week

There is 1 Class I study[e115] comparing interferon beta-1a subcutaneous 44 micrograms 3 times per week with placebo in 342 individuals with CIS. The risk of conversion to MS over 2 years was significantly lower with interferon beta-1a subcutaneous 3 times per week, with an RR of 0.55 (95% CI, 0.38–0.78).

Conclusion

For individuals with CIS, interferon beta-1a subcutaneous 3 times per week is more effective than placebo in reducing the proportion of people converting to MS over 2 years (high confidence in the evidence, 1 Class I study; confidence upgraded owing to magnitude of effect).

Interferon beta-1b subcutaneous alternate day

There is 1 Class II study[e116] comparing interferon beta-1b subcutaneous alternate day with placebo in 468 individuals with CIS. This study was rated Class II owing to lack of allocation concealment. The risk of conversion to MS over 2 years was significantly lower with interferon beta-1b subcutaneous alternate day, with an RR of 0.59 (95% CI, 0.46–0.76).

Conclusion

For individuals with CIS, interferon beta-1b subcutaneous alternate day is probably more effective than placebo in reducing the proportion of people converting to MS over 2 years (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect).

Teriflunomide

There is 1 Class II study[e117] comparing teriflunomide 14 mg with placebo in 411 individuals with CIS. This study was Class II owing to less than 80% completion. The risk of conversion to MS over 2 years was significantly lower with teriflunomide, with an RR of 0.64 (95% CI, 0.44–0.91).

Conclusion

For individuals with CIS, teriflunomide is probably more effective than placebo in reducing the proportion of people converting to MS over 2 years (moderate confidence in the evidence, 1 Class II study; confidence upgraded owing to magnitude of effect).

PRACTICE RECOMMENDATIONS

Appendix e-9 provides a description of the steps and rules for formulating recommendations. For the rationale profiles for the practice recommendations, see appendix e-10.

Starting DMT: recommendations

Starting: recommendation 1

Rationale

Receiving the diagnosis of MS is a stressful life event.[e118,e119] People receiving major diagnoses may not recall much of the information given to them at the time.[e120] Providing information about DMT at a follow-up interaction is likely to allow a better understanding of these medications and their risks and benefits.

Statement 1

Clinicians should counsel people with newly diagnosed MS about specific treatment options with DMT at a dedicated treatment visit (Level B).

Starting: recommendation 2

Rationale

Respecting patient preferences is an important component of care for chronic conditions. Because of the variety of DMTs available, evaluating patient preferences may improve acceptance of and adherence to DMT.

Statement 2a

Clinicians must ascertain and incorporate/review preferences in terms of safety, route of administration, lifestyle, cost, efficacy, common AEs, and tolerability in the choice of DMT in people with MS being considered for DMT (Level A).

Statement 2b

Clinicians must engage in an ongoing dialogue regarding treatment decisions throughout the disease course with people with MS (Level A).

Starting: recommendation 3

Rationale

DMTs reduce but do not eliminate MS relapses and MRI activity. Educating people with MS about realistic expectations regarding DMT effects is important.[e121] Clinicians should inform people with MS that they may still need symptomatic treatment in addition to DMT.[e122]

Statement 3a

Clinicians should counsel people with MS that DMTs are prescribed to reduce relapses and new MRI lesion activity. DMTs are not prescribed for symptom improvement in people with MS (Level B).

Statement 3b

Clinicians must counsel people with MS on DMTs to notify the clinicians of new or worsening symptoms (Level A).

Starting: recommendation 4

Rationale

Because DMT use requires commitment to ongoing therapy and an understanding of AEs, readiness to initiate DMT and factors causing reluctance may have an impact on adherence to DMT use.

Statement 4

Clinicians should evaluate readiness or reluctance to initiate DMT and counsel on its importance in people with MS who are candidates to initiate DMT (Level B).

Starting: recommendation 5

Rationale

In people with MS, comorbid disease, such as depression, anxiety, and vascular risk factors, and adverse health behaviors (e.g., physical inactivity, smoking) are associated with worse outcomes.[e123,e124]Addressing depression before initiating DMT may improve decision making and adherence to DMT. Concomitant medications may have important interactions with DMTs.[e107]

Statement 5

Clinicians should counsel about comorbid disease, adverse health behaviors, and potential interactions of the DMT with concomitant medications when people with MS initiate DMT (Level B).

Starting: recommendation 6

Rationale

Because DMT requires adherence to treatment to provide full efficacy, and because that adherence to treatment may be an issue for people with MS,[e125,e126] discussing adherence issues before initiating DMT is part of good clinical practice. Efforts to increase adherence may improve outcomes.

Statement 6a

Clinicians should evaluate barriers to adherence to DMT in people with MS (Level B).

Statement 6b

Clinicians should counsel on the importance of adherence to DMT when people with MS initiate DMTs (Level B).

Starting: recommendation 7

Rationale

People presenting with a first demyelinating event and who do not meet the 2010 International Criteria for MS are commonly encountered in clinical practice. Multiple prospective observational trials have consistently confirmed that people with a single clinical demyelinating event with 2 or more brain or spinal cord lesions remain at increased risk of a future MS diagnosis, with the highest risk incurred within 5 years of the initial event.[e127−e130] Evidence from multiple Class I and II trials confirms that DMTs are associated with a significant delay in second clinical relapse or new brain MRI-detected lesions in people with a first demyelinating event who are considered to be at high risk for MS on the basis of brain MRI-detected lesions. There is insufficient evidence concerning the comparative efficacy of specific DMTs for this purpose. Decisions concerning the selection of specific DMTs for people presenting with a first demyelinating event should abide by prescribing principles espoused in other recommendations. Individuals presenting with an incident demyelinating event who have no brain lesions are at low risk of a future MS diagnosis.

Statement 7a

Clinicians should discuss the benefits and risks of DMTs for people with a single clinical demyelinating event with 2 or more brain lesions that have imaging characteristics consistent with MS (Level B).

Statement 7b

After discussing the risks and benefits, clinicians should prescribe DMT to people with a single clinical demyelinating event and 2 or more brain lesions characteristic of MS who decide they want this therapy (Level B).

Starting: recommendation 8

Rationale

The benefit of initiating DMT has not been studied in currently untreated people with CIS or relapsing forms of MS who have not had relapses in 2 or more years and do not have active new MRI lesion activity on recent imaging. In such people, it is unknown what the risk of harm is from initiating DMTs, including AEs, major AEs, and burden of taking a long-term medication, relative to the benefit of reducing relapse rate.

Statement 8

Clinicians may recommend serial imaging at least annually for the first 5 years and close follow-up rather than initiating DMT in people with CIS or relapsing forms of MS who are not on DMT, have not had relapses in the preceding 2 years, and do not have active new MRI lesion activity on recent imaging (Level C).

Starting: recommendation 9

Rationale

Multiple studies of DMTs in people with relapsing forms of MS who have had recent relapses or MRI activity or both have shown benefit of DMT in terms of reducing relapses and reducing MRI activity. This includes people with a single clinical episode who meet 2010 International Criteria for MS.[e117,e131]

Statement 9

Clinicians should offer DMTs to people with relapsing forms of MS with recent clinical relapses or MRI activity (Level B).

Starting: recommendation 10

Rationale

Lack of adherence to treatment of chronic diseases is a wide-ranging problem. The result of poor adherence is reduced effectiveness and increased health care costs.[e132–e137] Regular interactions and assessments by clinicians facilitate prompt identification and treatment of AEs, increased tolerability of the medication, and safety monitoring.[e121,e137] Some DMTs for MS have specific REMS with recommendations for follow-up frequency.[e138–e141]

Statement 10a

Clinicians should monitor for medication adherence, AEs, tolerability, safety, and effectiveness of the therapy in people with MS on DMTs (Level B).

Statement 10b

Clinicians should follow up either annually or according to medication-specific REMS in people with MS on DMTs (Level B).

Starting: recommendation 11

Rationale

DMTs have potential risks in pregnant women[e142] to varying degrees. Discussing pregnancy with women with MS before initiating DMT is a part of good clinical practice. If women with MS are planning pregnancy soon, DMT use may need to be deferred until after pregnancy.[e143] In

addition, because DMTs vary in terms of pregnancy risks,[e142] DMT choice may be influenced by plans for pregnancy.

Statement 11

Clinicians should monitor the reproductive plans of women with MS and counsel regarding reproductive risks and use of birth control during DMT use in women of childbearing potential who have MS (Level B).

Starting: recommendation 12

Rationale

Chemotherapy, such as cyclophosphamide, may affect male fertility.[e144] With teriflunomide treatment, there may be a risk of teratogenicity from male sperm, which could last for 2 years after treatment cessation if the patient is not treated with chelation therapy.[e145]

Statement 12

Clinicians should counsel men with MS on their reproductive plans regarding treatment implications before initiating treatment with teriflunomide or cyclophosphamide (Level B).*

*Level A recommendations cannot be based on related evidence alone. Recommendation downgraded to Level B.

Starting: recommendation 13

Rationale

Post approval of mitoxantrone, new evidence has shown a high risk of cardiomyopathy, ovarian failure, male infertility, chromosomal aberrations, and promyelocytic leukemia[e146–e149] associated with mitoxantrone use. Other effective medications with lower risk, which were unavailable at the time of FDA approval of mitoxantrone, are now available for treating MS.

Statement 13

Because of the high frequency of severe AEs, clinicians should not prescribe mitoxantrone to people with MS unless the potential therapeutic benefits greatly outweigh the risks (Level B).*

*Level A recommendations cannot be based on related evidence alone. Recommendation downgraded to Level B.

Starting: recommendation 14

Rationale

MS is a heterogeneous disease and is characterized by highly variable degrees of disease activity in the relapsing phase and by varying rates of worsening during the progressive phases.[e150,e151] Definitions of highly active MS vary and can include measures of relapsing activity and MRI markers of disease activity, such as numbers of gadolinium-enhanced lesions.[e152,e153] Subgroup analyses from phase III pivotal trials of alemtuzumab, fingolimod, and natalizumab showed a reduction in relapses and MRI measures in people with MS with highly active disease.[e154–e156] Compared with interferon beta therapy, treatment with these therapies resulted in more favorable outcomes in the subgroup of people with MS with highly active disease.[e33,e34,e51,e83] However, the risks and benefits of each treatment strategy need to be considered on a patient-by-patient basis.

Statement 14

Clinicians should prescribe alemtuzumab, fingolimod, or natalizumab for people with MS with highly active MS (Level B).

Starting: recommendation 15

Rationale

DMTs should be available to all people with relapsing forms of MS. Because of disparities in health care provision in different settings,[e1] there may be situations where approved DMTs are

not available to an individual. In these situations, DMTs may be obtained with support from the pharmaceutical industry or from organizations, such as the National Organization of Rare Diseases, county organizations, or government organizations. If such support is unavailable, certain lower cost medications may become a choice for care. Azathioprine has mixed results and evidence for which confidence is low to support efficacy in relapsing forms of MS. Cladribine has evidence of benefit for both the oral and parenteral formulations, but currently only the parenteral formulations are available.

Statement 15a

Clinicians may direct people with MS who are candidates for DMTs to support programs (Level C).

Statement 15b

Clinicians may recommend azathioprine or cladribine for people with relapsing forms of MS who do not have access to approved DMTs (Level C).*

*Failed to meet consensus because of benefit relative to harm. Recommendation downgraded to Level C.

Starting: recommendation 16

Rationale

People with MS with a positive JCV antibody test have a higher risk of developing PML while using natalizumab, particularly people with MS who have been treated for more than 2 years or have had prior immunosuppressive treatment. There are now other highly effective treatments that may be used that have not been shown to have a similar PML risk. The PML risk increases with the level of anti-JCV antibody response (index). For example, in those using natalizumab for 25 to 36 months with no prior use of immunosuppressants, the PML risk is 0.2 per 1,000 in those with an index of 0.9 or less, 0.3 per 1,000 in those with an index of 0.9 to 1.5, and 3 per 1,000 in those with an index greater than 1.5. Further data on risk assessment is likely to become available over time to help inform treatment decisions in this area.

Statement 16

Clinicians may initiate natalizumab treatment in people with MS with positive anti-JCV antibody indexes above 0.9 only when there is a reasonable chance of benefit compared with the low but serious risk of PML (Level C).*

*Failed to meet consensus because of variation in patient preferences. Recommendation downgraded to Level C.

Starting: recommendation 17

Rationale

Ocrelizumab is the only DMT shown to alter disease progression in individuals with PPMS who are ambulatory. The RCT of rituximab in PPMS was promising but inconclusive.[e105] Although RCTs of fingolimod, glatiramer acetate, and interferon beta-1b failed to demonstrate an effect on disability progression in individuals with PPMS, significant effects on MRI measures of disease activity were found with all 3 treatments.[e92,e93,e101] Clinical trials have not evaluated the benefits of DMT in individuals with PPMS who are nonambulatory with respect to other clinically relevant domains, including vision, cognition, and upper limb function.

Statement 17

Clinicians should offer ocrelizumab to people with PPMS who are likely to benefit from this therapy unless there are risks of treatment that outweigh the benefits (Level B).*

*Failed to meet consensus because of variation in patient preferences. The recommendation is "<should> offer ocrelizumab." The comments made during the modified Delphi voting on recommendations indicated that the failure to meet consensus because of variation in patient preferences was resulted from panelists' varying interpretations of the recommendation. In their comments, panelists agreed that people with MS want to know their treatment options; whether people with MS accept the offered treatment is their decision and where the variation in preference lies. The wording and level (Level B) of this recommendation remain as stated.

Switching DMT: recommendations

Switching: recommendation 1

Rationale

Ongoing disease activity, measured either by clinical relapses or new MRI-detected lesions (including unequivocally new T2 or new gadolinium-enhanced lesions), could lead to physical or cognitive worsening over time.[e157−e160] Now that several DMTs are available and have demonstrated efficacy for the prevention of clinical relapses and new MRI-detected lesions, physicians and people with MS often face the decision of switching from one DMT to another because of a perceived lack of efficacy. Such lack of response to a DMT has been difficult to define, as most people with MS are not free of all disease activity; investigators have considered using the number of clinical attacks or new MRI-detected lesions in the preceding 12 months to define lack of response.[e158,e160] DMTs take a variable amount of time to become clinically active, and new lesion formation may occur after initiation but before the time of full efficacy, confounding interpretation of follow-up MRI scans.[e34,e51,e53,e66,e81,e161] Consequently, many clinicians obtain new baseline MRI 3 to 6 months after initiating DMTs to monitor from a "treated" baseline.[e162] The optimal interval for ongoing monitoring is uncertain, as short-term stability as evidenced by clinical and MRI criteria may not consistently predict long-term stability. In addition, because of different mechanisms of activity among the DMTs, monitoring strategies may vary.

Statement 1a

Clinicians should monitor MRI disease activity from the clinical onset of disease to detect the accumulation of new lesions in order to inform treatment decisions in people with MS using DMTs (Level B).

Statement 1b

Clinicians should recognize that relapses or new MRI-detected lesions may develop after initiation of a DMT and before the treatment becomes effective in people with MS who are using DMTs (Level B).

Statement 1c

Clinicians should discuss switching from one DMT to another in people with MS who have been using a DMT long enough for the treatment to take full effect and are adherent to their therapy when they experience 1 or more relapses, 2 or more unequivocally new MRI-detected lesions, or increased disability on examination, over a 1-year period of using a DMT (Level B).

Switching: recommendation 2

Rationale

None of the available DMTs is completely effective against relapses and MRI activity. When a patient shows breakthrough disease activity (continued relapses, MRI activity), trying a medication with a different mechanism or efficacy profile may be beneficial. Although all possible clinical scenarios cannot be answered by drug trials, current evidence supports higher efficacy of alemtuzumab, natalizumab, fingolimod, and ocrelizumab compared with previously approved self-injectable DMTs. Tolerability and likelihood of adherence are other factors that are important in decisions about switching DMTs. Physician judgment and patient preferences are critical in this process.

Statement 2

Clinicians should evaluate the degree of disease activity, adherence, AE profiles, and mechanism of action of DMTs when switching DMTs in people with MS with breakthrough disease activity during DMT use (Level B).*

*Failed to meet consensus because of variation in patient preferences. The recommendation is that clinicians evaluate a number of clinical and pharmacologic characteristics when switching medications in people with MS with breakthrough disease activity. Patient preference does not affect evaluation recommendations. Patient preference will affect the decision of the medication choice. This recommendation stands at Level B.

Switching: recommendation 3

Rationale

Multiple DMTs are available for MS treatment. Switching therapies may be appropriate in people with MS who are experiencing AEs or complications with a DMT. Adherence to injectable DMTs is often incomplete.[e163] Injection fatigue (physical or emotional) or injection-related pain or discomfort may be a common reason for poor adherence.

Statement 3

Clinicians should discuss a change to noninjectable or less frequently injectable DMTs in people with MS who report intolerable discomfort with the injections or in those who report "injection fatigue" on injectable DMTs (Level B).

Switching: recommendation 4

Rationale

Adherence to a DMT may also be affected by medication AEs.[e126,e137] All DMTs have common AEs that may affect adherence (table e-2).

Statement 4a

Clinicians should inquire about medication AEs with people with MS who are taking a DMT and attempt to manage these AEs, as appropriate (Level B).

Statement 4b

Clinicians should discuss a medication switch with people with MS for whom these AEs negatively influence adherence (Level B).

Switching: recommendation 5

Rationale

Persistent laboratory abnormalities, such as elevated liver enzymes and decreased white blood cell counts, may prompt a discussion about switching DMT (table e-2).

Statement 5a

Clinicians should monitor laboratory abnormalities found on requisite laboratory surveillance (as outlined in the medication's package insert) in people with MS who are using a DMT (Level B).

Statement 5b

Clinicians should discuss switching DMT or reducing dosage or frequency (where there are data on different doses [e.g., interferons, teriflunomide, azathioprine]) when there are persistent laboratory abnormalities (Level B).*

*There is no substantial lack of consensus in variation in patient preferences because more than 80% of respondents thought variation in preference is minimal or modest. Recommendation stands at Level B.

Switching: recommendation 6

Rationale

Progressive multifocal leukoencephalopathy (PML) is a serious safety concern[e164] that may affect compliance and necessitate consideration of a treatment switch. The PML risk is estimated at 4 per 1,000 overall with natalizumab[e165]; however, the presence and index level of JCV antibodies, longer duration use, and prior immunosuppression increase PML risk with natalizumab even further.[e164] Recent updated risk estimates show that the risk of developing PML is small at antibody index values of 0.9 or less, and increases with index values greater than 1.5 in people with MS who have been treated with natalizumab for more than 2 years.[e107] There are rare reports of PML with the use of both fingolimod and dimethyl fumarate.[e166–e169] There are reports of PML in people with MS who are HIV-negative and using rituximab for conditions other than MS.[e170] There is a potential risk of PML with ocrelizumab use, particularly with prior immunosuppressive therapies, based on its similarity to other anti-CD20 antibodies.[e139]

Statement 6a

Clinicians should counsel people with MS considering natalizumab, fingolimod, rituximab, ocrelizumab, and dimethyl fumarate about the PML risk associated with these agents (Level B).

Statement 6b

Clinicians should discuss switching to a DMT with a lower PML risk with people with MS taking natalizumab who are or become JCV antibody positive, especially with an index of above 0.9 while on therapy (Level B).

Switching: recommendation 7

Rationale

Immunosuppressive medications may increase the risk of opportunistic infection and malignancy, especially with prolonged use. These risks are often undefined with newer medication. Cases of cryptococcal infections have been reported with fingolimod use.[e171] Herpes family virus infections have been reported with fingolimod and natalizumab use.[e172–e174] A potential increased risk of basal cell carcinoma was recently added to the fingolimod product label.[e169]

Statement 7a

Clinicians should counsel that new DMTs without long-term safety data have an undefined risk of malignancy and infection for people with MS starting or using new DMTs (Level B).

Statement 7b

If a patient with MS develops a malignancy while using a DMT, clinicians should promptly discuss switching to an alternate DMT, especially for people with MS using azathioprine, methotrexate, mycophenolate, cyclophosphamide, fingolimod, teriflunomide, alemtuzumab, or dimethyl fumarate (Level B).

Statement 7c

People with MS with serious infections potentially linked to their DMT should switch DMTs (does not pertain to PML management in people with MS using DMT) (Level B).

Switching: recommendation 8

Rationale

Neutralizing antibodies may be produced against natalizumab and have been associated with allergic reactions.[e175,e176] These antibodies may reduce the efficacy of the medication, especially if they are persistent.

Statement 8a

Clinicians should check for natalizumab antibodies in people with MS who have infusion reactions before subsequent infusions, or in people with MS who experience breakthrough disease activity with natalizumab use (Level B).

Statement 8b

Clinicians should switch DMTs in people with MS who have persistent natalizumab antibodies (Level B).

Switching: recommendation 9

Rationale

People with MS taking natalizumab may discontinue natalizumab because of fear of PML risk or for pregnancy planning. Natalizumab discontinuation increases the risk of MRI-detected disease activity and MS relapse within 6 months of discontinuation, with some people with MS having

an increase in disease activity above their baseline activity, referred to as rebound activity.[e177] Data are limited for assessing the appropriate choice of an alternate DMT after natalizumab discontinuation. There is evidence that initiating fingolimod 8 to 12 weeks after natalizumab discontinuation reduces new MRI-detected lesions compared with initiation 16 weeks after natalizumab discontinuation. Initiating fingolimod 8 to 12 weeks after natalizumab discontinuation increases the proportion of people with MS who are relapse free compared with initiation after 16 weeks.[e178,e179] Although RCT data are unavailable, retrospective cohort data suggest that switching from natalizumab to rituximab may result in lower rates of clinical and radiologic disease activity compared with switching to fingolimod.[e180]

Statement 9a

Physicians must counsel people with MS considering natalizumab discontinuation that there is an increased risk of MS relapse or MRI-detected disease activity within 6 months of discontinuation (Level A).

Statement 9b

Physicians and people with MS choosing to switch from natalizumab to fingolimod should initiate treatment within 8 to 12 weeks after natalizumab discontinuation (for reasons other than pregnancy or pregnancy planning) to diminish the return of disease activity (Level B).

Switching: recommendation 10

Rationale

Relapse risk is reduced during pregnancy and increases in the postpartum period.[e181] Pregnancy exposure to DMTs may pose potential risks to the fetus to varying degrees, which vary from severe malformations to no major increased risk of malformations. Risks of important early-life health outcomes such as infections, vaccination responses, asthma, and neurocognitive disorders are unknown. FDA-approved medications vary in terms of FDA recommendation for pregnancy (e.g., glatiramer acetate "Instruct people with MS that if they are pregnant or plan to become pregnant while taking glatiramer acetate they should inform their physician"; "Women of childbearing potential should be advised to avoid becoming pregnant"] and teriflunomide ["Must be avoided during pregnancy"]). Each DMT has a separate FDA statement about pregnancy-

associated risks (see individual package inserts and table e-3 of the full-length guideline). Discussing these potential risks and how best to minimize them is a part of good clinical practice. The majority of human safety data for exposure to DMTs during pregnancy is derived from accidental exposure early in pregnancy. There is a paucity of safety information with second- and third-trimester exposure.[e182]

Statement 10a

Clinicians should counsel women to stop their DMT before conception for planned pregnancies unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy (Level B).

Statement 10b

Clinicians should discontinue DMTs during pregnancy if accidental exposure occurs, unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy (Level B).

Statement 10c

Clinicians should not initiate DMTs during pregnancy unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy (Level B).

Stopping DMT: Recommendations

Stopping: recommendation 1

Rationale

No RCTs have directly addressed the question of whether, when, or why to discontinue DMTs in an individual with RRMS who has no evidence of relapses or disability progression and has stable brain imaging. The natural history of untreated RRMS is for relapses and disability accumulation to occur. Early studies suggest that most individuals with RRMS ultimately

advance to SPMS if observed for long enough intervals, although disease course is highly variable.[e17] People with MS who are stable on DMTs may question the continued value of using DMTs. If people with MS on DMTs stop these medications, continued monitoring may show subclinical disease activity or relapse activity that would indicate a possible need for treatment resumption. In an RCT of 175 individuals taking natalizumab who had been relapse free for 1 year and had no gadolinium-enhanced lesions on MRI, participants were randomized to continue natalizumab use, switch to placebo, or switch to other therapies. Relapses occurred in 4% of those continuing natalizumab use and in 15% to 29% of those in other treatment arms over 24 weeks. An observational study comparing outcomes in individuals who did or did not stop DMT after a period of at least 5 years without relapses found a similar risk of relapses between the groups but an increased risk of disability progression among those who stopped DMT. Younger age and lower EDSS scores were significant predictors of relapse (clinical or MRI) after treatment discontinuation. People with MS who are on DMTs with no evidence of ongoing disease activity may be benefiting from their DMT with disease suppression. There are presently no biological markers of medication efficacy that can guide decision making in this area.

Statement 1a

In people with RRMS who are stable on DMT and want to discontinue therapy, clinicians should counsel people with MS regarding the need for ongoing follow-up and periodic reevaluation of the decision to discontinue DMT (Level B).

Statement 1b

Clinicians should advocate that people with MS who are stable (that is, no relapses, no disability progression, stable imaging) on DMT should continue their current DMT unless the patient and physician decide a trial off therapy is warranted (Level B).

Stopping: recommendation 2

Rationale

People with SPMS who have relapses or active MRI-detected new lesion formation benefit from DMT. In people with SPMS who are ambulatory with or without assistance, interferon beta reduces the risk of relapse but does not delay disability progression as measured by the EDSS, a

measure that emphasizes ambulation. No RCTs have directly addressed the question of whether or when to discontinue DMTs in people with SPMS. Clinical trials have not evaluated the benefits of DMT in individuals with SPMS who are nonambulatory with respect to other clinically relevant domains, including vision, cognition, and upper limb function. Relapses are associated with more rapid disability progression in SPMS but tend to occur in those at younger ages (younger than 55 years) and earlier in the disease course.[e183,e184] Among individuals with SPMS (those with and those without clinical relapses) for at least 2 years at the time of treatment withdrawal, an EDSS of 6 or greater was associated with a 50% lower risk of relapses or MRI-detected activity after treatment discontinuation. The benefits of therapy should outweigh the risks. The use of ineffective therapy may pose harms to the affected individual, society, and the health system.

Statement 2a

Clinicians should assess the likelihood of future relapse in individuals with SPMS by assessing patient age, disease duration, relapse history, and MRI-detected activity (e.g., frequency, severity, time since most recent relapse or gadolinium-enhanced lesion) (Level B).

Statement 2b

Clinicians may advise discontinuation of DMT in people with SPMS who do not have ongoing relapses (or gadolinium-enhanced lesions on MRI activity) and have not been ambulatory (EDSS 7 or greater) for at least 2 years (Level C).*

*Failed to meet consensus because of variation in patient preferences. Recommendation downgraded to Level C.

Stopping: recommendation 3

Rationale

DMTs tested in people with CIS delay progression to MS onset. However, some people with CIS may not develop MS.[e20] Risks of active relapsing disease activity are higher in younger people with CIS.[e130,e185,e186] In the absence of disease activity, people with CIS who are on DMTs may question the value of continuing DMTs indefinitely. There remains a gap in knowledge

about stopping DMTs in people with CIS. Discussing the risks of continuing DMTs vs the risks of their use being unnecessary as part of ongoing treatment is a part of good clinical practice.

Statement 3

Clinicians should review the associated risks of continuing DMTs vs those of stopping DMTs in people with CIS using DMTs who have not been diagnosed with MS (Level B).*

*Failed to meet consensus owing to variation in preferences. Recommendation is that clinicians <should> review the risk of continuing DMTs. The failure to meet consensus resulted from misinterpretation of the recommendation. People with CIS and MS do not vary in their preference for physician review of their situation; the preference varies in what they ultimately decide to do. This recommendation stands at Level B.

CLINICAL CONTEXT FOR ALL EVIDENCE

This practice guideline reflects the complexity of decision making for clinicians and people with MS when considering initiating, switching, or stopping DMTs. The guideline panel has striven to reflect a patient-centric approach that incorporates assessment of attitudes, readiness to start or change DMTs, adherence to therapy, patient specific factors such as comorbidities, and an ongoing discussion of DMT use in people with MS on DMTs. The panel reviewed not only FDA-approved DMTs but also medications that have been used off label where data are present to analyze their efficacy. The panel engaged in a transparent process and incorporated extensive public review of the initial protocol, questions considered in the systematic review, and an early version of the systematic review and recommendations.

No guideline of this complexity will satisfy all audiences. The panel recognizes that the field of MS treatment is rapidly changing and that the recommendations here may require reanalysis in light of new directions in the field and new evidence pertaining to DMT use. The present AAN development process includes planning for future updates for guidelines. The panel anticipates that this practice guideline will need to be updated in the not-too-distant future.

SUGGESTIONS FOR FUTURE RESEARCH

Practice challenges remain in choosing which DMT for MS to prescribe and when to use it. The following describes key gaps identified in the literature and recommended future research that, if addressed, would greatly improve informed decision making.

Gaps in knowledge

More work is needed to define both acceptable treatment response and breakthrough disease during DMT for MS use.

Data are lacking on the effect of DMTs on outcome measures such as quality of life, MS symptoms, and cognitive measures.

An operational definition of highly active MS is lacking. Such a definition is necessary to enhance comparability between studies and to guide treatment decisions and prognostication.

Presently available research is relatively short-term compared with the disease duration. More long-term follow-up data are needed on patient response to treatment.

Data are lacking on treatment response in age groups excluded from existing RCTs (older age groups, pediatric age groups).

There is a lack of predictive markers for individualized patient response to therapy.

Data are lacking to compare different treatment strategies in the initial management of MS (e.g., high-potency therapy vs standard therapy, strategies for switching therapy compared with those for continuing a therapy)

There is limited comparative effectiveness research in real-world populations.

Long-term safety data are needed for DMTs, particularly in patients with comorbid conditions.

There are limited safety data on DMT use in pregnant women.

Data are also limited data on outcomes of stopping DMTs in various MS subgroups.

Future research

High-quality evidence is needed concerning the effect of DMT for MS on outcomes deemed important by clinicians and people with MS beyond standard trials outcomes. Such outcome measure could include quality of life, preservation of cognition, and MS symptoms (e.g., fatigue, urinary urgency, pain, visual function).

DMT for MS comparative efficacy studies are needed with transparent reporting in different MS subpopulations, including those who have had continued relapses or MRI-detected disease activity or both while taking previous DMTs for MS; those with highly active disease; those with CIS; and those in the primarily progressive, nonrelapsing phase of the disease.

Clinical trials are needed to evaluate the benefits of DMTs in individuals with SPMS who are nonambulatory with respect to other clinically relevant domains, including cognition and upper limb function.

Studies are needed to examine whether initial high-potency treatment early in the disease course (compared with other DMTs) improves long-term outcomes.

There is a need for comparative effectiveness studies comparing highly active DMTs in the treatment of MS and different DMTs in the treatment of CIS.

Studies are warranted to determine whether switching DMTs vs continuing a DMT, despite continued disease activity, results in improved long-term outcomes.

Continued research is urged to identify biomarkers that can predict DMT efficacy in different patient subpopulations.

More research, particularly of newer agents, is needed to minimize risk to the pregnant woman and her fetus. Particular concerns include the following: (1) There is a need to determine (a) when DMT for MS should be stopped before conception, (b) whether some agents are safer than others, and (c) which agents might be safe enough to continue through conception and pregnancy in people with MS with active disease. (2) It is important to collect more data examining the risk of return of disease activity during pregnancy or the postpartum period on the mother's long-term risk of disability and quality of life with preconception or early pregnancy discontinuation of a DMT or withholding treatments during lactation.

More studies are needed to inform decisions about the possibility of DMT discontinuation, particularly concerning when there is a high risk of relapse or disability after DMT discontinuation, and in which circumstance, if any, discontinuation poses little or no harm.

It is clear that, to answer the many questions surrounding variations in treatment in real-world populations, trial designs such as pragmatic clinical trials in clinical populations are needed.

Table e-1. Considerations/populations for which the guideline panel suggests caution regarding specific FDA-approved multiple sclerosis therapies

Medication	Special considerations/populations
Alemtuzumab (Lemtrada)	Thyroid disease
Azathioprine (Imuran)	Hepatic disease Pancreatic disease Asian populations (higher risk TPMT low activity) People with MS low or deficient in TPMT
Cladribine	People with MS who are immunosuppressed Renal or hepatic disease
Corticosteroids	Diabetes, other standard considerations
Daclizumab (Zinbryta)[a]	Hepatic disease Immune-mediated disorders; autoimmune disease
Dimethyl fumarate (Tecfidera)	Leukopenia
Fingolimod (Gilenya)	Leukopenia Hepatic disease Uveitis, macular edema Diabetes VZV seronegativity Atrioventricular conduction block Medications potentially affecting cardiac conduction Basal cell carcinoma
Glatiramer acetate (Copaxone, Glatopa)	Cosmetic concerns (skin induration)
Immunoglobulins	Allergy

	IgA deficiency
Interferons (Betaseron/Betaferon/Extavia, Avonex, Rebif, Plegridy)	Leukopenia Hepatic disease Depression Significant spasticity
Methotrexate	Renal disease Ascites, pleural effusions Hepatic disease
Mitoxantrone (Novantrone)	Cardiac disease Neutropenia less than 1,500 cells/mm^3
Mycophenolate mofetil (CellCept)	Allergy
Natalizumab (Tysabri)	Hepatic Disease History of immunosuppression JCV seropositivity Prolonged use longer than 2 years Hepatic disease
Ocrelizumab	HBV infection
Rituximab	HBV infection
Teriflunomide (Aubagio)	Hepatic disease Leukopenia Hypertension Short-term plans for pregnancy History of tuberculosis

Abbreviations: HBV = hepatitis B virus; JCV = John Cunningham virus; TPMT = thiopurine methyltransferase; VZV = varicella zoster virus.

[a]See safety note on page 35.

Low or deficient activity reduces tolerance of adverse effects of azathioprine and other thiopurine therapies.

Table e-2. Risks of multiple sclerosis therapies and potential mitigation strategies

Medication	Risks	Mitigation strategy
Alemtuzumab	Autoimmune events	Monthly CBC and CMP
	Hyperthyroidism	TSH every 3 mo
	Immune thrombocytopenia	
	Immune glomerulonephritis	
	Skin cancer	Annual skin check
	Infusion reaction	Prophylaxis before infusions
	Severe viral infections	Viral prophylaxis
Azathioprine	Immune suppression	Monitoring labs
	Hypersensitivity	TPMT testing
	LFT abnormalities	Clinical monitoring
	Pancreatitis	
	Long-term risk of cancer	
Cladribine	Opportunistic infection	Monitoring labs
	Immunosuppression	
Corticosteroids	Multiple	Standard monitoring
Cyclophosphamide	Immunosuppression	Monitoring
	Alopecia	Counseling
	Nausea	Antinausea medications
	Bladder tumors	Urologic follow-up

Daclizumab HYP[a]	Hypersensitivity reactions Severe hepatic injury Immune-mediated disorders	Premedication Hepatic monitoring Clinical monitoring
Dimethyl fumarate	Lymphopenia Flushing Gastrointestinal symptoms PML	CBC at baseline, every 3 mo Education, nonenteric ASA Take with food, counseling Monitoring
Fingolimod	Cardiac events on first dose Herpes infection Macular edema Hepatic enzyme derangements Lymphopenia PML	Baseline EKG, FDO, cardiology consultation if abnormal EKG VZV serology screen; vaccination if negative Baseline and 3-mo eye evaluation, OCT Baseline and 3-mo LFT Baseline and 3-mo CBC Clinical monitoring
Glatiramer acetate (Various)	Skin reactions Immediate postinjection systemic reaction	Education, proper technique Education
Immunoglobulins	Infusion reactions Fluid overload	Premedication Monitoring
Interferon betas (Various)	Flulike symptoms Elevated hepatic enzymes Leukopenia	NSAIDs, hydration Baseline and monitoring LFT Baseline and monitoring CBC

	Headache Depression Skin necrosis, reactions (some preparations)	Baseline headache screen Screen and monitor for depression Neutralizing antibodies as needed
Methotrexate	Hepatic injury Pulmonary fibrosis	LFTs Monitoring
Mitoxantrone	Cardiomyopathy Treatment-related acute leukemia	Cardiac monitoring of LVEF Baseline and monitoring CBC
Mycophenolate mofetil	Immune suppression Opportunistic infection	Monitoring
Natalizumab	Allergic reaction PML risk Increased hepatic function tests	Monitoring JCV antibody testing every 6 mo; for patients testing JCV Ab+ with prior immunosuppression or Index greater than 1.5, MRI q6m, screen for PML; limit infusions to 24 mo unless there is overwhelming evidence to continue Baseline and monitoring hepatic function tests
Ocrelizumab	Infusion reaction Reactivation of HBV infection Opportunistic infection potential	Premedication, monitoring HBV testing Monitoring
Rituximab	Infusion reaction Reactivation of HBV infection Opportunistic infections	Premedication, monitoring HBV testing Monitoring
Teriflunomide	Teratogenesis	Contraindicated in pregnancy, ensure contraception

	Hepatic dysfunction Reactivation of latent tuberculosis Alopecia	Baseline and every 6 mo LFT; contraindicated for existing hepatic disease Screen for tuberculosis (e.g., PPD) Clinical monitoring

Abbreviations: ASA = acetylsalicylic acid; CBC = complete blood count; CMP = complete metabolic profile; EKG = electrocardiogram; FDO = first dose observation; HBV = hepatitis B virus; JCV = John Cunningham virus; JCV Ab+ = anti-JCV antibodies; LFT = liver function tests; LVEF = left ventricular ejection fraction; NSAIDS = nonsteroidal anti-inflammatory drugs; OCT = Ocular coherence tomography; PML = progressive multifocal leukoencephalopathy; PPD = purified protein derivative skin test; TPMT = thiopurine methyltransferase; TSH = thyroid stimulating hormone; VZV = varicella zoster virus.

[a]See safety note on page 35.

Table e-3. DMTs for MS, FDA approval and indications, REMS program, FDA pregnancy recommendations

Medication type	**Medication**	**FDA approval, MS indication**	**Recommended monitoring (per FDA prescribing information)****	**REMS**	**Pregnancy FDA statement**
Infusion	Alemtuzumab 12 mg IV daily x 5 d y 1, +/- daily x 3 d y 2	Yes; relapsing forms of MS; generally reserved for people with MS who have an inadequate response to 2	Baseline and monthly CBC and creatinine and urinalysis; thyroid function quarterly; monitoring for 4 y after last infusion	Yes	Should be used in pregnancy only if the potential benefit justifies risk to the fetus

		or more drugs for MS			
Oral	Azathioprine, various doses	No	Pretreatment TPMT, CBC, CMP. Posttreatment CBC weekly first mo, twice monthly for second and third mo, then monthly; periodic LFTs	No	Whenever possible, use of azathioprine in pregnant women with MS should be avoided.
Oral or Injectable	Cladribine (see package insert for specific warnings) oral short courses varying dose; subcutaneous various doses	No	Hematologic monitoring; periodic renal and hepatic function	No	Contraindicated during pregnancy and lactation
Usually pulse infusion	Corticosteroids varying types, doses	No	Clinical monitoring	No	Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Infusion	Cyclophosphamide; multiple protocols, including induction, pulse therapy	No	CBC and differential, LFTs, nadir CBC at 14 d post dose, repeat testing before next dosing		If this medication is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus.

Oral	Dimethyl fumarate 240 mg by mouth twice daily	Yes; relapsing forms of MS	Pretreatment CBC with lymphocyte count; 6 mo after starting and every 6−12 mo thereafter*	No	Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus
Oral	Fingolimod 0.5 mg by mouth daily	Yes; relapsing forms of MS	Pretreatment cardiac evaluation, VZV immunity check, basic labs, eye and skin exam; first dose observation 6 hr	Yes	Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus
Injectable	Glatiramer acetate (Copaxone) 20 mg subcutaneous daily or 40 mg subcutaneous 3 times per wk	Yes; relapsing forms of MS	None	No	Should be used during pregnancy only if clearly needed
Injectable	Glatiramer acetate (Glatopa) 20 mg subcutaneous daily	Yes; relapsing forms of MS	None	No	Should be used during pregnancy only if clearly needed
Infusion	Immunoglobulin, various dosing regimens	No	IgA level at baseline for IgA deficiency in IgA-nondepleted forms of IVIg; appropriate clinical and lab monitoring recommended	No	No human or animal data; use only if clearly indicated.
Injectable	Interferon beta-1a 30 micrograms IM weekly	Yes; relapsing forms of MS	LFTs, CBC; periodic thyroid function tests	No	Should be used during pregnancy only if the potential benefit justifies the

					potential risk to the fetus.
Injectable	Interferon beta-1a 22 or 44 micrograms subcutaneous 3 times per wk	Yes: relapsing forms of MS	CBC, LFT 1, 3, 6 mo after initiation and then periodically. Thyroid function every 6 mo with history of thyroid dysfunction	No	Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus
Injectable	Interferon beta-1b 0.25 mg subcutaneous alternate day	Yes: relapsing forms of MS	CBC + diff, CMP 1, 3, and 6 mo after initiation and then periodically	No	Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus
Injectable	Pegylated interferon beta-1a 125 micrograms subcutaneous every 14 d	Yes: relapsing forms of MS	LFTs, CBC; periodic thyroid function tests	No	Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus
Oral, injectable	Methotrexate oral or subcutaneous, various dosing regimens	No	Pretreatment CBC + diff, LFTs, renal function, chest x-ray; monthly CBC, renal and hepatic functions every 1−2 mo	No	Contraindicated in pregnant women with psoriasis or rheumatoid arthritis (no MS statements on pregnancy available)
Infusion	Mitoxantrone 12 mg/m^2 every 3 mo maximal lifetime dose 140 mg/m^2	Yes; mitoxantrone is indicated for reducing neurologic disability or the frequency of clinical	Baseline cardiac assessment (EKG, quantitative LVEF evaluation using appropriate methodology); CBC with	No	Women of childbearing potential should be advised to avoid becoming pregnant.

		relapses in people with MS with secondary (chronic) progressive, progressive relapsing, or worsening RRMS (i.e., people with MS whose neurologic status is significantly abnormal between relapses). Mitoxantrone is not indicated for treating people with primary progressive MS.	platelets before each course of mitoxantrone; LFTs before each course of mitoxantrone; pregnancy test before each course; ongoing monitoring of cardiac function during/yearly after mitoxantrone use		
Various	Mycophenolate mofetil, various dosing schedules	No	Follow drug monitoring schedule in package insert.	Yes	If this medication is used during pregnancy, or if the patient becomes pregnant while taking this medication, the patient should be apprised of the potential hazard to the fetus. In certain situations, the patient and her health care provider may decide that the

					maternal benefits outweigh the risks to the fetus. (NB these recommendations are or other treatment indications than MS)
Infusion	Natalizumab 300 mg IV over one h every 4 wk	Yes; indicated as monotherapy for the treatment of people with relapsing forms of MS; physicians should consider whether the expected benefit of natalizumab is sufficient to offset this risk.	Not clarified; usual testing includes periodic LFTs, JCV Ab+ testing serum every 3 mo, MRI every 3−6 mo, depending on risk	Yes	Natalizumab should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Infusion	Ocrelizumab	Yes; relapsing or primary progressive forms of MS	Hepatitis B virus screening required before the first dose	No	There are no adequate data on the developmental risks associated with use of Ocrevus (ocrelizumab) in pregnant women.
Infusion	Rituximab	No	Not clarified; various monitoring protocols depending on condition	No	There are no adequate and well-controlled studies of rituximab use in pregnant women.

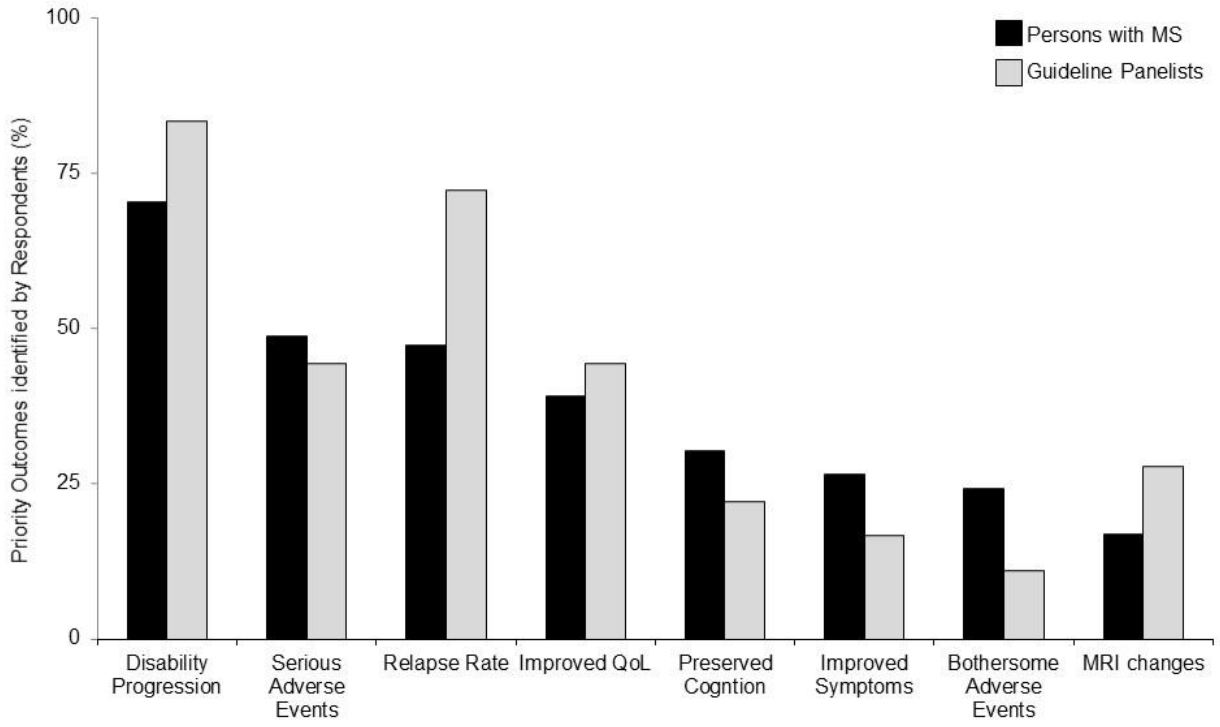
Oral	Teriflunomide 7 or 14 mg by mouth daily	Yes; relapsing forms of MS	Pretreatment transaminase and bilirubin within 6 mo, CBC, pregnancy test, screen for latent TB, check BP. LFTs monthly for 6 mo after initiating	No	Contraindicated in pregnant women or women of childbearing potential who are not using reliable contraception; pregnancy must be avoided during teriflunomide treatment or before completion of an accelerated elimination procedure after teriflunomide treatment.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; CBC = complete blood count; CMP = complete metabolic profile; EKG = electrocardiography; IgA = immunoglobulin A; IV = intravenous; IVIg = IV immunoglobulin; JCV Ab+ = anti-John Cunningham virus antibodies; LFT = liver function tests; LVEF = left ventricular ejection fraction; MS = multiple sclerosis; REMS = risk evaluation and mitigation strategies; RRMS = relapsing–remitting MS; TB = tuberculosis; TPMT = thiopurine methyltransferase; VZV = varicella zoster virus.

*Many clinicians check CBC and lymph count every 3 mo.

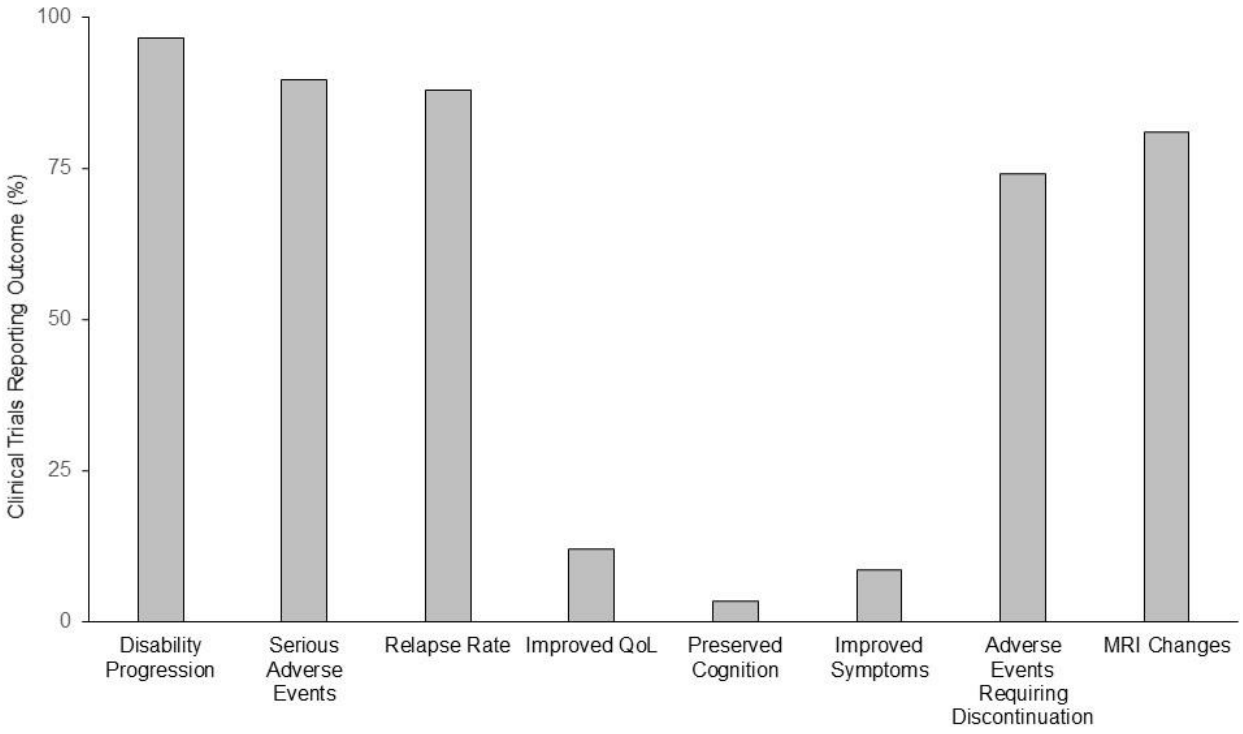
**Older agents, particularly medications not specifically FDA approved for MS, have less-well-defined monitoring recommendations in FDA package insert.

Figure e-1. Outcomes of greatest importance to selection of a disease-modifying therapy for MS, as defined by persons with MS and guideline panelists



The proportion of persons with multiple sclerosis (n = 2,156) and guideline panelists (n = 18) designating an outcome as first-, second-, or third-highest priority ("priority outcomes") when selecting a disease-modifying therapy for MS is depicted (rank-ordered from most- to least-common responses). QoL = quality of life.

Figure e-2. Primary and secondary outcomes reported in clinical trials of disease-modifying therapy for multiple sclerosis



The frequency of reporting of primary and secondary outcome measures in 58 Class I and Class II clinical trials of DMTs in MS are depicted (rank-ordered from most to least commonly reported outcomes). Class of evidence was assigned in accordance with AAN schemes for classification of evidence.[22]

QoL = quality of life.

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Appendix e-1. AAN GDDI mission

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

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

Appendix e-2. AAN GDDI members 2015–2017

The AAN has structured its subcommittee overseeing guideline development in several ways in recent years. The GDDI was first formed in 2014; it existed under a previous name and structure when this guideline project was inaugurated. At the time this guideline was approved to advance beyond subcommittee development, the subcommittee was constituted as below.

Cynthia Harden, MD (Chair); Steven R. Messé, MD (Co-Vice-Chair); Sonja Potrebic, MD, PhD (Co-Vice-Chair); Eric J. Ashman, MD; Stephen Ashwal, MD; Brian Callaghan, MD; Gregory S. Day, MD, MSc; Diane Donley, MD; Richard M. Dubinsky, MD, MPH; Jeffrey Fletcher, MD; Gary S. Gronseth, MD (Senior Evidence-based Medicine Methodology Expert); Michael Haboubi, DO; John J. Halperin, MD; Yolanda Holler-Managan, MD; Annette M. Langer-Gould, MD, PhD; Nicole Licking, DO; Mia T. Minen, MD; Pushpa Narayanaswami, MBBS, DM; Maryam Oskoui, MD; Alejandro A. Rabinstein, MD; Alexander Rae-Grant, MD; Kevin Sheth, MD; Kelly Sullivan, PhD; Eric J. Ashman, MD (Ex-Officio); Jacqueline French, MD (Ex-Officio, Guideline Process Historian)

Appendix e-3. Complete search strategy

Original search

Databases: MEDLINE

1. multiple sclerosis/ or multiple sclerosis, relapsing-remitting/ or neuromyelitis optica/

2. demyelinating diseases/ or demyelinating autoimmune diseases, cns/

3. multiple sclerosis.tw.

4. or/1-3

5. ((first or initial or isolat*) adj3 (demyelinating or episode or event* or presentation*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

6. (cis or ris).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

7. "clinically isolated".mp.

8. suggestive*.mp.

9. 4 and (5 or 6 or 7 or 8)

10. 4 and early.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

11. 9 or 10

12. conversion.mp. and 11 [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

13. (glatiramer or ifnb or "ifn beta" or "interferon beta" or "interferon b").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

14. (dmd or dmt or "disease modifying").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

15. Interferon-beta/

16. methotrexate.mp. or Methotrexate/

17. cyclophosphamide.mp. or Cyclophosphamide/

18. azathioprine.mp. or Azathioprine/

19. exp Adrenal Cortex Hormones/

20. (corticosteroid* or methylprednisolone).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

21. mitoxantrone.mp. or Mitoxantrone/

22. Antibodies, Monoclonal, Humanized/ or natalizumab.mp.

23. (teriflunomide or mycophenolate or laquinimod or rituximab or daclizumab or alemtuzumab or figolimod or dimethylfumarate or "dimethyl fumarate" or ocrelizumab).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

24. or/13-23

25. 11 and 24

26. ..l/ 25 yr=2012-2015

27. 26 and (progress* or conversion or new or annualized or outcome* or followup or "follow up").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

28. 26 and ((disability or adverse).mp. or ae.fs.) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

29. limit 26 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or observational study or pragmatic clinical trial or randomized controlled trial)

30. 26 and (cohort* or prospective* or retrospective* or trial*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

31. or/27-30

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

	Searches	Results
1	demyelinating disease/	11554
2	((first or initial or isolat* or subclinic*) adj3 demyelinat*).mp.	426
3	(cis or ris).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	113341
4	suggestive*.tw. or early.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1449302
5	multiple sclerosis.mp. or Multiple Sclerosis/	72887
6	demyelinating autoimmune diseases, cns/ or multiple sclerosis/	48384
7	(clinical* adj3 isolated).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	7901
8	(2 or 3 or 4 or 7) and 6	4464
9	1 and (2 or 3 or 4 or 7)	1391

10	8 or 9	5450
11	(dmt* or (disease adj2 modif*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	20116
12	azathioprine.mp. or Azathioprine/	21808
13	daclizumab.mp.	1107
14	exp Immunoglobulins/	863588
15	methotrexate.mp. or Methotrexate/	50467
16	fingolimod.mp. or Fingolimod Hydrochloride/	2253
17	mitoxantrone.mp. or Mitoxantrone/	6184
18	Mycophenolic Acid/ or mycophenolate.mp.	11931
19	natalizumab.mp. or Natalizumab/	1983
20	rituximab.mp. or Rituximab/	18363
21	Crotonates/ or teriflunomide.mp.	663
22	interferon beta.mp. or exp Interferon-beta/	12038
23	(ifn adj (b or beta)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	7842
24	cladribine.mp. or Cladribine/	1835
25	cyclophosphamide.mp. or Cyclophosphamide/	67586
26	glatiramer.mp. or Glatiramer Acetate/	1877
27	glucocorticoids.mp. or exp Glucocorticoids/	197666
28	Quinolones/ or laquinimod.mp.	10901
29	rebif.mp. or Interferon beta-1a/	1559
30	Antibodies, Monoclonal/ or alemtuzumab.mp.	193406
31	ocrelizumab.mp.	130
32	or/11-31	1191900
33	10 and 32	1333
34	limit 33 to yr="2016 - 2017"	13
35	33 and (cis or isolat*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	394
36	35 and 2016*.ed.	26

37	34 or 36	38

CENTRAL – same strategy – zero hits

EMBASE 1988 – week 46

Searches	Results	Type
1	demyelinating disease/	12955
2	((first or initial or isolat* or subclinic*) adj3 demyelinat*).mp.	675
3	(cis or ris).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	108721
4	suggestive*.tw. or early.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	1543396
5	multiple sclerosis.mp. or Multiple Sclerosis/	99463
6	demyelinating disease/	12955
7	(clinical* adj3 isolated).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	10008
8	(2 or 3 or 4 or 7) and 6	3252
9	1 and (2 or 3 or 4 or 7)	3252
10	8 or 9	3252
11	(dmt* or (disease adj2 modif*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	34464
12	azathioprine.mp. or Azathioprine/	72399
13	daclizumab.mp.	5593
14	exp Immunoglobulins/	356969
15	methotrexate.mp. or Methotrexate/	131751
16	fingolimod.mp. or Fingolimod Hydrochloride/	6496
17	mitoxantrone.mp. or Mitoxantrone/	20722
18	Mycophenolic Acid/ or mycophenolate.mp.	28508
19	natalizumab.mp. or Natalizumab/	7738
20	rituximab.mp. or Rituximab/	57463
21	Crotonates/ or teriflunomide.mp.	2015
22	interferon beta.mp. or exp Interferon-beta/	26167

23	(ifn adj (b or beta)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	8259	
24	cladribine.mp. or Cladribine/		5744
25	cyclophosphamide.mp. or Cyclophosphamide/		159795
26	glatiramer.mp. or Glatiramer Acetate/		6899
27	glucocorticoids.mp. or exp Glucocorticoids/		518385
28	Quinolones/ or laquinimod.mp.		16343
29	rebif.mp. or Interferon beta-1a/		6567
30	Antibodies, Monoclonal/ or alemtuzumab.mp.		169888
31	ocrelizumab.mp.		774
32	or/11-31		1223761
33	10 and 32		1270
34	limit 33 to yr="2016 - 2017"		89
35	33 and 2016*.em.		156
36	34 or 35		157
37	36 not case report/		133
38	limit 37 to human		128
39	clinical study/ or exp case control study/ or exp case study/ or exp clinical trial/ or exp "clinical trial (topic)"/ or exp intervention study/ or exp major clinical study/ or exp prospective study/ or exp retrospective study/		3909956
40	exp cohort analysis/ or exp control group/ or exp cross-sectional study/ or exp double blind procedure/ or exp evidence based practice/		1697956
41	38 and (39 or 40)		81

Summary of Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) Search Strategy 1946 to Present

	Searches	Results
1	Exp Antibodies, Monoclonal, Humanized/	27000
2	Daclizumab	946
3	Zenapax.mp	55
4	azathioprine.mp. or Azathioprine/	
5	exp Immunoglobulins/	
6	methotrexate.mp. or Methotrexate/	

7	fingolimod.mp. or Fingolimod Hydrochloride/
8	mitoxantrone.mp. or Mitoxantrone/
9	Mycophenolic Acid/ or mycophenolate.mp.
10	natalizumab.mp. or Natalizumab/
11	rituximab.mp. or Rituximab/
12	Crotonates/ or teriflunomide.mp.
13	interferon beta.mp. or exp Interferon-beta/
14	cladribine.mp. or Cladribine/
15	cyclophosphamide.mp. or Cyclophosphamide/
16	glatiramer.mp. or Glatiramer Acetate/
17	glucocorticoids.mp. or exp Glucocorticoids/
18	Quinolones/ or laquinimod.mp.
19	rebif.mp. or Interferon beta-1a/
20	Antibodies, Monoclonal/ or alemtuzumab.mp.
21	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22	Multiple sclerosis.mp. or exp Multiple Sclerosis
23	21 and 22
24	Limit 23 to yr="2013 – 2015 (current)"

Updated search

Followed identical process as the original search

Queries

Appendix e-4. AAN rules for classification of evidence for risk of bias

Therapeutic scheme

Class I

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

The following are also required:

a. concealed allocation

b. no more than 2 primary outcomes specified

c. exclusion/inclusion criteria clearly defined

d. adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias.

e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:

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

f. For crossover trials, both period and carryover effects examined and statistical adjustments performed, if appropriate

Class II

An RCT of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above (see Class I) or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above (see Class I). (Alternatively, a randomized crossover trial missing 1 of the following 2 characteristics: period and carryover effects described or baseline characteristics of treatment order groups presented.) All relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences.

Class III

All other controlled trials (including studies with external controls such as well-defined natural history controls). (Alternatively, a crossover trial missing both of the following 2 criteria: period and carryover effects described or baseline characteristics of treatment order groups presented.) A description of major confounding differences between treatment groups that could affect outcome.** Outcome assessment is masked, objective, or performed by someone who is not a member of the treatment team.

Class IV

Studies that (1) did not include patients with the disease, (2) did not include patients receiving different interventions, (3) had undefined or unaccepted interventions or outcomes measures, or (4) had no measures of effectiveness or statistical precision presented or calculable.

*Note that numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any 1 of the 3 is missing, the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Appendix e-5. Evidence tables

To access the evidence tables, see appendix e-5, published in a separate PDF document at Neurology.org.

Appendix e-6. Studies excluded from analysis

Author	Year	Journal	Title	Reason for exclusion
Azathioprine studies excluded				
Milanese, C et al	1993	*Journal of Neurology*	A double-blind study on azathioprine efficacy in multiple sclerosis: final report	Study does not separate into RRMS vs SPMS
Kalincik	2012	*Clinical Neurology and Neurosurgery*	Interferon, azathioprine, and corticosteroids in MS 6-year follow-up of ASA cohort	Class IV study
Casetta	2012	*European Neurological Journal*	Azathioprine for MS	Review article
Casetta	2009	*Journal of Neurology, Neurosurgery, and Psychiatry*	Azathioprine for MS	Review article
British and Dutch Multiple Sclerosis Azathioprine Trial Group	1988	*Lancet*	Double-masked trial of azathioprine in multiple sclerosis	Did not separate into RRMS vs SPMS
Kalincik, T et al	2012	*Clinical Neurology and Neurosurgery*	Interferon azathioprine and corticosteroids in multiple sclerosis: 6-year follow-up of the ASA cohort	Class IV study
Cendrowski, W.	1971	*Acta Neurologica Scandinavia*	Therapeutic trial of Imuran (azathioprine) in multiple sclerosis	Class IV study
Ghezzi, A et al	1989	*Elsevier Science Publishers B.V.*	Clinical controlled randomized trial of azathioprine in multiple sclerosis	Class IV study
Massacesi	2014	*PLoS ONE*	Azathioprine versus beta interferons for relapsing-remitting multiple sclerosis: a multicentre randomized non-inferiority trial	Study already retrieved in earlier search and included
Cladribine studies excluded				
Stelmasiak et al	2009	*Multiple Sclerosis*	Effect of parenteral cladribine on relapse	Unable to extract any data from study

			rates in patients with relapsing forms of multiple sclerosis: results of a two year double blind placebo-controlled crossover study	
Comi et al	2013	*Journal of Neurology*	MRI outcomes with cladribine tablets for multiple sclerosis in the CLARITY study	Only MRI data included
Filippi et al	2000	*Neurology*	Whole brain volume changes in patients with progressive MS treated with cladribine	Only MRI data included
Leist, T.	2013	*Neurology*	Oral cladribine delays time to conversion to clinically definite ms in patients with a first demyelinating event: Top line results from the phase III oracle ms study	Abstract only
Sipe et al	1994	*Lancet*	Cladribine in treatment of chronic progressive multiple sclerosis	Unable to extract any data from study
Leist	2014	*Lancet Neurology*	Effect of oral cladribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE MS): a phase 3 randomised trial	Study already retrieved in earlier search and included
Corticosteroid studies excluded				
Zivadinov	2008	*Journal of Neurological Sciences*	Effect of intravenous methylprednisolone on the number, size, and confluence of plaques in relapsing-remitting multiple sclerosis	Reanalysis of included study (Zivadinov 2001)
Cyclophosphamide studies excluded				

Atkins	2016	*Lancet*	Immunoablation and autologous haemopoietic stem-cell transplantation for aggressive multiple sclerosis: a multicentre single-group phase 2 trial	Not randomized, no control
Hauser et al	1983	*New England Journal of Medicine*	Intensive immunosuppression in progressive multiple sclerosis	Class IV study
Weiner, H.L et al	1989	*Neurology*	Double-blind study of true vs. sham plasma exchange in patients treated with immunosuppression for acute attacks of multiple sclerosis	Class IV study: No comparator, all received cyclophosphamide
Weiner, H.L et al	1993	*Neurology*	Intermittent cyclophosphamide pulse therapy in progressive multiple sclerosis: Final report of the Northeast Cooperative Multiple Sclerosis Treatment Group	Class IV study: No comparator
Daclizumab studies excluded				
Giovannoni et al	2014	*Journal of Neurology*	Effect of daclizumab high yield process in patients with highly active RRMS	Post hoc analysis of SELECT study
Arnold	2014	*Multiple Sclerosis*	Brain MRI results of DECIDE	Additional MRI data from DECIDE study
Giovannoni	2013	*Neurology*	The safety and efficacy of daclizumab HYP in RRMS in the selection extension study: primary results	Abstract only
Giovannoni	2014	*Journal of Neurology*	Efficacy of daclizumab HYP across subgroups of varying RRMS disease severity:	Post hoc analysis of SELECT

			Results from SELECT study	
Guo		*Value in Health*	Predicting the long-term clinical effectiveness of daclizumab in RRMS	Post hoc analysis; abstract only
Kappos	2014	*Multiple Sclerosis*	Primary results of DECIDE: A randomized, double-blind, double-dummy, active controlled trial of daclizumab HYP vs. Interferon beta-1a in RRMS patients	Abstract of DECIDE study
Mehta	2013	*Neurology*	Efficacy of daclizumab HYP treatment in patients with highly active RRMS: results from the SELECT study	Abstract of SELECT study
Radue	2013	*Multiple Sclerosis*	Decrease in T1 black hole volume over 2 years of daclizumab HYP treatment	Additional MRI outcomes from SELECT study
Radue	2013	*Neurology*	Daclizumab HYP reduces the evolution of new gadolinium enhancing lesions to T1-black holes: results from SELECT study	Abstract only; additional MRI outcomes from SELECT study
Radue	2013	*Multiple Sclerosis*	Reduction in brain atrophy with extended daclizumab HYP treatment: results of SELECT and SELECT extension study	Abstract only; additional MRI outcomes
Radue	2014	*Neurology*	Reduction in brain atrophy with extended daclizumab HYP treatment: results of SELECT and SELECT extension study	Abstract only; additional MRI outcomes
Selmaj	2014	*Multiple Sclerosis*	Safety and tolerability of daclizumab HYP	Abstract only, DECIDE study

			treatment in RRMS: Results of DECIDE study	
Vollmer	2013	*Neurology*	Daclizumab HYP treatment reduced the impact of multiple sclerosis relapse on HRQOL	Abstract only
Radue	2015	*Neurology*	Long-term efficacy of daclizumab HYP in relapsing-remitting multiple sclerosis: 3-y results from the selected extension study	Abstract only
Rose	2015	*Neurology*	Daclizumab HYP reduced brain MRI lesion activity compared with interferon beta-1a: Results from the DECIDE study	Abstract only
Kappos	2015	*New England Journal of Medicine*	Daclizumab HYP versus interferon beta-1a in relapsing multiple sclerosis	Study already retrieved in earlier search and included
Gold	2016	*BMC Neurology*	Safety and efficacy of daclizumab in relapsing-remitting multiple sclerosis: 3-year results from the SELECTED open-label extension study	Class IV study included as related evidence
Giovannoni	2014	*Lancet Neurology*	Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECTION): a multicentre, randomised, double-blind extension trial	Study already retrieved in earlier search and included
Giovannoni	2014	*Journal of Neurology*	Effect of daclizumab high-yield process in patients with highly active relapsing-remitting multiple sclerosis	Post hoc analysis of data already included
Arnold	2014	*Multiple sclerosis*	Brain MRI results of DECIDE: A randomized, double-	Abstract only

			blind trial of DAC HYP vs. IFNbeta-1a in RRMS patients	
Dimethyl fumarate studies excluded				
Miller	2015	*Neurology*	Effects of delayed release dimethyl fumarate on MRI measures in the phase 3 CONFIRM study	Similar data included in Fox 2012 article
Kappos	2014	Multiple Sclerosis	Quality of life outcomes with BG-12 (dimethyl fumarate) in patients with RRMS: the DEFINE study	Data included in Cochrane review
Kita	2014	*Multiple Sclerosis*	Effects of BG-12 (dimethyl fumarate) on HRQOL in patients with RRMS: findings from the CONFIRM study	Data included in Cochrane review
Arnold	2014	*Journal of Neurology*	Magnetization transfer ratio in the delayed-release dimethyl fumarate DEFINE study	Outcome outside scope defined by clinical questions
Kappos	2014	*European Journal of Neurology*	Time course of clinical and neuroradiologic effects of delayed-release dimethyl fumarate in multiple sclerosis	Post hoc analysis of DEFINE and CONFIRM studies
Gold	2015	*Multiple Sclerosis*	Efficacy and safety of delayed-release dimethyl fumarate in patients newly diagnosed with RRMS	Post hoc analysis of DEFINE and CONFIRM studies
Kita	2014	*Clinical Therapeutics*	Effects of delayed-release dimethyl fumarate on HRQOL in patients with RRMS: an integrated analysis of the Phase 3 DEFINE and CONFIRM studies	Integrated analysis of DEFINE and CONFIRM study data
Von Hehn	2014	*Multiple sclerosis*	Effect of bismuth subsalicylate on	Abstract

			gastrointestinal events associated with delayed-release dimethyl fumarate	
Rosenkranz	2015	*New England Journal of Medicine*	PML in a patient with lymphocytopenia treated with dimethyl fumarate	Included-as related evidence
Khoiny	2014	*Neurology*	Bullous eruption with dimethyl fumarate	Abstract
Gold	2014	*Multiple Sclerosis*	Delayed release dimethyl fumarate and pregnancy: Preclinical studies and pregnancy outcomes from clinical trials and postmarketing experience	Abstract
Viglietta	2015	*Annals of Clinical and Translational Neurology*	Efficacy of delayed-release dimethyl fumarate in relapsing-remitting multiple sclerosis: integrated analysis of the phase 3 trials	Combines data from 2 studies already included in guideline panel analysis
Gold	2016	*Multiple Sclerosis*	Long-term effects of delayed-release dimethyl fumarate in multiple sclerosis: Interim analysis of ENDORSE, a randomized extension study	Included as related evidence
Fingolimod studies excluded				
Cascione	2013	*Journal of Medical Economics*	Randomized open label study to evaluate patient-reported outcomes with fingolimod after changing prior disease modifying therapy for relapsing	No results presented in article

			MS: EPOC study rational and design	
Devonshire	2012	*Lancet Neurology*	Relapse and disability outcomes in patients with MS treated with fingolimod: subgroup analyses of the double-blind randomized placebo controlled FREEDOMS study	FREEDOMS data already included
Kappos	2006	*New England Journal of Medicine*	Oral fingolimod for relapsing MS	Used 1.25- and 5-mg doses- these doses are not approved for use by FDA
Comi	2010	*Multiple Sclerosis*	Phase II study of oral fingolimod in MS: 3-year results	Used 1.25- and 5-mg doses- these doses are not approved for use by FDA
Montalban	2011	*Multiple Sclerosis*	Oral fingolimod in relapsing MS: impact on health-related quality of life in a phase II study	Used 1.25- and 5-mg doses- these doses are not approved for use by FDA
O'Connor	2009	*Neurology*	Oral fingolimod in MS: 2-year results of a phase II extension study	Used 1.25- and 5-mg doses- these doses are not approved for use by FDA
Cohen	2013	*Journal of Neurology*	Fingolimod versus intramuscular interferon in patient subgroups from TRANSFORMS	Subanalysis of already included study
Radue	2012	*Archives of neurology*	Impact of fingolimod therapy on MRI outcomes in patients with MS	Subanalysis of already included study
Kira	2014	*BMC Neurology*	Fingolimod therapy in Japanese patients with relapsing MS over 12 months: results of a phase II	Open-label extension study

			observational extension	
Kappos	2015	*Neurology*	Long-term effects of fingolimod in MS: the randomized FREEDOMS extension trial	Class IV study
Izquierdo	2014	*Multiple Sclerosis*	Five-year results from a phase 2 study of oral fingolimod in relapsing multiple sclerosis	Extension study; used doses not approved for clinical use
Derfuss	2015	*Neurology*	Relapse outcomes in patients with multiple sclerosis treated with fingolimod: Subgroup analyses of three phase 3 fingolimod trials	Abstract only
Fox	2014	*Multiple Sclerosis*	Outcomes of switching directly to oral fingolimod from injectable therapies: Results of the randomized, open-label, multicenter, Evaluate Patient OutComes (EPOC) study in relapsing multiple sclerosis	Not blinded, does not include outcomes defined by inclusion criteria
Arvin	2015	*JAMA Neurology*	Varicella-zoster virus infections in patients treated with fingolimod: risk assessment and consensus recommendations for management	Included as related evidence
Glatiramer acetate studies excluded				
Arnold	2013	*Journal of Neurology*	Neuroprotection with glatiramer acetate: evidence from the PreCISe trial	End point was MRS, which was not one of the standard MR measures included; substudy of included study

Ford	2010	*Multiple Sclerosis*	Continuous long-term immunomodulatory therapy in relapsing MS: results from the 15-year analysis of the US prospective open-label study of glatiramer acetate	Included as related evidence
Filippi	2006	*Lancet Neurology*	Effects of oral glatiramer acetate on clinical and MRI-monitored disease activity in patients with relapsing MS: a multicenter, double-blind, randomized placebo-controlled study	Treatment not available clinically for use
La Mantia	2015	*JNNP*	Comparative efficacy of interferon beta versus glatiramer acetate for RRMS	Review article
Wolinksy	2015	*Multiple Sclerosis*	GLACIER: An open-label, randomized, multicenter study to assess the safety and tolerability of glatiramer acetate 40 mg three-times weekly versus 20 mg daily in patients with relapsing-remitting multiple sclerosis	Open label, does not include main outcomes assessed in our clinical questions
Zivadinov	2015	*Journal of Neurology*	Effect of glatiramer acetate three-times weekly on the evolution of new, active multiple sclerosis lesions into T1-hypointense "black holes": a post hoc magnetic resonance imaging analysis	GALA study data already included, this reports additional MRI endpoints

Zivadinov	2015	*Journal of Neuroimaging*	The effect of three times a week glatiramer acetate on cerebral T1 hypointense lesions in relapsing-remitting multiple sclerosis	GALA study data already included, this reports additional MRI end points
Cohen	2014	*Multiple Sclerosis*	Generic glatiramer acetate is equivalent to Copaxone on efficacy and safety: Results of the randomized double-blind GATE trial in multiple sclerosis	Abstract only
Boyko	2016	*Multiple Sclerosis*	Effects of generic glatiramer acetate (BCD-063) on magnetic resonance imaging outcomes in patients with relapsing multiple sclerosis. A randomized double-blind 48 weeks clinical trial	Abstract only
Interferon alpha-2a studies excluded				
Myhr	1999	*Neurology*	Interferon-α2a reduces MRI disease activity in relapsing-remitting multiple sclerosis	Not approved for clinical use
Durelli, L et al	1994	*Neurology*	Chronic systemic high-dose recombinant interferon alfa-2a reduces exacerbation rate, MRI signs of disease activity, and lymphocyte interferon gamma production in relapsing-remitting multiple sclerosis	Not approved for clinical use
Kinkel, R. P	2014	*Multiple Sclerosis and Related Disorders*	Early MRI activity predicts treatment nonresponse with intramuscular interferon beta-1a in	Secondary analysis; Not does evaluate DMT or any treatment

			clinically isolated syndrome	
Singer, B et al	2012	*BMC Neurology*	Comparative injection-site pain and tolerability of subcutaneous serum-free formulation of interferon β-1a versus subcutaneous interferon β-1b: results of the randomized, multicenter, Phase IIIb REFORMS study	Specified outcomes not assessed: only assessed pain
Interferon beta-1a studies excluded				
Cohen, J.A et al	2009	*Neurology*	Results of the Avonex Combination Trial (ACT) in relapsing-remitting MS	No useable data
De Stefano	2012	*Journal of Neurology*	Effect of two dosing frequencies of subcutaneous interferon beta-1a on lesion volumes in patients with a first clinical demyelinating event suggestive of multiple sclerosis: Results of the phase III REFLEX study extension (REFLEXION	Abstract only
Freedman, M.S.	2012	*Neurology*	Efficacy of two dosing frequencies of subcutaneous interferon beta-1a on the risk of conversion from a first demyelinating event to multiple sclerosis and on MRI measures of disease:	Abstract only

			3-year results of phase III, double-blind, multicentre trials (REFLEX and REFLEXION)	
Polma	2003	*Multiple Sclerosis*	Oral interferon beta-1a in relapsing-remitting multiple sclerosis: a double blind-randomized study	Drug not available clinically: Oral interferon not available for use clinically
Barkhof	2012	*Multiple Sclerosis*	Effect of two dosing frequencies of subcutaneous interferonb-1a on brain volume changes in patients with a first clinical demyelinating event: 36-month results of a phase III, double-blind, multicentre trial (REFLEX) and its extension (REFLEXION)	Abstract only
Comi	2012	*Multiple Sclerosis*	Effect of two dosing frequencies of subcutaneous interferonb-1a on conversion to MS and MRI measures of disease in patients with a first clinical demyelinating event: 3-year results of phase III, double-blind, multicentre trials (REFLEX/ REFLEXION)	Abstract only
Nafissi	2012	*Clinical Neurology and Neurosurgery*	Comparing efficacy and side effects of a weekly intramuscular biogeneric/biosimilar interferon beta-1a with Avonex in relapsing remitting multiple sclerosis: A double blind	Drug not available clinically

			randomized clinical trial	
Newsome	2015	*Neurology*	Peginterferon beta-1a is effective as early as twelve weeks following treatment initiation in patients with relapsing multiple sclerosis	Abstract only
Uher, T.	2015	*European Journal of Neurology*	Early magnetic resonance imaging predictors of clinical progression after 48 months in clinically isolated syndrome patients treated with intramuscular interferon beta-1a	Class IV study: No comparator, observational
Kieseier	2015	*Multiple Sclerosis*	Peginterferon beta-1a in multiple sclerosis: 2-year results from ADVANCE	No comparator data included
Calabresi	2014	*Lancet Neurology*	Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study	Study already retrieved in earlier search and included
Motamed	2007	*Clinical Neurology and Neurosurgery*	The effect of interferon beta 1a on relapses and progression of disability in patients with clinically isolated syndromes suggestive of multiple sclerosis	Class IV study
Barkof	2014	*Multiple sclerosis*	The influence of patient demographics, disease characteristics and treatment on brain volume loss in Trial	Subanalysis of already included study

			Assessing Injectable Interferon vs FTY720 oral in RRMS, a phase III study of fingolimod in MS	
Arnold	2014	*BMC Neurology*	Effect of peginterferon beta-1a on MRI measures and achieving no evidence of disease activity: results from a randomized controlled trial in relapsing-remitting multiple sclerosis	Data already included
Zivadinov, R.	2013	*Radiology*	Thalamic atrophy is associated with development of clinically definite multiple sclerosis	No comparator, observational
Uher, T.	2014	*Journal of Neurological Sciences*	Relationship between gray matter volume and cognitive learning in CIS patients on disease-modifying treatment	Class IV: Change in treatment not randomized, no comparator, observational
Uher, T.	2014	*Journal of Neurology*	Longitudinal MRI and neuropsychological assessment of patients with clinically isolated syndrome	No comparator, observational
Varosanec, M.	2015	*American Journal of Neuroradiology*	Longitudinal mixed-effect model analysis of the association between global and tissue-specific brain atrophy and lesion accumulation in patients with clinically isolated syndrome	No comparator, observational
Ristori, G.	2014	*Neurology*	Effects of Bacille Calmette-Guerin	Class IV: No comparator for

			after the first demyelinating event in the CNS	DMT alone, vaccine add-on
Interferon beta-1b studies excluded				
Caloyeras	2012	*Clinical Therapeutics*	Cost-effectiveness analysis of interferon beta-1b for the treatment of patients with a first clinical event suggestive of multiple sclerosis	Cost-benefit analysis using data published in another source already included
Durell	2002	*Lancet*	Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomized multicenter study (INCOMIN)	Class IV study: according to the AAN therapeutic classification of evidence scheme
Edan	2012	*Multiple Sclerosis*	Early initiation of interferon beta-1b after a first clinical event suggestive of multiple sclerosis: Clinical outcomes and use of disease-modifying therapy from the benefit extension study	Abstract only, full paper is included
Edan	2013	*Multiple Sclerosis*	Early initiation of interferon beta-1b after a first clinical event suggestive of multiple sclerosis: Clinical outcomes and use of disease-modifying therapy from the BENEFIT extension study	Abstract only, full paper is included
Edan	2013	*Neurology*	Long term impact of early initiation of interferon beta-1b after a first clinical event suggestive of multiple sclerosis: Additional relapse rate, EDSS, and	Abstract only, full paper is included

			MSSS analyses after 8 years	
Freedman, M. S.	2014	*Therapeutic Advances in Neurological Disorders*	Evidence for the efficacy of interferon beta-1b in delaying the onset of clinically definite multiple sclerosis in individuals with clinically isolated syndrome	Class IV study: Retrospective analysis that does not address treatment efficacy
Freedman, M. S.	2013	*Multiple Sclerosis*	Predictors of disease activity in patients with clinically isolated syndrome (CIS) treated with interferon beta 1b in the BENEFIT trial	Review article
Reder et al	2010	*Neurology*	Cross-sectional study assessing long-term safety of interferon beta-1b for RRMS	Included as related evidence; Long term follow-up study
Tur	2011	*Archives of Neurology*	Interferon beta-1b for the treatment of primary progressive multiple sclerosis	Follow-up study 5 years after participation in clinical trial
Nagtegaal	2014	*Multiple Sclerosis*	Interferon beta-1b reduces black holes in a randomised trial of clinically isolated syndrome	BENEFIT trial already included; this reports additional imaging data
Laquinimod studies excluded				
Comi	2010	*Multiple Sclerosis*	Oral laquinimod in patients with RRMS: 36 week double blind active extension of the multi-centre, randomized, double-blind, parallel-group placebo controlled study	Not approved for clinical use

Comi	2012	*New England Journal of Medicine*	Placebo-controlled trial of oral laquinimod for MS	Not approved for clinical use
Filippi	2013	Journal of Neurology, Neurosurgery, and Psychiatry	Placebo-controlled trial of oral laquinimod in MS: MRI evidence of an effect on brain tissue damage	Not approved for clinical use
Comi	2008	*Lancet*	Effect of laquinimod on MRI-monitored disease activity in patients with RRMS: a multicenter, randomized, double-blind, placebo-controlled phase IIb study	Not approved for clinical use
Vollmer	2014	*Journal of Neurology*	A randomized placebo-controlled phase III trial of laquinimod for MS	Not approved for clinical use
Polman	2005	*Neurology*	Treatment with laquinimod reduces development of active MRI lesions in relapsing MS	Not approved for clinical use
Mycophenolate mofetil studies excluded				
Kira	2014	*Journal of Neurology, Neurosurgery, and Psychiatry*	Evidence for efficacy of a drug widely used without authorization in multiple sclerosis: mycophenolate mofetil	Not a trial
Michel	2014	*Journal of Neurology, Neurosurgery, and Psychiatry*	Mycophenolate mofetil in MS: a multicenter retrospective study on 344 patients	Class IV study
Nicholas	2013	*Neurology*	Combination interferon beta-1a and mycophenolate mofetil in RRMS: Effects on safety, relapse rate and disability	Abstract only
Pandit	2014	*Neurology India*	Mycophenolate mofetil in the treatment of MS	Class IV study

Natalizumab studies excluded				
O'Connor et al	2005	*Multiple Sclerosis*	Relapse rates and enhancing lesions in a phase II trial of natalizumab in multiple sclerosis	Post hoc analysis
Hutchinson et al	2009	*Journal of Neurology*	The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analyses of AFFIRM and SENTINEL	Subgroup analysis; review of two included studies
Kalincik et al	2015	*Annals of Neurology*	Switch to natalizumab versus fingolimod in active RRMS	Class IV study
Miller	2003	*New England Journal of Medicine*	A controlled trial of natalizumab for relapsing MS	Did not analyze results based on MS type.
Steiner	2016	*Neurology*	Natalizumab versus placebo in patients with secondary progressive multiple sclerosis (SPMS): Results from ASCEND, a multicenter, double-blind, placebo-controlled, randomized phase 3 clinical trial	Abstract only
Kapoor	2016	*Multiple Sclerosis*	Subgroup analyses of natalizumab treatment response in ASCEND, a multicenter, double-blind, placebo-controlled, randomized phase 3 clinical trial in patients with secondary progressive multiple sclerosis (SPMS)	Abstract only
Kaufman	2015	*Journal of Neurology*	Radiologic MS disease activity during natalizumab treatment	RESTORE study included- additional data not needed for

			interruption: findings from RESTORE	the guideline panel review
Rituximab studies excluded				
Castillo	2013	*PLoS One*	Rituximab in relapsing and progressive forms of MS: a systematic review	Systematic review
Perrone	2014	*Multiple Sclerosis*	Rituximab in the treatment of secondary-progressive MS	Abstract only
Salzer	2016	*Neurology*	Rituximab in multiple sclerosis: A retrospective observational study on safety and efficacy	Class IV study
Alping	2015	*Multiple sclerosis*	Superior efficacy and tolerability of rituximab as compared to fingolimod for MS patients switching from natalizumab due to positive JC virus serology	Abstract only
Teriflunomide studies excluded				
Miller AE et al	2014	Journal of Neurology	Teriflunomide reduces relapses with sequelae and relapses leading to hospitalizations: results from the TOWER study	Post-hoc analysis
O'Connor et al	2013	*Journal of Neurology*	Teriflunomide reduces relapse related neurological sequelae, hospitalizations and steroid use	Post-hoc analysis
Miller AE et al	2012	*Multiple Sclerosis*	Pre-specified subgroup analyses of a placebo-controlled phase III trial	Sub-group analysis

			(TEMSO) of oral teriflunomide in relapsing multiple sclerosis	
Miller, A.	2014	*Neurology*	Topic: Efficacy and safety of once-daily oral teriflunomide in patients with first clinical episode consistent with multiple sclerosis	Abstract only
Wolinsky	2014	*Journal of Neurology*	Effect of teriflunomide on MRI activity in patients with early MS: Outcomes from the phase 3 TOPIC study	Abstract only
Miller	2014	*Lancet Neurology*	Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial	Study already retrieved in earlier search and included
Nelson	2016	*Neurology*	Outcomes in patients with progressive MS: Analysis of teriflunomide long-term extension data	Abstract only
O'Connor	2016	*Neurology*	Long-term safety and efficacy of teriflunomide	Included as related evidence Class III
Studies not addressing a disease-modifying therapy				
Ascherio	2012	*Multiple Sclerosis*	Serum 25-hydroxyvitamin D concentrations among patients in BENEFIT predicts conversion to multiple sclerosis, MRI lesions, and brain volume loss	Not does evaluate a DMT
Dorr	2012	*Trials*	Efficacy of vitamin D supplementation in multiple sclerosis	Presenting trial data only

			(EVIDIMS Trial): study protocol for a randomized controlled trial	
D'Alessandro	2013	*Journal of Neurology*	Risk of multiple sclerosis following clinically isolated syndrome: a 4-year prospective study	Observational study that=-=[p did not evaluate DMT
Fox	2012	*Multiple Sclerosis*	A randomized clinical trial of autologous T-cell therapy in multiple sclerosis: subset analysis and implications for trial design	Drug not included in list of DMT, and phase II trial with no end points
Cree	2015	*Nature Reviews Neurology*	Demyelinating disease: Is TOPIC the last trial for clinically isolated syndrome?	Review article
Edan	2014	*Neurology*	Patient-reported quality of life in the benefit trial	Abstract only
Goodin	2012	*Neurology*	Survival in MS	Long-term follow-up study; included as related evidence
Jokubaitis, V. G.	2015	*Annals of Clinical and Translational Neurology*	Predictors of disability worsening in clinically isolated syndrome	Does not evaluate a DMT or any treatment; Class IV study
Kalincik, T.	2012	*PLoS ONE*	Volumetric MRI markers and predictors of disease activity in early multiple sclerosis: a longitudinal cohort study	Does not evaluate a DMT or any treatment
Kavaliunas A.	2015	*Multiple Sclerosis*	The influence of immunomodulatory	No DMT diagnosis

			treatment on the clinical course of multiple sclerosis	
Kerbrat, A.	2015	*European Journal of Neurology*	Ten-year prognosis in multiple sclerosis: a better outcome in relapsing-remitting patients but not in primary progressive patients	Does not evaluate a DMT or any treatment
Montalban, X	2014	*Lancet Neurology*	Diagnosis and trials of clinically isolated syndrome	Editorial
Simon, J. H.	2015	*Multiple Sclerosis*	Ten-year follow-up of the 'minimal MRI lesion' subgroup from the original CHAMPS Multiple Sclerosis Prevention Trial	Does not evaluate a DMT or any treatment
Sorensen	2016	*European Journal of Neurology*	Minocycline added to subcutaneous interferon beta-1a in multiple sclerosis: randomized RECYCLINE study	Does not evaluate a DMT
Tintore	2015	Brain	Defining high, medium, and low impact prognostic factors for developing multiple sclerosis	DMT per regional guidelines
Kalincik	2012	*Clinical Neurology and Neurosurgery*	Interferon, azathioprine, and corticosteroids in multiple sclerosis: 6-year follow-up of the ASA cohort	Class IV study
Ehler, J.	2014	*Therapeutic Apheresis and Dialysis*	Therapeutic plasma exchange in glucocorticosteroid-unresponsive patients with	Drug evaluated is not a DMT

			clinically isolated syndrome	
Ehler	2015	*PLoS ONE*	Response to therapeutic plasma exchange as a rescue treatment in clinically isolated syndromes and acute worsening of multiple sclerosis: a retrospective analysis of 90 patients	Drug evaluated is not a DMT

Appendix e-7. Rules for determining confidence in evidence

- Modal modifiers used to indicate the final confidence in evidence in the conclusions
    - High confidence: highly likely or highly probable
    - Moderate confidence: likely or probable
    - Low confidence: possibly
    - Very low confidence: insufficient evidence
- Initial rating of confidence in the evidence for each intervention outcome pair
    - High: requires 2 or more Class I studies
    - Moderate: requires 1 Class I study or 2 or more Class II studies
    - Low: requires 1 Class II study or 2 or more Class III studies
    - Very low: requires only 1 Class III study or 1 or more Class IV studies
- Factors that could result in downgrading confidence by 1 or more levels
    - Consistency
    - Precision
    - Directness
    - Publication bias
    - Biological plausibility
- Factors that could result in downgrading confidence by 1 or more levels or upgrading confidence by 1 level
    - Magnitude of effect
    - Dose response relationship
    - Direction of bias

Appendix e-8. Evidence synthesis tables

Population	Study (first author, y)	Classification	Study name	Reason for downgrade/upgrade	No.	Intervention	Comparator	Outcome	Result
CIS									
	Leist, 2014[e111]	Class II	ORACLE MS	Less than 80% completion	410	Oral cladribine	Placebo	Time to develop MS	RR 0.33 (95% CI 0.21-0.51)
	Comi, 2009[e112]	Class I	PRECISE	NA	481	Glatiramer acetate subcutaneous daily	Placebo	Risk of conversion to MS over 3 y	RR 0.58 (95% CI 0.44, 0.75)
	Achiron, 2004[e113]	Class II	—	Lack of allocation concealment	90	IVIg	Placebo	Risk of conversion to MS over 1 y	RR 0.50 (95% CI 0.28, 0.88)
	Jacobs, 2000[e114]	Class II	CHAMPS	Lack of allocation concealment	383	Interferon beta-1a IM weekly	Placebo	Risk of conversion to MS over 3 y	RR 0.71 (95% CI 0.56, 0.89)
	Comi, 2001[e115]	Class I	ETOMS	NA	342	Interferon beta-1a subcutaneous 3 times per wk	Placebo	Risk of conversion to MS over 2 y	RR 0.55 (95% CI 0.38, 0.78)
	Kappos, 2006[e116]	Class II	BENEFIT	Lack of allocation concealment	468	Interferon beta-1b subcutaneous alternate d	Placebo	Risk of conversion to MS over 2 y	RR 0.59 (95% CI 0.46, 0.76)
	Miller, 2014[e117]	Class II	TOPIC	Less than 80% completion	411	Terifluno mide	Placebo	Risk of conversion to MS over 2 y	RR 0.64 (95% CI 0.44, 0.91)
RRMS									
	Cohen, 2012[e33]	Class I	CARE MS I	NA					
	CAMMS223, 2008[e106]	Class II	CAMMS	Allocation concealment unclear	914	Alemtuzumab	Interferon beta-1a subcutaneous 3 times per wk	One relapse at 2 y	RR 0.43 (95% CI 0.29, 0.61)
	Goodkin, 1991[e35]	Class II	—	Allocation concealment unclear	59	Azathioprine	P	One relapse at 2 y	RR 0.74 (95% CI 0.50, 1.07)
	Massacessi, 2014[e36]	Class II	—	Less than 80%					

				completion					
	Etemadifar, 2007[e37]	Class II	—	Allocation concealment unclear, more than 2 primary outcomes	244	Azathioprine	Interferon beta 1a	ARR	RR 0.64 (95% CI 0.44, 0.92)
	Romine, 1999[e38]	Class II	—	Allocation concealment unclear		Subcutaneous cladribine			
	Giovannoni, 2010[e39]	Class II	CLARITY	Allocation concealment unclear, baseline characteristics	1,376	Oral cladribine	Placebo	ARR	RMD 0.19 (95% CI 0.14, 0.24)
	Zivadinov, 2001[e40]	Class IV	—	Blinded only for radiologic outcomes, allocation concealment unclear; Class II for radiologic outcomes; Class IV for clinical outcomes	81	Pulse methylprednisolone	Placebo	One relapse at 2 y	1.16 (95% CI 0.851, 1.591)
	Sorensen, 2009[e41]	Class II	NORMIMS	Less than 80% completion					
	Ravnborg, 2010[e42]	Class II	MECOMBIN	Less than 80% completion	471	Pulse methylprednisoloneplus interferon beta-1a subcutaneous 3 times per wk	Placebo plus interferon beta-1a subcutaneous3 times per wk	One relapse at 2 y	RR 0.33 (95% CI 0.20, 0.54)
	Killian, 1988[e43]	Class III	—	Randomized trial, unblinded, primary outcome not defined, study group differed	14	Cyclophosphamide	Placebo	One relapse at 1 y	RR 0.67 (95% CI 0.25, 1.44)

	Gold, 2013[e44]	Class I	SELECT	NA	397	DAC-HYP	Placebo	Relapse at 1 y	RR 0.54 (95% CI 0.38, 0.75)
	Kappos, 2015[e45]	Class II	DECIDE	Less than 80% completion	1,841	DAC-HYP	Interferon beta-1a IM weekly	Relapse at 3 y	RR 0.67 (95% CI 0.60, 0.75)
	Fox, 2012[e46]	Class I	CONFIRM	NA					
	Gold, 2012[e47]	Class II	DEFINE	Less than 80% completion	1,540	Dimethyl fumarate	Placebo	Proportion with at least 1 relapse at 2 y	RR 0.64 (95% CI 0.54, 0.77)
	Kappos, 2010[e48]	Class I	FREEDOMS	NA					
	Calabresi, 2014[e49]	Class II	FREEDOMS II	Less than 80% completion, allocation concealment unclear	1,556	Fingolimod	Placebo	One relapse at 2 y	RR 0.57 (95% CI 0.50, 0.65)
	Kappos, 2010[e48]	Class I	FREEDOMS	NA					
	Saida, 2012[e50]	Class I	—	NA					
	Calabresi, 2014[e49]	Class II	FREEDOMS II	Less than 80% completion, allocation concealment unclear	1,670	Fingolimod	Placebo	ARR	RMD 0.21 (95% CI 0.16, 0.26)
	Cohen, 2010[e51]	Class I	TRANSFORMS	NA		Fingolimod	Interferon beta-1a IM weekly	One relapse at 12 mo	RR 0.58 (95% CI 0.46, 0.75)
	Fox, 2012[e46]	Class I	CONFIRM	NA					
	Khan, 2013[e52]	Class I	GALA	NA					
	Johnson, 1995[e53]	Class II	—	Allocation concealment unclear	2,368	Glatiramer acetate	Placebo	ARR	RMD 0.18 (95% CI 0.09, 0.28)
	Fox, 2012[e46]	Class I	CONFIRM	NA					
	Bornstein, 1987[e54]	Class II	—	Allocation concealment unclear					
	Johnson, 1995[e53]	Class II	—	Allocation concealment unclear	1,012	Glatiramer acetate	Placebo	One relapse at 2 y	RR 0.82 (95% CI 0.69, 0.97)
	Mikol, 2008[e55]	Class II	REGARD	Allocation concealment unclear	764	Glatiramer acetate	Interferon beta-1a subcutane	One relapse at 2 y	RR 0.93 (95% CI 0.77,1.14)

							ous 3 times per wk		
	Cavadid, 2009[e56]	Class II	—	Allocation concealment unclear					
	O'Connor, 2009[e57]	Class I	BEYOND	NA	1,420	Glatiramer acetate	Interferon beta-1b subcutaneous alternate day	One relapse at 2 y	RR 1.19 (95% CI 0.75,1.90)
	Fazekas, 1997[e60]	Class I	—	NA					
	Fazekas, 2008[e61]	Class I	—	NA					
	Achiron, 1998[e62]	Class II	—	More than 2 primary outcomes					
	Lewanska, 2002[e63]	Class II	—	Allocation concealment unclear	460	IVIg	Placebo	ARR	RMD 0.37 (95% CI -0.21,0.94)
	Fazekas, 1997[e60]	Class I	—	NA					
	Achiron, 1998[e62]	Class II	—	Allocation concealment unclear	190	IVIg	Placebo	One relapse at 2 y	RR 0.74 (95% CI 0.61,0.87)
	Vollmer, 2014[e64]	Class I	BRAVO	NA					
	Jacobs, 1996[e65]	Class II	—	Allocation concealment unclear	1,198	Interferon beta-1a IM weekly	Placebo	One relapse at 2 y	RR 0.79 (95% CI 0.68,0.92)
	PRISMS, 1998[e66]	Class I	PRISMS	NA	560	Ifnb1a subcutaneous 3 times per wk	Placebo	One relapse at 2 y	RR 0.84 (95% CI 0.77,0.92)
	Panitch, 2002[e67]	Class II	EVIDENCE	Less than 80% completion	677	Ifnb1a subcutaneous 3 times per wk	Interferon beta-1a IM weekly	One relapse at 1 y	RR 0.84 (95% CI 0.72,0.99)
	Group, 1993[e68]	Class II	—	Allocation concealment unclear	227	Ifnb1b subcutaneous alternate day	Placebo	One relapse at 2 y	RR 0.82 (95% CI 0.70,0.95)
	Currier, 1993[e69]	Class III	—	Relevant baseline characteristics not presented	20	Methotrexate	Placebo	One relapse at 18 mo	RR 0.35 (95% CI 0.10,1.04)

	Ashtari, 2011[e70]	Class III	—	Primary outcome not stated, allocation concealment unclear, did not follow noninferiority/equivalence trial methodology as described in risk of bias	80	Methotrexate	Interferon beta-1a IM weekly	Relapses over 12 mo	No statistically significant difference
	Millefiorini, 1997[e71]	Class I	—	NA	51	Mitoxantrone	Placebo	Proportion with at least one relapse at 2 y	RR 0.47 (95% CI 0.27,0.77)
	Etemadifar, 2010[e72]	Class II	—	Allocation concealment unclear					
	Remington, 2010[e73]	Class II	TIME MS	Allocation concealment unclear	50	Mycophenolate	Interferon beta-1a IM weekly	One relapse at 1 y	RR 0.63 (95% CI 0.18,2.23)
	Frohman, 2010[e74]	Class II	—	Allocation concealment unclear	35	Mycophenolate	Interferon beta-1a IM weekly	Relapse at 6 mo	RR 1.18 (95% CI 0.22,6.16)
	Polman, 2006[e75]	Class I	—	NA	942	Natalizumab	Placebo	One relapse at 2 y	RR 0.56 (95% CI 0.49,0.64)
	Hauser, 2016[e76]	Class I	OPERA I	NA					
	Hauser, 2016[e76]	Class I	OPERA II	NA	1,656	Ocrelizumab	Interferon beta-1a	ARR	RMD 0.130 (0.078,0.182)
	Calabresi, 2014[e77]	Class I	ADVANCE	NA	1,012	Pegylated interferon	Placebo	One relapse at 1 y	RR 0.62 (95% CI 0.49,0.78)
	Hauser, 2008[e78]	Class II	HERMES	Allocation concealment unclear	104	Rituximab	Placebo	Risk of relapse	RR 0.51 (95% CI 0.28,0.94)
	O'Connor, 2011[e79]	Class II	TEMSO	Allocation concealment unclear	1,088	Teriflunomide	Placebo	One relapse at 2 y	RR 0.88 (95% CI 0.79,0.98)
	O'Connor, 2006[e80]	Class II	—	Allocation concealment unclear					
	O'Connor, 2011[e79]	Class II	TEMSO	Less than 80% completion					

	Confavreux, 2014[e81]	Class II	TOWER	Less than 80% completion	1,597	Terifluno mide	Placebo	ARR	RMD 0.18 (95% CI 0.11,0.25)
People with RRMS with disease activity while on a DMT									
	Coles, 2012[e34]	Class I	CAREMS II	NA	628	Alemtuzumab 12 mg/d	Ifnb1a subcutaneous 3 times per wk	Relapse at 2 y	RR 0.59 (95% CI 0.51,0.69)
	Rudick, 2006[e83]	Class I	SENTINEL	NA	1,171	Interferon beta-1a IM weekly plus natalizumab	Ifnb1a subcutaneous 3 times per wk P	Relapse at 2 y	RR 0.62 (95% CI 0.55,0.70)
	Goodman, 2009[e84]	Class II	GLANCE	Allocation concealment unclear	110	Glatiramer acetate plus natalizumab	Glatiramer acetate plus placebo	Relapse at 6 mo	RR 0.80 (95% CI 0.42,1.52)
Progressive forms of MS (type)									
	Ellison, 1989[e85] (not specified)	Class II	—	Allocation concealment unclear, baseline characteristics	64	Azathioprine	Placebo	Relapses at 2 y	RR 0.53 (95% CI 0.25,1.10)
	Rice, 2000[e86] (SPMS)	Class II	—	Allocation concealment unclear	111	Subcutaneous cladribine	Placebo	Disability progression	RR 0.78 (95% CI 0.44,1.42)
	Goodkin, 1998[e87] (SPMS)	Class II	—	Allocation concealment unclear, baseline characteristics	108	High-dose corticosteroids	Low-dose corticosteroids	Relapses at 2 y	RR 0.33 (95% CI 0.08,1.44)
	Rahimdel, 2015[e88] (SPMS)	Class II	—	Allocation concealment unclear, no	71	Corticosteroids plus mitoxantrone	Placebo plus mitoxantrone	EDSS	RMD 0.03 (95% CI -0.91,0.97)

				primary endpoint					
	CCMSG, 1991[e89] (not specified)	Class II	—	Allocation concealment unclear					
	Likosky, 1991[e90]	Class II	—	Allocation concealment unclear	97	Cyclophosphamide	Placebo	Disability progression	RR 1.37 (95% CI 0.88,2.13)
	Bornstein, 1991[e91] (not specified)	Class II	—	Allocation concealment unclear	106	Glatiramer acetate	Placebo	Disability progression	RR 0.69 (95% CI 0.33,1.46)
	Wolinsky, 2007[e92] (PPMS)	Class II	PROMISE	Allocation concealment unclear, less than 80% completion	943	Glatiramer acetate	Placebo	Disability progression	RR 0.69 (95% CI 0.33,1.46)
	Lublin, 2016[e93] (PPMS)	Class II	INFORMS	Less than 80% completion rate	823	Fingolimod	Placebo	Proportion with confirmed disability	RR 1.00 (95% CI 0.91,1.09)
	Hommes, 2004[e94] (not specified)	Class II	—	Allocation concealment unclear					
	Pohlau, 2007[e95] (not specified)	Class II	—	Allocation concealment unclear, less than 80% completion	515	IVIg	Placebo	One relapse at 2 y	RR 0.96 (95% CI 0.79,1.16)
	Cohen, 2002[e96] (SPMS)	Class II	IMPACT	Allocation concealment unclear	436	Interferon beta-1a IM weekly	Placebo	Risk of relapse at 2 y	RR 0.72 (95% CI 0.54.0.95)
	Leary, 2003[e97]	Class I	—	NA	50	Interferon beta-1a IM weekly	Placebo	Disability progression	RR 1.19 (95% CI 0.78,1.21)
	Li, 2001[e98] (SPMS)	Class I	SPECTRIMS	NA	618	Interferon beta-1a subcutaneous 3 times per wk	Placebo	Mean number of relapses annually	RMD 0.21 (95% CI 0.15,0.27)
	Kappos, 1998[e99] (SPMS)	Class II	European Study Group	Less than 80% completion rate					
	NASG, 2004[e100] (SPMS)	Class II	NASG	Less than 80% completion rate	1,333	Interferon beta-1b subcutane	Placebo	1 relapse over 3 y	RR 0.84 (95% CI 0.75,0.93)

						ous alternate d			
	Montalban, 2009[e101]	Class II	—	Allocation concealment unclear	73	Interferon beta-1b subcutaneous alternate d	Placebo	Disability progression	RR 0.69 (95% CI 0.32,1.43)
	Goodkin, 1995[e102] (not specified)	Class II	—	Allocation concealment unclear	60	Methotrexate	P	Relapse over 2 y	RR 1.12 (95% CI 0.41,3.13)
	Hartung, 2002[e103] (worsening RRMS, SPMS)	Class II	MIMS	Allocation concealment unclear	124	Mitoxantrone	Placebo	Relapse over 2 y	RR 0.68 (95% CI 0.48,0.94)
	Montalban, 2017[e104]	Class II	ORATORIO	Less than 80% completion rate	731	Ocrelizumab	Placebo	Disability progression	RR 0.76 (95% CI 0.59,0.98)
	Hawker, 2009[e105] (PPMS)	Class II	OLYMPUS	Allocation concealment unclear	439	Rituximab	Placebo	Disease progression	RR 0.78 (95% CI 0.60,1.02)

Abbreviations: ARR = annualized relapse rate; CIS = clinically isolated syndrome; DAC HYP = daclizumab high-yield process; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; IM = intramuscular; IVIg – intravenous immunoglobulin; MS = multiple sclerosis; NA = not applicable; ORACLE MS = Oral Cladribine in Early Multiple Sclerosis; PRECISE = PRECISE = Evaluate Early Glatiramer Acetate Treatment in Delaying Conversion to Clinically Definite Multiple Sclerosis of Subjects Presenting With Clinically Isolated Syndrome; PPMS = primary progressive MS; RMD = raw mean difference; RRMS = relapsing−remitting MS; SPECTRIMS = Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-Beta-1a in MS; SPMS = secondary progressive MS.

Appendix e-9. Steps and rules for formulating recommendations

Constructing the recommendation and its rationale

Rationale for recommendation summarized in the rationale includes 3 categories of premises

- Evidence-based conclusions for the systematic review
- Stipulated axiomatic principles of care
- Strong evidence from related conditions not systematically reviewed

Actionable recommendations include the following mandatory elements

- The patient population that is the subject of the recommendation
- The person performing the action of the recommendation statement
- The specific action to be performed
- The expected outcome to be attained

Assigning a level of obligation

Modal modifiers used to indicate the final level of obligation (LOO)

- Level A: *Must*
- Level B: *Should*
- Level C: *May*
- Level U: No recommendation supported

LOO assigned by eliciting panel members' judgments regarding multiple domains, using a modified Delphi process. Goal is to attain consensus after a maximum of 3 rounds of voting. Consensus is defined by:

- ≥ 80% agreement on dichotomous judgments
- ≥80% agreement, within 1 point for ordinal judgments
- If consensus obtained, LOO assigned at the median. If not obtained, LOO assigned at the 10th percentile

Three steps used to assign final LOO

1. Initial LOO determined by the cogency of the deductive inference supporting the recommendation on the basis of ratings within 4 domains. Initial LOO anchored to lowest LOO supported by any domain.
    - Confidence in evidence. LOO anchored to confidence in evidence determined by modified form of the Grading of Recommendations Assessment, Development and Evaluation process
        - Level A: High confidence
        - Level B: Moderate confidence
        - Level C: Low confidence
        - Level U: Very low confidence
    - Soundness of inference assuming all premises are true. LOO anchored to proportion of panel members convinced of soundness of the inference
        - Level A: 100%
        - Level B: ≥ 80% to < 100%
        - Level C: ≥ 50% to < 80%
        - Level U or R: < 50%
    - Acceptance of axiomatic principles: LOO anchored to proportion of panel members who accept principles
        - Level A: 100%
        - Level B: ≥ 80% to < 100%
        - Level C: ≥ 50% to < 80%
        - Level U or R: < 50%
    - Belief that evidence cited from rerated conditions is strong: LOO anchored to proportion of panel members who believe the related evidence is strong
        - Level B: ≥ 80% to 100% (recommendations dependent on inferences from nonsystematically reviewed evidence cannot be anchored to a Level A LOO)
        - Level C: ≥ 50% to < 80%
        - Level U or R: < 50%

2. LOO is modified mandatorily on the basis of the judged magnitude of benefit relative to harm expected to be derived from complying with the recommendation
    - Magnitude relative to harm rated on 4-point ordinal scale
        - Large benefit relative to harm: benefit judged large, harm judged none
        - Moderate benefit relative to harm: benefit judged large, harm judged minimal; or benefit judged moderate, harm judged none
        - Small benefit relative to harm: benefit judged large, harm judged moderate; or benefit judged moderate, harm judged minimal; or benefit judged small, harm judged none
        - Benefit to harm judged too close to call: benefit and harm judged to be substantially similar
    - Regardless of cogency of the recommendation the LOO can be no higher than that supported by the rating of the magnitude of benefit relative to harm
        - Level A: large benefit relative to harm
        - Level B: moderate benefit relative to harm
        - Level C: small benefit relative to harm
        - Level U: too close to call
    - LOO can be increased by one grade if LOO corresponding to benefit relative to harm greater than LOO corresponding to the cogency of the recommendation

3. LOO optionally downgraded on the basis of the following domains
    - Importance of the outcome: critical, important, mildly important, not important
    - Expected variation in patient preferences: none, minimal, moderate, large
    - Financial burden relative to benefit expected: none, minimal, moderate, large
    - Availability of intervention: universal, usually, sometimes, limited

The rationale profiles shown in appendix e-10 summarize the results of panel ratings for each domain described above. The profiles also indicate the corresponding assigned LOOs. The last column in each indicates whether consensus was obtained for that domain.

Appendix e-10: Rationale of factors considered in developing the practice recommendations

In this appendix, *EVID* refers to evidence systematically reviewed; *RELA* to strong evidence derived from related conditions; *PRIN* to axiomatic principles of care; and *INFER* to inferences made from one or more statements in the recommendation rationale.

In the tables that follow, consensus is considered to have been reached if 80% or more of the guideline panel agree on the strength of a given domain. For nonpremise domains, intensity of shading corresponds to the number of panel members who were in agreement (shading of greater intensity indicates a larger number of panel members who reached agreement). The strength of the recommendation is anchored to the strength of the inference. The recommendation strength can be downgraded for any modifier; it can be upgraded only by one level for a moderate to large benefit relative to harm. In addition, domains include the premises and factors on which the recommendations are based. Please see appendix e-9 for the steps and rules for formulating recommendation strength.

PRACTICE RECOMMENDATIONS

Starting DMT recommendations

Starting: recommendation 1

Rationale

Receiving the diagnosis of MS is a stressful life event (PRIN).[e118,e119] People receiving major diagnoses may not recall much of the information given to them at the time (RELA).[e120] Providing information about DMT at a follow-up interaction is likely to allow a better understanding of these medications and their risks and benefits (PRIN).

Statement 1

Clinicians should counsel people with newly diagnosed MS about specific treatment options with DMT at a dedicated treatment visit (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ Benefit 0	Benefit > Harm 1	Benefit >> Harm 7	Benefit >>> Harm 7	Yes
Importance of outcomes	Not Important or 0	Mildly 3	Very 9	Critically Important 3	Yes
Variation in preferences	Large 0	Moderate 1	Modest 10	Minimal 4	Yes
Feasible	Rarely 1	Occasionally 1	Usually 10	Always 4	Yes
Cost relative to net benefit	Very Large 1	Large 1	Moderate 9	Small 4	Yes
Strength of recommendation	R/U	C	B	A	

Starting: recommendation 2

Rationale

Respecting patient preferences is an important component of care for chronic conditions (PRIN). Because of the variety of DMTs available (EVID), evaluating patient preferences may improve acceptance of and adherence to DMT (INFER).

Statement 2a

Clinicians must ascertain and incorporate/review preferences in terms of safety, route of administration, lifestyle, cost, efficacy, common AEs, and tolerability in the choice of DMT in people with MS being considered for DMT (Level A).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High 10	
Benefit relative to Harm	Harm ≥ Benefit 0	Benefit > Harm 1	Benefit >> Harm 4	Benefit >>> Harm 10	Yes
Importance of outcomes	Not Important or 0	Mildly 1	Very 6	Critically Important 8	Yes
Variation in preferences	Large 0	Moderate 1	Modest 3	Minimal 11	Yes
Feasible	Rarely 0	Occasionally 1	Usually 4	Always 10	Yes
Cost relative to net benefit	Very Large 0	Large 1	Moderate 4	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

Statement 2b

Clinicians must engage in an ongoing dialogue regarding treatment decisions throughout the disease course with people with MS (Level A).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High 10	
Benefit relative to Harm	Harm ≥ Benefit 0	Benefit > Harm 0	Benefit >> Harm 1	Benefit >>> Harm 14	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 5	Critically Important 10	Yes
Variation in preferences	Large 1	Moderate 0	Modest 3	Minimal 11	Yes
Feasible	Rarely 0	Occasionally 0	Usually 4	Always 11	Yes
Cost relative to net benefit	Very Large 0	Large 0	Moderate 3	Small 12	Yes
Strength of recommendation	R/U	C	B	A	

Starting: recommendation 3

Rationale

DMTs reduce but do not eliminate MS relapses and MRI activity (EVID). Educating people with MS about realistic expectations regarding DMT effects is important (PRIN).[e121] Clinicians should inform people with MS that they may still need symptomatic treatment in addition to DMT (PRIN).[e122]

Statement 3a

Clinicians should counsel people with MS that DMTs are prescribed to reduce relapses and new MRI lesion activity. DMTs are not prescribed for symptom improvement in people with MS (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference and Evidence	Very low	Low	Moderate	High 10	
Benefit relative to Harm	Harm ≥ Benefit 0	Benefit > Harm 1	Benefit >> Harm 3	Benefit >>> Harm 11	Yes
Importance of outcomes	Not important or 0	Mildly 1	Very 10	Critically 4	Yes
Variation in preferences	Large 0	Moderate 0	Modest 3	Minimal 12	Yes
Feasible	Rarely 0	Occasionally 0	Usually 7	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 5	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

Statement 3b

Clinicians must counsel people with MS on DMTs to notify the clinicians of new or worsening symptoms (Level A).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference and Evidence	Very low	Low	Moderate	High 10	
Benefit relative to Harm	Harm ≥ Benefit 0	Benefit > Harm 1	Benefit >> Harm 2	Benefit >>> Harm 12	Yes
Importance of outcomes	Not important or 0	Mildly 1	Very 5	Critically 9	Yes
Variation in preferences	Large 0	Moderate 1	Modest 4	Minimal 10	Yes
Feasible	Rarely 0	Occasionally 0	Usually 6	Always 9	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 5	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

Starting: recommendation 4

Rationale

Because DMT use requires commitment to ongoing therapy and an understanding of AEs (PRIN) (EVID), readiness to initiate DMT and factors causing reluctance may have an impact on adherence to DMT use (INFER).

Statement 4

Clinicians should evaluate readiness or reluctance to initiate DMT and counsel on its importance in people with MS who are candidates to initiate DMT (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ Benefit 1	Benefit > Harm 0	Benefit >> Harm 0	Benefit >>> Harm 14	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 6	Critically Important 9	Yes
Variation in preferences	Large 1	Moderate 1	Modest 4	Minimal 9	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 12	Yes
Cost relative to net benefit	Very Large 0	Large 0	Moderate 3	Small 12	Yes
Strength of recommendation	R/U	C	B	A	

Starting: recommendation 5

Rationale

In people with MS, comorbid disease, such as depression, anxiety, and vascular risk factors, and adverse health behaviors (e.g., physical inactivity, smoking) are associated with worse outcomes (RELA).[e123,e124] Addressing depression before initiating DMT may improve decision making and adherence to DMT (INFER). Concomitant medications may have important interactions with DMTs (RELA).[e107]

Statement 5

Clinicians should counsel about comorbid disease, adverse health behaviors, and potential interactions of the DMT with concomitant medications when people with MS initiate DMT (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ Benefit 0	Benefit > Harm 0	Benefit >> Harm 2	Benefit >>> Harm 13	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 7	Critically Important 8	Yes
Variation in preferences	Large 0	Moderate 0	Modest 6	Minimal 9	Yes
Feasible	Rarely 0	Occasionally 1	Usually 4	Always 10	Yes
Cost relative to net benefit	Very Large 0	Large 0	Moderate 4	Small 11	Yes
Strength of recommendation	R/U	C	B	A	

Starting: recommendation 6

Rationale

Because DMT requires adherence to treatment to provide full efficacy (INFER), and because that adherence to treatment may be an issue for people with MS (RELA),[e125,e126] discussing adherence issues before initiating DMT is part of good clinical practice (INFER). Efforts to increase adherence may improve outcomes (INFER).

Statement 6a

Clinicians should evaluate barriers to adherence to DMT in people with MS (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High 10	
Benefit relative to Harm	Harm ≥ Benefit 0	Benefit > Harm 0	Benefit >> Harm 1	Benefit >>> Harm 14	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 10	Critically Important 5	Yes
Variation in preferences	Large 0	Moderate 0	Modest 3	Minimal 12	Yes
Feasible	Rarely 0	Occasionally 0	Usually 5	Always 10	Yes
Cost relative to net benefit	Very Large 0	Large 0	Moderate 2	Small 13	Yes
Strength of recommendation	R/U	C	B	A	

Statement 6b

Clinicians should counsel on the importance of adherence to DMT when people with MS initiate DMTs (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High 10	
Benefit relative to Harm	Harm ≥ Benefit 0	Benefit > Harm 0	Benefit >> Harm 1	Benefit >>> Harm 14	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 10	Critically Important 5	Yes
Variation in preferences	Large 0	Moderate 0	Modest 3	Minimal 12	Yes
Feasible	Rarely 0	Occasionally 0	Usually 5	Always 10	Yes
Cost relative to net benefit	Very Large 0	Large 0	Moderate 2	Small 13	Yes
Strength of recommendation	R/U	C	B	A	

Starting: recommendation 7

Rationale

People presenting with a first demyelinating event and who do not meet the 2010 International Criteria for MS are commonly encountered in clinical practice. Multiple prospective observational trials have consistently confirmed that people with a single clinical demyelinating event with 2 or more brain or spinal cord lesions remain at increased risk of a future MS diagnosis, with the highest risk incurred within 5 years of the initial event.[e127–e130] Evidence from multiple Class I and II trials confirms that DMTs are associated with a significant delay in second clinical relapse or new brain MRI-detected lesions in people with a first demyelinating event who are considered to be at high risk for MS on the basis of brain MRI-detected lesions (EVID). There is insufficient evidence concerning the comparative efficacy of specific DMTs for this purpose. Decisions concerning the selection of specific DMTs for people presenting with a first demyelinating event should abide by prescribing principles espoused in other recommendations (RELA). Individuals presenting with an incident demyelinating event who have no brain lesions are at low risk of a future MS diagnosis.

Statement 7a

Clinicians should discuss the benefits and risks of DMTs for people with a single clinical demyelinating event with 2 or more brain lesions that have imaging characteristics consistent with MS (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference and Evidence	Very low	Low	Moderate	High 10	
Benefit relative to Harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 6	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or 0	Mildly 1	Very 5	Critically 9	Yes
Variation in preferences	Large 0	Moderate 2	Modest 9	Minimal 4	Yes
Feasible	Rarely 0	Occasionally 1	Usually 10	Always 4	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 10	Small 4	Yes
Strength of recommendation	R/U	C	B	A	

Statement 7b

After discussing the risks and benefits, clinicians should prescribe DMT to people with a single clinical demyelinating event and 2 or more brain lesions characteristic of MS who decide they want this therapy (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference and Evidence	Very low	Low	Moderate	High 10	
Benefit relative to Harm	Harm ≥ benefit 0	Benefit > harm 2	Benefit >> harm 7	Benefit >>> harm 6	Yes
Importance of outcomes	Not important or 0	Mildly 1	Very 7	Critically 7	Yes
Variation in preferences	Large 2	Moderate 4	Modest 8	Minimal 1	Yes
Feasible	Rarely 0	Occasionally 2	Usually 11	Always 2	Yes
Cost relative to net benefit	Very large 2	Large 3	Moderate 10	Small 0	Yes
Strength of recommendation	**R/U**	**C**	**B**	**A**	

Starting: recommendation 8

Rationale

The benefit of initiating DMT has not been studied in currently untreated people with CIS or relapsing forms of MS who have not had relapses in 2 or more years and do not have active new MRI lesion activity on recent imaging (EVID). In such people, it is unknown what the risk of harm is from initiating DMTs, including AEs, major AEs, and burden of taking a long-term medication, relative to the benefit of reducing relapse rate (INFER).

Statement 8

Clinicians may recommend serial imaging at least annually for the first 5 years and close follow-up rather than initiating DMT in people with CIS or relapsing forms of MS who are not on DMT, have not had relapses in the preceding 2 years, and do not have active new MRI lesion activity on recent imaging (Level C).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference and Evidence	Very low	Low	Moderate	High 10	
Benefit relative to Harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 9	Benefit >>> harm 5	Yes
Importance of outcomes	Not important or 0	Mildly 0	Very 9	Critically 6	Yes
Variation in preferences	Large 0	Moderate 9	Modest 5	Minimal 1	Yes
Feasible	Rarely 0	Occasionally 1	Usually 10	Always 4	Yes
Cost relative to net benefit	Very large 0	Large 3	Moderate 10	Small 2	Yes
Strength of recommendation	R/U	C	B	A	

Starting: recommendation 9

Rationale

Multiple studies of DMTs in people with relapsing forms of MS who have had recent relapses or MRI activity or both (EVID) have shown benefit of DMT in terms of reducing relapses and reducing MRI activity (EVID). This includes people with a single clinical episode who meet 2010 International Criteria for MS (EVID).[e117,e131]

Statement 9

Clinicians should offer DMTs to people with relapsing forms of MS with recent clinical relapses or MRI activity (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High 10	
Benefit relative to Harm	Harm ≥ Benefit 1	Benefit > Harm 0	Benefit >> Harm 4	Benefit >>> Harm 11	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 6	Critically Important 10	Yes
Variation in preferences	Large 0	Moderate 2	Modest 10	Minimal 4	Yes
Feasible	Rarely 0	Occasionally 0	Usually 14	Always 2	Yes
Cost relative to net benefit	Very Large 1	Large 6	Moderate 8	Small 1	Yes
Strength of recommendation	R/U	C	B	A	

Starting: recommendation 10

Rationale

Lack of adherence to treatment of chronic diseases is a wide-ranging problem (RELA). The result of poor adherence is reduced effectiveness and increased health care costs (RELA).[e132–e136] Regular interactions and assessments by clinicians facilitate prompt identification and treatment of AEs, increased tolerability of the medication, and safety monitoring (RELA).[e121,e137] Some DMTs for MS have specific REMS with recommendations for follow-up frequency (RELA).[e138–e141]

Statement 10a

Clinicians should monitor for medication adherence, AEs, tolerability, safety, and effectiveness of the therapy in people with MS on DMTs (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ Benefit 0	Benefit > Harm 0	Benefit >> Harm 2	Benefit >>> Harm 13	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 8	Critically Important 7	Yes
Variation in preferences	Large 0	Moderate 1	Modest 3	Minimal 11	Yes
Feasible	Rarely 0	Occasionally 0	Usually 4	Always 11	Yes
Cost relative to net benefit	Very Large 0	Large 0	Moderate 5	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

Statement 10b

Clinicians should follow up either annually or according to medication-specific REMS in people with MS on DMTs (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ Benefit 0	Benefit > Harm 0	Benefit >> Harm 4	Benefit >>> Harm 11	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 8	Critically Important 7	Yes
Variation in preferences	Large 0	Moderate 2	Modest 7	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 0	Usually 7	Always 8	Yes
Cost relative to net benefit	Very Large 0	Large 0	Moderate 8	Small 7	Yes
Strength of recommendation	R/U	C	B	A	

Starting: recommendation 11

Rationale

DMTs have potential risks in pregnant women (RELA)[e142] to varying degrees. Discussing pregnancy with women with MS before initiating DMT is a part of good clinical practice (INFER). If women with MS are planning pregnancy soon, DMT use may need to be deferred until after pregnancy (RELA).[e143] In addition, because DMTs vary in terms of pregnancy risks (RELA),[e142] DMT choice may be influenced by plans for pregnancy (INFER).

Statement 11

Clinicians should monitor the reproductive plans of women with MS and counsel regarding reproductive risks and use of birth control during DMT use in women of childbearing potential who have MS (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ Benefit 0	Benefit > Harm 0	Benefit >> Harm 5	Benefit >>> Harm 10	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 9	Critically Important 6	Yes
Variation in preferences	Large 0	Moderate 3	Modest 7	Minimal 5	Yes
Feasible	Rarely 0	Occasionally 0	Usually 6	Always 9	Yes
Cost relative to net benefit	Very Large 0	Large 0	Moderate 3	Small 12	Yes
Strength of recommendation	R/U	C	B	A	

Starting: recommendation 12

Rationale

Chemotherapy, such as cyclophosphamide, may affect male fertility (RELA).[e144] With teriflunomide treatment, there may be a risk of teratogenicity from male sperm, which could last for 2 years after treatment cessation if the patient is not treated with chelation therapy (RELA).[e145]

Statement 12

Clinicians should counsel men with MS on their reproductive plans regarding treatment implications before initiating treatment with teriflunomide or cyclophosphamide (Level B).*

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High 10	
Benefit relative to Harm	Harm ≥ Benefit 0	Benefit > Harm 1	Benefit >> Harm 2	Benefit >>> Harm 12	Yes
Importance of outcomes	Not Important or 0	Mildly 1	Very 5	Critically Important 9	Yes
Variation in preferences	Large 0	Moderate 2	Modest 2	Minimal 11	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 12	Yes
Cost relative to net benefit	Very Large 0	Large 0	Moderate 4	Small 11	Yes
Strength of recommendation	R/U	C	B	A	

*Level A recommendations cannot be based on related evidence (RELA) alone. Recommendation downgraded to Level B.

Starting: recommendation 13

Rationale

Post approval of mitoxantrone, new evidence has shown a high risk of cardiomyopathy, ovarian failure, male infertility, chromosomal aberrations, and promyelocytic leukemia (RELA)[e146–e149]

associated with mitoxantrone use. Other effective medications with lower risk, which were unavailable at the time of FDA approval of mitoxantrone (RELA), are now available for treating MS.

Statement 13

Because of the high frequency of severe AEs, clinicians should not prescribe mitoxantrone to people with MS unless the potential therapeutic benefits greatly outweigh the risks (Level B).*

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference and Evidence	Very low	Low	Moderate	High 10	
Benefit relative to Harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 13	Yes
Importance of outcomes	Not important or 0	Mildly 0	Very 3	Critically 12	Yes
Variation in preferences	Large 0	Moderate 0	Modest 4	Minimal 11	Yes
Feasible	Rarely 0	Occasionally 0	Usually 1	Always 14	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 13	Yes
Strength of recommendation	R/U	C	B	A	

*Level A recommendations cannot be based on related evidence (RELA) alone. Recommendation downgraded to Level B.

Starting: recommendation 14

Rationale

MS is a heterogeneous disease and is characterized by highly variable degrees of disease activity in the relapsing phase and by varying rates of worsening during the progressive phases

(RELA).[e150,e151] Definitions of highly active MS vary and can include measures of relapsing activity and MRI markers of disease activity, such as numbers of gadolinium-enhanced lesions (RELA).[e152,e153] Subgroup analyses from phase III pivotal trials of alemtuzumab, fingolimod, and natalizumab showed a reduction in relapses and MRI measures in people with MS with highly active disease (RELA).[e154–e156] Compared with interferon beta therapy, treatment with these therapies resulted in more favorable outcomes in the subgroup of people with MS with highly active disease (RELA).[e33,e34,e51,e83] However, the risks and benefits of each treatment strategy need to be considered on a patient-by-patient basis (PRIN).

Statement 14

Clinicians should prescribe alemtuzumab, fingolimod, or natalizumab for people with MS with highly active MS (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ Benefit 0	Benefit > Harm 0	Benefit >> Harm 11	Benefit >>> Harm 4	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 9	Critically Important 6	Yes
Variation in preferences	Large 1	Moderate 4	Modest 10	Minimal 0	Yes
Feasible	Rarely 0	Occasionally 1	Usually 12	Always 2	Yes
Cost relative to net benefit	Very Large 1	Large 5	Moderate 8	Small 1	Yes
Strength of recommendation	R/U	C	B	A	

Starting: recommendation 15

Rationale

DMTs should be available to all people with relapsing forms of MS (PRIN). Because of disparities in health care provision in different settings (RELA),[e1] there may be situations where approved DMTs are not available to an individual (INFER). In these situations, DMTs may be obtained with support from the pharmaceutical industry or from organizations, such as the National Organization of Rare Diseases, county organizations, or government organizations (INFER). If such support is unavailable, certain lower cost medications may become a choice for care (INFER). Azathioprine has mixed results and evidence for which confidence is low to support efficacy in relapsing forms of MS (EVID). Cladribine has evidence of benefit for both the oral and parenteral formulations, but currently only the parenteral formulations are available (EVID).

Statement 15a

Clinicians may direct people with MS who are candidates for DMTs to support programs (Level C).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High 10	
Benefit relative to Harm	Harm ≥ Benefit 0	Benefit > Harm 2	Benefit >> Harm 4	Benefit >>> Harm 9	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 13	Critically Important 2	Yes
Variation in preferences	Large 0	Moderate 3	Modest 5	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 8	Usually 7	Always 0	Yes
Cost relative to net benefit	Very Large 0	Large 1	Moderate 6	Small 8	Yes
Strength of recommendation	R/U	C	B	A	

Statement 15b

Clinicians may recommend azathioprine or cladribine for people with relapsing forms of MS who do not have access to approved DMTs (Level C).*

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference and Evidence	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ benefit 1	Benefit > harm 3	Benefit >> harm 7	Benefit >>> harm 4	No
Importance of outcomes	Not important or 0	Mildly 1	Very 10	Critically 4	Yes
Variation in preferences	Large 2	Moderate 5	Modest 8	Minimal 0	Yes
Feasible	Rarely 0	Occasionally 3	Usually 11	Always 1	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 12	Small 2	Yes
Strength of recommendation	R/U	C	B	A	

*Failed to meet consensus because of benefit relative to harm. Recommendation downgraded to Level C.

Starting: recommendation 16

Rationale

People with MS with a positive JCV antibody test have a higher risk of developing PML while using natalizumab, particularly people with MS who have been treated for more than 2 years or have had prior immunosuppressive treatment (EVID). There are now other highly effective treatments that may be used that have not been shown to have a similar PML risk (EVID). The PML risk increases with the level of anti-JCV antibody response (index). For example, in those using natalizumab for 25 to 36 months with no prior use of immunosuppressants, the PML risk is 0.2 per 1,000 in those with an index of 0.9 or less, 0.3 per 1,000 in those with an index of 0.9 to 1.5, and 3 per 1,000 in those with an index greater than 1.5 (RELA). Further data on risk assessment is likely to become available over time to help inform treatment decisions in this area (INFER).

Statement 16

Clinicians may initiate natalizumab treatment in people with MS with positive anti-JCV antibody indexes above 0.9 only when there is a reasonable chance of benefit compared with the low but serious risk of PML (Level C).*

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference and Evidence	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ benefit 0	Benefit > harm 3	Benefit >> harm 5	Benefit >>> harm 7	Yes
Importance of outcomes	Not important or 0	Mildly 1	Very 4	Critically 10	Yes
Variation in preferences	Large 2	Moderate 3	Modest 7	Minimal 3	No
Feasible	Rarely 0	Occasionally 2	Usually 8	Always 5	Yes
Cost relative to net benefit	Very large 0	Large 4	Moderate 9	Small 2	Yes
Strength of recommendation	R/U	C	B	A	

*Failed to meet consensus because of variation in patient preferences. Recommendation downgraded to Level C.

Starting: recommendation 17

Rationale

Ocrelizumab is the only DMT shown to alter disease progression in individuals with PPMS who are ambulatory (EVID). The RCT of rituximab in PPMS was promising but inconclusive (EVID).[e105] Although RCTs of fingolimod, glatiramer acetate, and interferon beta-1b failed to demonstrate an effect on disability progression in individuals with PPMS, significant effects on MRI measures of disease activity were found with all 3 treatments (EVID).[e92,e93,e101] Clinical trials have not evaluated the benefits of DMT in individuals with PPMS who are nonambulatory

with respect to other clinically relevant domains, including vision, cognition, and upper limb function (EVID).

Statement 17

Clinicians should offer ocrelizumab to people with PPMS who are likely to benefit from this therapy unless there are risks of treatment that outweigh the benefits (Level B).*

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference and Evidence	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ benefit 1	Benefit > harm 1	Benefit >> harm 10	Benefit >>> harm 3	Yes
Importance of outcomes	Not important or 0	Mildly 2	Very 12	Critically 1	Yes
Variation in preferences	Large 2	Moderate 2	Modest 9	Minimal 2	No
Feasible	Rarely 0	Occasionally 4	Usually 10	Always 1	Yes
Cost relative to net benefit	Very large 2	Large 7	Moderate 6	Small 0	Yes
Strength of recommendation	R/U	C	B	A	

*Failed to meet consensus because of variation in patient preferences. The recommendation is "<should> offer ocrelizumab." The comments made during the modified Delphi voting on recommendations indicated that the failure to meet consensus because of variation in patient preferences was resulted from panelists' varying interpretations of the recommendation. In their comments, panelists agreed that people with MS want to know their treatment options; whether people with MS accept the offered treatment is their decision and where the variation in preference lies. The wording and level (Level B) of this recommendation remain as stated.

Switching DMT recommendations

Switching: recommendation 1

Rationale

Ongoing disease activity, measured either by clinical relapses or new MRI-detected lesions (including unequivocally new T2 or new gadolinium-enhanced lesions), could lead to physical or cognitive worsening over time (RELA).[e157−e160] Now that several DMTs are available and have demonstrated efficacy for the prevention of clinical relapses and new MRI-detected lesions (EVID), physicians and people with MS often face the decision of switching from one DMT to another because of a perceived lack of efficacy. Such lack of response to a DMT has been difficult to define, as most people with MS are not free of all disease activity; investigators have considered using the number of clinical attacks or new MRI-detected lesions in the preceding 12 months to define lack of response (RELA).[e158,e160] DMTs take a variable amount of time to become clinically active, and new lesion formation may occur after initiation but before the time of full efficacy, confounding interpretation of follow-up MRI scans (RELA).[e34,e51,e53,e66,e81,e161] Consequently, many clinicians obtain new baseline MRI 3 to 6 months after initiating DMTs to monitor from a "treated" baseline (RELA).[e162] The optimal interval for ongoing monitoring is uncertain, as short-term stability as evidenced by clinical and MRI criteria may not consistently predict long-term stability (INFER). In addition, because of different mechanisms of activity among the DMTs, monitoring strategies may vary (INFER).

Statement 1a

Clinicians should monitor MRI disease activity from the clinical onset of disease to detect the accumulation of new lesions in order to inform treatment decisions in people with MS using DMTs (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference and Evidence	Very low	Low	Moderate	High 10	
Benefit relative to Harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 8	Benefit >>> harm 7	Yes
Importance of outcomes	Not important or 0	Mildly 1	Very 11	Critically 3	Yes
Variation in preferences	Large 0	Moderate 6	Modest 7	Minimal 2	Yes
Feasible	Rarely 0	Occasionally 2	Usually 11	Always 2	Yes
Cost relative to net benefit	Very large 0	Large 3	Moderate 10	Small 2	Yes
Strength of recommendation	R/U	C	B	A	

Statement 1b

Clinicians should recognize that relapses or new MRI-detected lesions may develop after initiation of a DMT and before the treatment becomes effective in people with MS who are using DMTs (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ Benefit 0	Benefit > Harm 0	Benefit >> Harm 6	Benefit >>> Harm 9	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 10	Critically Important 5	Yes
Variation in preferences	Large 0	Moderate 1	Modest 9	Minimal 5	Yes
Feasible	Rarely 1	Occasionally 0	Usually 8	Always 7	Yes
Cost relative to net benefit	Very Large 0	Large 1	Moderate 7	Small 7	Yes
Strength of recommendation	R/U	C	B	A	

Statement 1c

Clinicians should discuss switching from one DMT to another in people with MS who have been using a DMT long enough for the treatment to take full effect and are adherent to their therapy when they experience 1 or more relapses, 2 or more unequivocally new MRI-detected lesions, or increased disability on examination, over a 1-year period of using a DMT (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ Benefit 1	Benefit > Harm 0	Benefit >> Harm 10	Benefit >>> Harm 4	Yes
Importance of outcomes	Not Important or 0	Mildly 1	Very 11	Critically Important 3	Yes
Variation in preferences	Large 0	Moderate 5	Modest 10	Minimal 0	Yes
Feasible	Rarely 0	Occasionally 2	Usually 12	Always 1	Yes
Cost relative to net benefit	Very Large 0	Large 3	Moderate 12	Small 0	Yes
Strength of recommendation	R/U	C	B	A	

Switching: recommendation 2

Rationale

None of the available DMTs is completely effective against relapses and MRI activity (EVID). When a patient shows breakthrough disease activity (continued relapses, MRI activity), trying a medication with a different mechanism or efficacy profile may be beneficial (INFER). Although all possible clinical scenarios cannot be answered by drug trials, current evidence supports higher efficacy of alemtuzumab, natalizumab, fingolimod,, and ocrelizumab compared with previously approved self-injectable DMTs (EVID high). Tolerability and likelihood of adherence are other factors that are important in decisions about switching DMTs (PRIN). Physician judgment and patient preferences are critical in this process (PRIN).

Statement 2

Clinicians should evaluate the degree of disease activity, adherence, AE profiles, and mechanism of action of DMTs when switching DMTs in people with MS with breakthrough disease activity during DMT use (Level B).*

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference and Evidence	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 5	Benefit >>> harm 10	Yes
Importance of outcomes	Not important or 0	Mildly 0	Very 9	Critically 6	Yes
Variation in preferences	Large 1	Moderate 3	Modest 6	Minimal 5	No
Feasible	Rarely 0	Occasionally 1	Usually 9	Always 5	Yes
Cost relative to net benefit	Very large 1	Large 1	Moderate 7	Small 6	Yes
Strength of recommendation	R/U	C	B	A	

*Failed to meet consensus because of variation in patient preferences. The recommendation is that clinicians evaluate a number of clinical and pharmacologic characteristics when switching medications in people with MS with breakthrough disease activity. Patient preference does not affect evaluation recommendations. Patient preference will affect the decision of the medication choice. This recommendation stands at Level B.

Switching: recommendation 3

Rationale

Multiple DMTs are available for MS treatment (EVID). Switching therapies may be appropriate in people with MS who are experiencing AEs or complications with a DMT (INFER). Adherence to injectable DMTs is often incomplete (RELA).[e163] Injection fatigue (physical or emotional) or injection-related pain or discomfort (EVID) may be a common reason for poor adherence (INFER).

Statement 3

Clinicians should discuss a change to noninjectable or less frequently injectable DMTs in people with MS who report intolerable discomfort with the injections or in those who report "injection fatigue" on injectable DMTs (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference and Evidence	Very low	Low	Moderate	High 10	
Benefit relative to Harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 7	Benefit >>> harm 7	Yes
Importance of outcomes	Not important or 0	Mildly 1	Very 11	Critically 3	Yes
Variation in preferences	Large 1	Moderate 1	Modest 9	Minimal 4	Yes
Feasible	Rarely 0	Occasionally 1	Usually 9	Always 5	Yes
Cost relative to net benefit	Very large 1	Large 1	Moderate 10	Small 3	Yes
Strength of recommendation	R/U	C	B	A	

Switching: recommendation 4

Rationale

Adherence to a DMT may also be affected by medication AEs (RELA).[e126,e137] All DMTs have common AEs that may affect adherence (table e-2) (EVID).

Statement 4a

Clinicians should inquire about medication AEs with people with MS who are taking a DMT and attempt to manage these AEs, as appropriate (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High 10	
Benefit relative to Harm	Harm ≥ Benefit 0	Benefit > Harm 0	Benefit >> Harm 2	Benefit >>> Harm 13	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 11	Critically Important 4	Yes
Variation in preferences	Large 0	Moderate 1	Modest 4	Minimal 10	Yes
Feasible	Rarely 0	Occasionally 1	Usually 5	Always 9	Yes
Cost relative to net benefit	Very Large 0	Large 1	Moderate 5	Small 9	Yes
Strength of recommendation	R/U	C	B	A	

Statement 4b

Clinicians should discuss a medication switch with people with MS for whom these AEs negatively influence adherence (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High 10	
Benefit relative to Harm	Harm ≥ Benefit 0	Benefit > Harm 0	Benefit >> Harm 5	Benefit >>> Harm 9	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 10	Critically Important 4	Yes
Variation in preferences	Large 1	Moderate 0	Modest 7	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 2	Usually 6	Always 6	Yes
Cost relative to net benefit	Very Large 0	Large 2	Moderate 8	Small 4	Yes
Strength of recommendation	R/U	C	B	A	

Switching: recommendation 5

Rationale

Persistent laboratory abnormalities, such as elevated liver enzymes and decreased white blood cell counts, may prompt a discussion about switching DMT (table e-2) (EVID).

Statement 5a

Clinicians should monitor laboratory abnormalities found on requisite laboratory surveillance (as outlined in the medication's package insert) in people with MS who are using a DMT (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ Benefit 0	Benefit > Harm 0	Benefit >> Harm 2	Benefit >>> Harm 13	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 9	Critically Important 6	Yes
Variation in preferences	Large 0	Moderate 0	Modest 8	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 0	Usually 5	Always 10	Yes
Cost relative to net benefit	Very Large 0	Large 0	Moderate 9	Small 6	Yes
Strength of recommendation	R/U	C	B	A	

Statement 5b

Clinicians should discuss switching DMT or reducing dosage or frequency (where there are data on different doses [e.g., interferons, teriflunomide, azathioprine]) when there are persistent laboratory abnormalities (Level B).*

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ Benefit 1	Benefit > Harm 1	Benefit >> Harm 3	Benefit >>> Harm 9	Yes
Importance of outcomes	Not Important or 0	Mildly 2	Very 7	Critically Important 5	Yes
Variation in preferences	Large 1	Moderate 2	Modest 8	Minimal 3	No
Feasible	Rarely 0	Occasionally 0	Usually 10	Always 4	Yes
Cost relative to net benefit	Very Large 2	Large 0	Moderate 9	Small 3	Yes
Strength of recommendation	R/U	C	B	A	

*There is no substantial lack of consensus in variation in patient preferences because more than 80% of respondents thought variation in preference is minimal or modest. Recommendation stands at Level B.

Switching: recommendation 6

Rationale

Progressive multifocal leukoencephalopathy (PML) is a serious safety concern (RELA)[e164] that may affect compliance and necessitate consideration of a treatment switch (INFER). The PML risk is estimated at 4 per 1,000 overall with natalizumab[e165]; however, the presence and index level of JCV antibodies, longer duration use, and prior immunosuppression increase PML risk with natalizumab even further (RELA).[e164] Recent updated risk estimates show that the risk of developing PML is small at antibody index values of 0.9 or less, and increases with index values greater than 1.5 in people with MS who have been treated with natalizumab for more than 2 years (RELA).[e107] There are rare reports of PML with the use of both fingolimod and dimethyl fumarate (RELA).[e166–e169] There are reports of PML in people with MS who are HIV-negative and using rituximab for conditions other than MS (RELA).[e170] There is a potential risk of PML with ocrelizumab use, particularly with prior immunosuppressive therapies, based on its similarity to other anti-CD20 antibodies (INFER).[e139]

Statement 6a

Clinicians should counsel people with MS considering natalizumab, fingolimod, rituximab, ocrelizumab, and dimethyl fumarate about the PML risk associated with these agents (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ Benefit 2	Benefit > Harm 0	Benefit >> Harm 3	Benefit >>> Harm 10	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 4	Critically Important 11	Yes
Variation in preferences	Large 1	Moderate 1	Modest 2	Minimal 11	Yes
Feasible	Rarely 0	Occasionally 1	Usually 1	Always 13	Yes
Cost relative to net benefit	Very Large 1	Large 0	Moderate 1	Small 13	Yes
Strength of recommendation	R/U	C	B	A	

Statement 6b

Clinicians should discuss switching to a DMT with a lower PML risk with people with MS taking natalizumab who are or become JCV antibody positive, especially with an index of above 0.9 while on therapy (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference and Evidence	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ benefit 1	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or 0	Mildly 0	Very 5	Critically 10	Yes
Variation in preferences	Large 0	Moderate 2	Modest 5	Minimal 8	Yes
Feasible	Rarely 0	Occasionally 1	Usually 7	Always 7	Yes
Cost relative to net benefit	Very large 1	Large 0	Moderate 7	Small 7	Yes
Strength of recommendation	R/U	C	B	A	

Switching: recommendation 7

Rationale

Immunosuppressive medications may increase the risk of opportunistic infection and malignancy, especially with prolonged use (EVID, PRIN). These risks are often undefined with newer medication (INFER). Cases of cryptococcal infections have been reported with fingolimod use (RELA).[e171] Herpes family virus infections have been reported with fingolimod and natalizumab use (RELA).[e172–e174] A potential increased risk of basal cell carcinoma was recently added to the fingolimod product label (RELA).[e169]

Statement 7a

Clinicians should counsel that new DMTs without long-term safety data have an undefined risk of malignancy and infection for people with MS starting or using new DMTs (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ Benefit 0	Benefit > Harm 2	Benefit >> Harm 0	Benefit >>> Harm 13	Yes
Importance of outcomes	Not Important or 1	Mildly 1	Very 8	Critically Important 6	Yes
Variation in preferences	Large 0	Moderate 1	Modest 5	Minimal 9	Yes
Feasible	Rarely 0	Occasionally 1	Usually 2	Always 12	Yes
Cost relative to net benefit	Very Large 0	Large 0	Moderate 3	Small 12	Yes
Strength of recommendation	R/U	C	B	A	

Statement 7b

If a patient with MS develops a malignancy while using a DMT, clinicians should promptly discuss switching to an alternate DMT, especially for people with MS using azathioprine, methotrexate, mycophenolate, cyclophosphamide, fingolimod, teriflunomide, alemtuzumab, or dimethyl fumarate (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ Benefit 1	Benefit > Harm 0	Benefit >> Harm 5	Benefit >>> Harm 9	Yes
Importance of outcomes	Not Important or 1	Mildly 0	Very 6	Critically Important 8	Yes
Variation in preferences	Large 2	Moderate 1	Modest 6	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 1	Usually 6	Always 8	Yes
Cost relative to net benefit	Very Large 1	Large 1	Moderate 6	Small 7	Yes
Strength of recommendation	R/U	C	B	A	

Statement 7c

People with MS with serious infections potentially linked to their DMT should switch DMTs (does not pertain to PML management in people with MS using DMT) (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ Benefit 0	Benefit > Harm 1	Benefit >> Harm 3	Benefit >>> Harm 10	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 7	Critically Important 7	Yes
Variation in preferences	Large 1	Moderate 1	Modest 5	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 0	Usually 5	Always 9	Yes
Cost relative to net benefit	Very Large 0	Large 1	Moderate 7	Small 6	Yes
Strength of recommendation	R/U	C	B	A	

Switching: recommendation 8

Rationale

Neutralizing antibodies may be produced against natalizumab and have been associated with allergic reactions (RELA).[e175,e176] These antibodies may reduce the efficacy of the medication (PRIN), especially if they are persistent.

Statement 8a

Clinicians should check for natalizumab antibodies in people with MS who have infusion reactions before subsequent infusions, or in people with MS who experience breakthrough disease activity with natalizumab use (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ Benefit 1	Benefit > Harm 0	Benefit >> Harm 9	Benefit >>> Harm 4	Yes
Importance of outcomes	Not Important or 1	Mildly 0	Very 12	Critically Important 2	Yes
Variation in preferences	Large 1	Moderate 1	Modest 8	Minimal 4	Yes
Feasible	Rarely 0	Occasionally 1	Usually 8	Always 5	Yes
Cost relative to net benefit	Very Large 0	Large 3	Moderate 9	Small 2	Yes
Strength of recommendation	R/U	C	B	A	

Statement 8b

Clinicians should switch DMTs in people with MS who have persistent natalizumab antibodies (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ Benefit 1	Benefit > Harm 0	Benefit >> Harm 9	Benefit >>> Harm 4	Yes
Importance of outcomes	Not Important or 1	Mildly 0	Very 12	Critically Important 2	Yes
Variation in preferences	Large 1	Moderate 1	Modest 8	Minimal 4	Yes
Feasible	Rarely 0	Occasionally 1	Usually 8	Always 5	Yes
Cost relative to net benefit	Very Large 0	Large 3	Moderate 9	Small 2	Yes
Strength of recommendation	R/U	C	B	A	

Switching: recommendation 9

Rationale

People with MS taking natalizumab may discontinue natalizumab because of fear of PML risk or for pregnancy planning (INFER). Natalizumab discontinuation increases the risk of MRI-detected disease activity (EVID) and MS relapse (RELA) within 6 months of discontinuation, with some people with MS having an increase in disease activity above their baseline activity, referred to as rebound activity.[e177] Data are limited for assessing the appropriate choice of an alternate DMT after natalizumab discontinuation. There is evidence that initiating fingolimod 8 to 12 weeks after natalizumab discontinuation reduces new MRI-detected lesions compared with initiation 16 weeks after natalizumab discontinuation (EVID). Initiating fingolimod 8 to 12 weeks after natalizumab discontinuation increases the proportion of people with MS who are relapse free compared with initiation after 16 weeks (RELA).[e178,e179] Although RCT data are unavailable, retrospective cohort data suggest that switching from natalizumab to rituximab may result in lower rates of clinical and radiologic disease activity compared with switching to fingolimod (RELA).[e180]

Statement 9a

Physicians must counsel people with MS considering natalizumab discontinuation that there is an increased risk of MS relapse or MRI-detected disease activity within 6 months of discontinuation (Level A).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High 10	
Benefit relative to Harm	Harm ≥ Benefit 0	Benefit > Harm 0	Benefit >> Harm 6	Benefit >>> Harm 9	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 5	Critically Important 10	Yes
Variation in preferences	Large 0	Moderate 1	Modest 2	Minimal 12	Yes
Feasible	Rarely 0	Occasionally 0	Usually 2	Always 13	Yes
Cost relative to net benefit	Very Large 1	Large 0	Moderate 2	Small 12	Yes
Strength of recommendation	R/U	C	B	A	

Statement 9b

Physicians and people with MS choosing to switch from natalizumab to fingolimod should initiate treatment within 8 to 12 weeks after natalizumab discontinuation (for reasons other than pregnancy or pregnancy planning) to diminish the return of disease activity (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference and Evidence	Very low	Low	Moderate	High	
Benefit relative to Harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 5	Benefit >>> harm 10	Yes
Importance of outcomes	Not important or 0	Mildly 0	Very 10	Critically 5	Yes
Variation in preferences	Large 0	Moderate 1	Modest 11	Minimal 3	Yes
Feasible	Rarely 0	Occasionally 0	Usually 10	Always 5	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 11	Small 4	Yes
Strength of recommendation	R/U	C	B	A	

Switching: recommendation 10

Rationale

Relapse risk is reduced during pregnancy and increases in the postpartum period (RELA).[e181] Pregnancy exposure to DMTs may pose potential risks to the fetus to varying degrees (RELA), which vary from severe malformations to no major increased risk of malformations. Risks of important early-life health outcomes such as infections, vaccination responses, asthma, and neurocognitive disorders are unknown. FDA-approved medications vary in terms of FDA recommendation for pregnancy (e.g., glatiramer acetate "Instruct people with MS that if they are pregnant or plan to become pregnant while taking glatiramer acetate they should inform their physician"; "Women of childbearing potential should be advised to avoid becoming pregnant"] and teriflunomide ["Must be avoided during pregnancy"]) (RELA). Each DMT has a separate FDA statement about pregnancy-associated risks (see individual package inserts and attached table). Discussing these potential risks and how best to minimize them is a part of good clinical practice (PRIN). The majority of human safety data for exposure to DMTs during pregnancy is derived from accidental exposure early in pregnancy. There is a paucity of safety information with second- and third-trimester exposure (RELA).[e182]

Statement 10a

Clinicians should counsel women to stop their DMT before conception for planned pregnancies unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference and Evidence	Very low	Low	Moderate	High 10	
Benefit relative to Harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 6	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or 0	Mildly 0	Very 7	Critically 8	Yes
Variation in preferences	Large 0	Moderate 3	Modest 5	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 1	Usually 4	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 8	Small 7	Yes
Strength of recommendation	R/U	C	B	A	

Statement 10b

Clinicians should discontinue DMTs during pregnancy if accidental exposure occurs, unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ Benefit 1	Benefit > Harm 0	Benefit >> Harm 6	Benefit >>> Harm 6	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 4	Critically Important 9	Yes
Variation in preferences	Large 1	Moderate 1	Modest 2	Minimal 9	Yes
Feasible	Rarely 0	Occasionally 1	Usually 0	Always 12	Yes
Cost relative to net benefit	Very Large 1	Large 0	Moderate 2	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

Statement 10c

Clinicians should not initiate DMTs during pregnancy unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference and Evidence	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ benefit 1	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or 0	Mildly 0	Very 7	Critically 8	Yes
Variation in preferences	Large 0	Moderate 1	Modest 4	Minimal 10	Yes
Feasible	Rarely 0	Occasionally 1	Usually 3	Always 11	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 6	Small 9	Yes
Strength of recommendation	R/U	C	B	A	

Stopping DMT Recommendations

Stopping: recommendation 1

Rationale

No RCTs have directly addressed the question of whether, when, or why to discontinue DMTs in an individual with RRMS who has no evidence of relapses or disability progression and has stable brain imaging (EVID). The natural history of untreated RRMS is for relapses and disability accumulation to occur. Early studies suggest that most individuals with RRMS ultimately advance to SPMS if observed for long enough intervals, although disease course is highly variable (RELA).[e17] People with MS who are stable on DMTs may question the continued value of using DMTs (INFER). If people with MS on DMTs stop these medications, continued monitoring may show subclinical disease activity or relapse activity that would indicate a possible need for treatment resumption (INFER). In an RCT of 175 individuals taking natalizumab who had been relapse free for 1 year and had no gadolinium-enhanced lesions on MRI, participants were randomized to continue natalizumab use, switch to placebo, or switch to other therapies. Relapses occurred in 4% of those continuing natalizumab use and in 15% to 29% of those in other treatment arms over 24 weeks (EVID). An observational study comparing outcomes in individuals who did or did not stop DMT after a period of at least 5 years without relapses found a similar risk of relapses between the groups but an increased risk of disability

progression among those who stopped DMT (RELA). Younger age and lower EDSS scores were significant predictors of relapse (clinical or MRI) after treatment discontinuation (RELA). People with MS who are on DMTs with no evidence of ongoing disease activity may be benefiting from their DMT with disease suppression (INFER). There are presently no biological markers of medication efficacy that can guide decision making in this area (EVID).

Statement 1a

In people with RRMS who are stable on DMT and want to discontinue therapy, clinicians should counsel people with MS regarding the need for ongoing follow-up and periodic reevaluation of the decision to discontinue DMT (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference and Evidence	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ benefit 0	Benefit > harm 2	Benefit >> harm 2	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or 0	Mildly 2	Very 5	Critically 8	Yes
Variation in preferences	Large 1	Moderate 2	Modest 8	Minimal 4	Yes
Feasible	Rarely 0	Occasionally 1	Usually 3	Always 11	Yes
Cost relative to net benefit	Very large 1	Large 0	Moderate 6	Small 8	Yes
Strength of recommendation	R/U	C	B	A	

Statement 1b

Clinicians should advocate that people with MS who are stable (that is, no relapses, no disability progression, stable imaging) on DMT should continue their current DMT unless the patient and physician decide a trial off therapy is warranted (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference and Evidence	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ benefit 1	Benefit > harm 1	Benefit >> harm 6	Benefit >>> harm 7	Yes
Importance of outcomes	Not important or 0	Mildly 1	Very 9	Critically 5	Yes
Variation in preferences	Large 2	Moderate 1	Modest 9	Minimal 3	Yes
Feasible	Rarely 0	Occasionally 1	Usually 5	Always 9	Yes
Cost relative to net benefit	Very large 1	Large 0	Moderate 10	Small 4	Yes
Strength of recommendation	R/U	C	B	A	

Stopping: recommendation 2

Rationale

People with SPMS who have relapses or active MRI-detected new lesion formation benefit from DMT (EVID). In people with SPMS who are ambulatory with or without assistance, interferon beta reduces the risk of relapse but does not delay disability progression as measured by the EDSS, a measure that emphasizes ambulation (EVID). No RCTs have directly addressed the question of whether or when to discontinue DMTs in people with SPMS (EVID). Clinical trials have not evaluated the benefits of DMT in individuals with SPMS who are nonambulatory with respect to other clinically relevant domains, including vision, cognition, and upper limb function (EVID). Relapses are associated with more rapid disability progression in SPMS but tend to occur in those at younger ages (younger than 55 years) and earlier in the disease course (RELA).[e183,e184] Among individuals with SPMS (those with and those without clinical relapses) for at least 2 years at the time of treatment withdrawal, an EDSS of 6 or greater was associated with a 50% lower risk of relapses or MRI-detected activity after treatment discontinuation (RELA). The benefits of therapy should outweigh the risks (PRIN). The use of ineffective therapy may pose harms to the affected individual, society, and the health system (PRIN).

Statement 2a

Clinicians should assess the likelihood of future relapse in individuals with SPMS by assessing patient age, disease duration, relapse history, and MRI-detected activity (e.g., frequency, severity, time since most recent relapse or gadolinium-enhanced lesion) (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference and Evidence	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 4	Benefit >>> harm 10	Yes
Importance of outcomes	Not important or 0	Mildly 3	Very 7	Critically 5	Yes
Variation in preferences	Large 1	Moderate 0	Modest 8	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 1	Usually 3	Always 11	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 8	Small 7	Yes
Strength of recommendation	R/U	C	B	A	

Statement 2b

Clinicians may advise discontinuation of DMT in people with SPMS who do not have ongoing relapses (or gadolinium-enhanced lesions on MRI activity) and have not been ambulatory (EDSS 7 or greater) for at least 2 years (Level C).*

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference and Evidence	Very low	Low	Moderate 10	High	
Benefit relative to Harm	Harm ≥ benefit 0	Benefit > harm 3	Benefit >> harm 8	Benefit >>> harm 4	Yes
Importance of outcomes	Not important or 0	Mildly 2	Very 12	Critically 1	Yes
Variation in preferences	Large 3	Moderate 4	Modest 7	Minimal 1	No
Feasible	Rarely 0	Occasionally 1	Usually 5	Always 9	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 9	Small 5	Yes
Strength of recommendation	R/U	C	B	A	

*Failed to meet consensus because of variation in patient preferences. Recommendation downgraded to Level C.

Stopping: recommendation 3

Rationale

DMTs tested in people with CIS delay progression to MS onset (EVID). However, some people with CIS may not develop MS (EVID).[e20] Risks of active relapsing disease activity are higher in younger people with CIS (RELA).[e130,e185,e186] In the absence of disease activity, people with CIS who are on DMTs may question the value of continuing DMTs indefinitely (INFER). There remains a gap in knowledge about stopping DMTs in people with CIS (INFER). Discussing the risks of continuing DMTs vs the risks of their use being unnecessary as part of ongoing treatment is a part of good clinical practice (PRIN).

Statement 3

Clinicians should review the associated risks of continuing DMTs vs those of stopping DMTs in people with CIS using DMTs who have not been diagnosed with MS (Level B).*

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference and Evidence	Very low	Low	Moderate	High 10	
Benefit relative to Harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 6	Benefit >>> harm 8	Yes
Importance of outcomes	Not important or 0	Mildly 0	Very 11	Critically 4	Yes
Variation in preferences	Large 1	Moderate 3	Modest 7	Minimal 4	No
Feasible	Rarely 0	Occasionally 1	Usually 5	Always 9	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 6	Small 8	Yes
Strength of recommendation	R/U	C	B	A	

*Failed to meet consensus owing to variation in preferences. Recommendation is that clinicians <should> review the risk of continuing DMTs. The failure to meet consensus resulted from misinterpretation of the recommendation. People with CIS and MS do not vary in their preference for physician review of their situation; the preference varies in what they ultimately decide to do. This recommendation stands at Level B.

Appendix e-11. Survey questions distributed to persons with multiple sclerosis from the NARCOMS Registry and panelists of the AAN guideline on DMTs for MS

Please order the following statements in order of importance to you when choosing a Multiple Sclerosis (MS) treatment (number 1 = most important, number 8 = least important).

A. Ability of treatment to prevent relapses due to MS

B. Ability of treatment to decrease long-term disability due to MS

C. Ability of treatment to prevent changes in memory and thinking due to MS

D. Ability of treatment to prevent brain changes seen on MRI due to MS

E. Ability of treatment to improve overall quality of life

F. Ability of treatment to improve symptoms of MS (e.g., fatigue, pain, numbness)

G. Safety of the treatment (e.g., risk of death associated with treatment)

H. Side effects of the treatment (e.g., fevers, chills, muscle aches associated with taking the medicine)

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