



AMERICAN ACADEMY OF
NEUROLOGY®

Disease-modifying Therapies for Adults with Multiple Sclerosis

Report by:

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

Practice Guideline Endorsement and Funding

This practice guideline was endorsed by the Consortium of Multiple Sclerosis Centers, the Multiple Sclerosis Association of America, and the National Multiple Sclerosis Society.

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 two in-person meetings.

Sharing This Information

The AAN develops these presentation slides as educational tools for neurologists and other health care practitioners. You may download and retain a single copy for your personal use.

Please contact guidelines@aan.com to learn about options for sharing this content beyond your personal use.

Presentation Objectives

- To present 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
- To present practice recommendations for starting, switching, and stopping DMTs

Overview

- Introduction
- Clinical questions
- AAN guideline process
- Methods
- Conclusions
- Practice recommendations

Introduction

- 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}
- Since 1993, several 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:
 - All modify measures of disease activity such as relapse rates, the emergence of new or enhancing lesions on MRI, disability, or other parameters.
 - None is curative.
 - All may have adverse effects (AEs), which may vary from bothersome to life-threatening.

Introduction

- The 2002 AAN clinical practice guideline on DMTs in MS^{e18} systematically reviewed injectable medications then approved for use in people with MS, including the following medications:
 - Interferon beta-1b (interferon beta-1b subcutaneous alternate day: BETASERON)
 - Interferon beta-1a intramuscular (IM) (interferon beta-1a IM weekly: AVONEX)
 - Interferon beta-1a subcutaneous (interferon beta-1a subcutaneous three times per week [Rebif])
 - Glatiramer acetate (COPAXONE)
- Medications commonly prescribed off label for the treatment of MS were not reviewed.^{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.

Introduction

- 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.

Introduction

- 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.
- This practice guideline reviews the following information:
 - 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
 - Indications for use in different MS types (RRMS, SPMS, primary progressive MS [PPMS])
 - Potential AEs related to DMT use, including AEs that may have an impact on medication tolerability, and uncommon events that may have serious, even irreversible, consequences for the patient
 - Patient preference and patient-prioritized outcomes for treatment, where data available^{e22}

Introduction

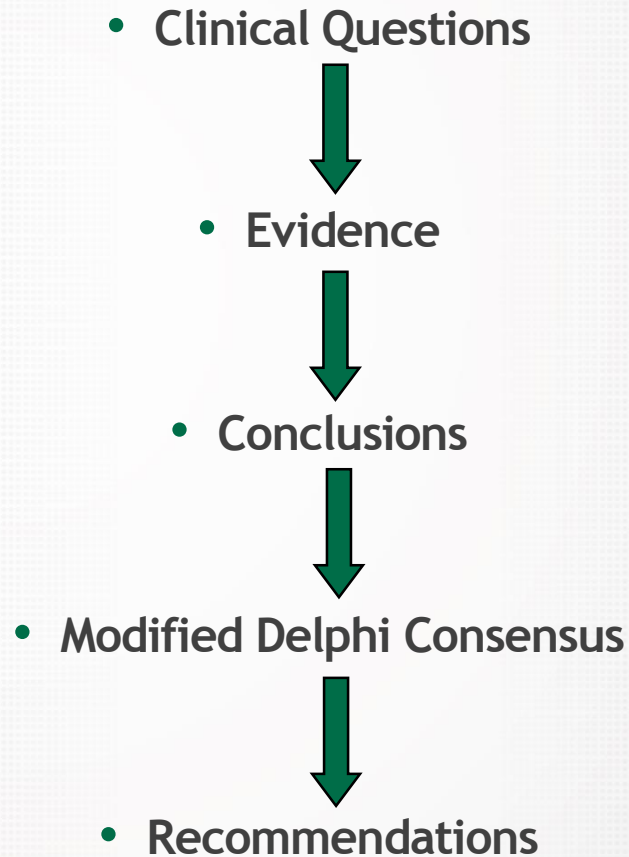
- When sufficient Class I and II evidence (appendix e-4 of the full-length guideline) was not available, related evidence and practical axioms of care were used to develop recommendations, consistent with the guideline development process.^{e22}
- A subgroup of the guideline panelists solicited opinions 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 randomized controlled trials (RCTs) and those encountered in clinical practice (i.e., generalizability) may affect the translation of findings into practice.

Clinical Questions

This practice guideline addresses 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 CIS, are DMTs superior to placebo in decreasing the risk of conversion to MS?

AAN Guideline Process*



*Guideline developed using the 2011 *AAN Clinical Practice Guideline Process Manual* as amended.

Literature Search/Review

Rigorous, Comprehensive, Transparent

Cochrane Database of Systematic Reviews was searched to November 2016 for Cochrane systematic reviews (SRs), which were updated by identical searches of MEDLINE, CENTRAL, EMBASE; for DMTs not previously reviewed, de novo SRs were performed.



Inclusion criteria:

- Peer-reviewed English-language articles in humans that pertain to DMTs for MS
- RCTs (for both efficacy and harms data)
- Cohort studies, case reports, case series (for harms data only)
- Individuals with MS aged 18 years or older
- Data on RRMS, SPMS, PPMS, CIS

Exclusion criteria:

- Treatment articles lacking control groups
- Studies involving individuals younger than age 18 years or not having an MS diagnosis

Systematic review

Two independent nonconflicted panelists
4,301 de novo
SR abstracts

73 articles for data
extraction

20 Cochrane reviews
for data extraction

AMSTAR score

70 RCTs

Systematic review

AAN Classification of Evidence (2011)

Class I

A clinical RCT 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 two 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 characteristics 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.

* Note that numbers I to iii in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

AAN Classification of Evidence (2011)

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 (see Class I) or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets items b–e (see Class I).

(Alternatively, a randomized crossover trial missing one of the following two 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.

AAN Classification of Evidence (2011)

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 two 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.

**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).

AAN Classification of Evidence (2011)

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.

Safety Note

Drug Removal from Market

- After US Food and Drug Administration (FDA) approval was received, daclizumab (ZINBRYTA) was voluntarily removed from market on March 2, 2018, by its manufacturers, Biogen and AbbVie, due to serious adverse events in relapsing MS.^{e22a}
- The guideline panel retained the evidence analysis and ratings in the SR; however, the drug is not included in the recommendations.
- The evidence analysis and rating of the drug is not discussed further here.

Clinical Question

Question 1

- **In people with RRMS, are DMTs superior to placebo or other DMTs as measured by ARR and the relative risk of relapse at two years?**

Analysis of Evidence

Question 1: Summary of Evidence – Reducing the ARR in RRMS

- DMTs compared with placebo
 - DMTs with high confidence for greater efficacy
 - Cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, natalizumab, pegylated interferon, teriflunomide
 - DMTs with moderate confidence for greater efficacy
 - Azathioprine, interferon beta-1a intramuscular (IM) once per week, interferon beta-1b subcutaneous alternate day, pulsed corticosteroids added to interferon beta-1a

Analysis of Evidence

Question 1: Summary of Evidence – Reducing the ARR in RRMS

- DMTs compared with other DMTs
 - DMTs with high confidence of greater efficacy
 - Alemtuzumab, ocrelizumab more effective than interferon beta-1a subcutaneous three times per week
 - Azathioprine more effective than beta interferons
 - Fingolimod more effective than interferon beta-1a IM once per week

Analysis of Evidence

Question 1: Summary of Evidence – Reducing the Relative Risk of Relapse in RRMS

- DMTs compared with placebo
 - DMTs with high confidence of greater efficacy
 - Dimethyl fumarate, fingolimod, immunoglobulins, interferon beta-1a IM once per week, interferon beta-1a subcutaneous three times per week, mitoxantrone, natalizumab, pegylated interferon (outcome measured at one year)
 - DMTs with moderate confidence of greater efficacy
 - Cladribine, glatiramer acetate, interferon beta-1b subcutaneous alternate day, pulsed corticosteroids added to interferon beta-1a, rituximab (outcome measured at one year), teriflunomide

Analysis of Evidence

Question 1: Summary of Evidence – Reducing the Relative Risk of Relapse in RRMS

- DMTs compared with other DMTs
 - DMT with high confidence of greater efficacy
 - Alemtuzumab more effective than interferon beta-1a subcutaneous three times per week

Clinical Question

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?**

Analysis of Evidence

Question 2: Summary of Evidence – Reducing the Risk of New or Enlarging T2 Lesions in RRMS

- DMTs compared with placebo
 - DMTs with high confidence of greater efficacy
 - Fingolimod, interferon beta-1a 44 micrograms subcutaneous three times weekly, natalizumab
 - DMT with moderate confidence of greater efficacy: Cladribine

Analysis of Evidence

Question 2: Summary of Evidence – Reducing the Risk of New or Enlarging T2 Lesions in RRMS

- DMTs compared with other DMTs
 - DMTs with high confidence of greater efficacy
 - Ocrelizumab more effective than interferon beta-1a subcutaneous three times weekly
 - DMTs with moderate confidence of greater efficacy
 - Alemtuzumab probably more effective than interferon beta-1a subcutaneous three times per week
 - Fingolimod probably more effective than interferon beta-1a IM once per week
 - Interferon beta-1a 44 micrograms subcutaneous three times weekly probably more effective than interferon beta-1a IM once weekly

Analysis of Evidence

Question 2: Summary of Evidence – Reducing the Volume or Number of T2 Lesions in RRMS

- DMTs compared with placebo
 - DMTs with high confidence of greater efficacy
 - Dimethyl fumarate, glatiramer acetate, interferon beta-1a 30 micrograms IM weekly, mitoxantrone, natalizumab, pegylated interferon
 - DMTs with moderate confidence of greater efficacy
 - Rituximab and teriflunomide

Analysis of Evidence

Question 2: Summary of Evidence – Reducing the Loss of Parenchymal Volume in RRMS

- DMTs compared with placebo
 - DMT with moderate confidence of greater efficacy: Pulsed corticosteroids

Analysis of Evidence

Question 2: Summary of Evidence – Reducing the Loss of Parenchymal Volume in RRMS

- DMTs compared with other DMTs
 - DMT with high confidence of greater efficacy
 - Ocrelizumab more effective than interferon beta-1a 44 micrograms subcutaneous three times per week
 - DMT with moderate confidence of greater efficacy
 - Alemtuzumab probably more effective than interferon beta-1a 44 micrograms subcutaneous three times per week

Clinical Question

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?**

Analysis of Evidence

Question 3: Summary of Evidence – Preventing Disease Progression as Measured by In-study Disease Progression Measures in RRMS

- DMTs compared with placebo
 - DMTs with high confidence of greater efficacy
 - Dimethyl fumarate, fingolimod, interferon beta-1a 30 micrograms IM weekly, interferon beta-1a 44 micrograms subcutaneous three times weekly, mitoxantrone, natalizumab, pegylated interferon, teriflunomide
 - DMT with moderate confidence of greater efficacy: Cladribine

Analysis of Evidence

Question 3: Summary of Evidence – Preventing Disease Progression as Measured by In-study Disease Progression Measures in RRMS

- DMTs compared with other DMTs
 - DMTs with high confidence of greater efficacy
 - Alemtuzumab more effective than interferon beta-1a subcutaneous three times weekly
 - Ocrelizumab more effective than interferon beta-1a 44 micrograms subcutaneous three times weekly
 - DMTs with moderate confidence of lesser efficacy
 - Interferon beta-1b alternate day probably less effective than glatiramer acetate

Clinical Question

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-detected T2 or gadolinium-enhanced lesion activity?**

Analysis of Evidence

Question 4: Summary of Evidence – Changing DMTs for Reducing Relapse Rate and MRI-detected Lesion Activity in RRMS

- DMTs compared with other DMTs
 - DMTs with high confidence of greater efficacy
 - After relapse from interferon beta or glatiramer acetate, alemtuzumab more effective than interferon beta-1a 44 micrograms subcutaneous three times per week for reducing the ARR, relapse risk, disability progression, and risk of new or enlarging T2 lesions over two years
 - After one or more relapses in preceding 12 months on interferon beta, adding natalizumab more effective than adding placebo in decreasing the risk of relapse over two years, the ARR, the risk of disability progression over two years, and risk of new or enlarging T2 lesions at one year

Analysis of Evidence

Question 4: Summary of Evidence – Changing DMTs for Reducing Relapse Rate and MRI-detected Lesion Activity in RRMS

- DMTs compared with other DMTs
 - DMTs with moderate confidence of greater efficacy
 - Natalizumab added to glatiramer acetate probably more effective than placebo added to glatiramer acetate for decreasing cumulative number of new or enlarging T2 lesions at six months

Note: Natalizumab not presently approved/recommended as add-on therapy to other DMTs (potential safety concerns associated with combined use of this medication)

Clinical Question

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?**

Analysis of Evidence

Question 5: Summary of Evidence – Reducing Relapse Rate/Risk

- DMTs compared with placebo
 - DMTs with high confidence of greater efficacy
 - Interferon beta-1b subcutaneous alternate day (SPMS)
 - DMTs with moderate confidence of greater efficacy
 - Interferon beta-1a 60 micrograms IM weekly (SPMS), mitoxantrone (worsening RRM and SPMS)

Analysis of Evidence

Question 5: Summary of Evidence – Reducing In-Study Disease (Disability) Progression

- DMTs compared with placebo
 - DMTs with moderate confidence of greater efficacy
 - Mitoxantrone (worsening RRMS or SPMS), ocrelizumab (PPMS)

Clinical Question

Question 6

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

For a comprehensive review of AEs associated with DMTs, see the complete guideline, available as a data supplement at Neurology.org.

Clinical Question

Question 7

- **In people with CIS, are DMTs superior to placebo in decreasing the risk of conversion to MS?**

Analysis of Evidence

Question 7: Summary of Evidence – Reducing In-Study Disease (Disability) Progression

- DMTs compared with placebo
 - DMTs with high confidence of greater efficacy
 - Glatiramer acetate, interferon beta-1a subcutaneous three times weekly
 - DMTs with moderate confidence of greater efficacy
 - Cladribine, immunoglobulins, interferon beta-1a 30 micrograms IM weekly, interferon beta-1b subcutaneous alternate day, teriflunomide

Clinical Context for All Evidence

- This practice guideline reflects the complexity of decision making when considering initiating, switching, or stopping DMT use for MS.
- The guideline panel has striven to reflect a patient-centric approach incorporating assessment of attitudes, readiness to start or change DMTs, therapy adherence, patient specific factors (e.g., comorbidities), and an ongoing discussion of DMT use in people with MS on DMTs.
- The panel reviewed both FDA-approved DMTs and medications that have been used off label for which efficacy data may be analyzed.
- The panel engaged in a transparent process, including extensive public review of the initial protocol, questions considered in the systematic review, and an early version of the systematic review and recommendations.

Clinical Context for All Evidence

- No guideline of this complexity will satisfy all audiences.
- The panel recognizes that the field of MS treatment is rapidly changing and the recommendations presented here may require reanalysis in light of new directions in the field and new evidence pertaining to DMT use.
- Issues with generalizability of randomized trials to heterogenous real-world populations and extrapolation of short-term outcomes limit some of the conclusions.
- The panel anticipates needing to update this guideline in the not-too-distant future.

Practice Recommendations

- In addition to evidence, AAN guidelines incorporate several consensus-based factors in constructing practice recommendations. The following four premise types are part of that process:
 - Evidence from the systematic review
 - Strong evidence from related conditions
 - Axiomatic principles of care
 - Inferences made from one or more statements in the rationale
- The above-listed premise types are presented as rationales before each recommendation statement. The premises contribute to the strength of those recommendation statements.
- See the full-length guideline (data supplement) for a fuller understanding of the recommendation statements on the slides that follow.

Recommendations: Starting DMT

Level A

- 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.
- Clinicians must engage in an ongoing dialogue regarding treatment decisions throughout the disease course with people with MS.
- Clinicians must counsel people with MS on DMTs to notify the clinicians of new or worsening symptoms.

Recommendations: Starting DMT

Level B

- Clinicians should counsel people with newly diagnosed MS about specific treatment options with DMT at a dedicated treatment visit.
- 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.
- Clinicians should evaluate readiness or reluctance to initiate DMT and counsel on its importance in people with MS who are candidates to initiate DMT.
- Clinicians should counsel about comorbid disease, adverse health behaviors, and potential interactions of the DMT with concomitant medications when people with MS initiate DMTs.
- Clinicians should evaluate barriers to adherence to DMT in people with MS.
- Clinicians should counsel on the importance of adherence to DMT when people with MS initiate DMTs.

Recommendations: Starting DMT

Level B

- Clinicians should discuss the benefits and risks of DMTs for people with a single clinical demyelinating event with two or more brain lesions that have imaging characteristics consistent with MS.
- After discussing the risks and benefits, clinicians should prescribe DMT to people with a single clinical demyelinating event and two or more brain lesions characteristic of MS who decide they want this therapy.
- Clinicians should offer DMTs to people with relapsing forms of MS with recent clinical relapses or MRI activity.
- Clinicians should monitor for medication adherence, AEs, tolerability, safety, and effectiveness of the therapy in people with MS on DMTs.
- Clinicians should follow up either annually or according to medication-specific risk evaluation and mitigation strategies (REMs) in people with MS on DMTs.

Recommendations: Starting DMT

Level B

- 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.
- Clinicians should counsel men with MS on their reproductive plans regarding treatment implications before initiating treatment with teriflunomide or cyclophosphamide.
- 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.
- Clinicians should prescribe alemtuzumab, fingolimod, or natalizumab for people with MS with highly active MS.
- 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.

Recommendations: Starting DMT

Level C

- Clinicians may recommend serial imaging at least annually for the first five 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 two years, and do not have active new MRI lesion activity on recent imaging.
- Clinicians may direct people with MS who are candidates for DMTs to support programs.
- Clinicians may recommend azathioprine or cladribine for people with relapsing forms of MS who do not have access to approved DMTs.
- Clinicians may initiate natalizumab treatment in people with MS with positive anti-John Cunningham virus (JCV) antibody indexes above 0.9 only when there is a reasonable chance of benefit compared with the low but serious risk of progressive multifocal leukoencephalopathy (PML).

Recommendations: Switching DMT

Level A



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

Recommendations: Switching DMT

Level B

- 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.
- 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.
- 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 one or more relapses, two or more unequivocally new MRI-detected lesions, or increased disability on examination, over a one-year period of using a DMT.
- 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.

Recommendations: Switching DMT

Level B

- 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.
- Clinicians should inquire about medication AEs with people with MS who are taking a DMT and attempt to manage these AEs, as appropriate.
- Clinicians should discuss a medication switch with people with MS for whom these AEs negatively influence adherence.
- 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.
- 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.

Recommendations: Switching DMT

Level B

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

Recommendations: Switching DMT

Level B

- 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).
- 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.
- Clinicians should switch DMTs in people with MS who have persistent natalizumab antibodies.

Recommendations: Switching DMT

Level B

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

Recommendations: Switching DMT

Level B

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

Recommendations: Stopping DMT

Level B

- In people with RRMS who are stable on DMT and want to discontinue therapy, clinicians should counsel people regarding the need for ongoing follow-up and periodic reevaluation of the decision to discontinue DMT.
- 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.
- 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).
- Clinicians should review the associated risks of continuing DMTs versus those of stopping DMTs in people with CIS using DMTs who have not been diagnosed with MS.

Recommendations: Stopping DMT

Level C



- 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 (Expanded Disability Status Scale score 7 or greater) for at least two years.

Suggestions for 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.
- 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.

Suggestions for Future Research

- 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.

Suggestions for Future Research

- More research, particularly of newer agents, is needed to minimize risk to the pregnant woman and her fetus. Particular concerns include the following:
 - There is a need to determine (1) when DMT for MS should be stopped before conception, (2) whether some agents are safer than others, and (3) which agents might be safe enough to continue through conception and pregnancy in people with MS with active disease.
 - 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.

Suggestions for Future Research

- 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.

References

References cited here can be found in the complete guideline, an online data supplement to the summary article. To locate these materials, please visit [AAN.com/guidelines](https://www.aan.com/guidelines).

Access Guideline and Summary Tools

- To access the complete guideline and related summary tools, visit [AAN.com/guidelines](https://www.aan.com/guidelines).
 - Summary guideline article
 - Complete guideline article (available as a data supplement to the published summary)
 - A summary for clinicians
 - Three summaries for patients/families

Questions?