AAN Summary of Practice Guideline for **Clinicians**

Practice Guideline: Disease-modifying Therapies for Adults with Multiple Sclerosis

This is a summary of the American Academy of Neurology (AAN) publication, "Practice guideline recommendations: Disease-modifying therapies for adults with multiple sclerosis," which was published in *Neurology*® online on April 23, 2018, and appears in the April 24, 2018, print issue.

Please refer to the full guideline at *AAN.com/guidelines* for more information, including definitions of the classifications of evidence and recommendations.

Starting Disease-modifying Therapy (DMT) Recommendations

Starting: Recommendation 1

Rationale

Receiving the diagnosis of multiple sclerosis (MS) is a stressful life event.[4,5] People receiving major diagnoses may not recall much of the information given to them at the time.[6] Providing information about DMT at a follow-up interaction is likely to allow a better understanding of these medications and their risks and benefits.

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

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.

Level A	Clinicians must ascertain and incorporate/review preferences in terms of safety, route of administration, lifestyle, cost, efficacy, common adverse effects (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.

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.[7] Clinicians should inform people with MS that they may still need symptomatic treatment in addition to DMT.[8]

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

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.

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

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.[9,10] Addressing depression before initiating DMT may improve decision making and adherence to DMT. Concomitant medications may have important interactions with DMTs.[11]

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

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,[12,13] discussing adherence issues before initiating DMT is part of good clinical practice. Efforts to increase adherence may improve outcomes.

Level B	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.

Starting: Recommendation 7

Rationale

People presenting with a first demyelinating event 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 two or more brain or spinal cord lesions remain at increased risk of a future MS diagnosis, with the highest risk incurred within five years of the initial event.[14–17] 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.

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.

Starting: Recommendation 8

Rationale

The benefit of initiating DMT has not been studied in currently untreated people with clinically isolated syndromes (CIS) or relapsing forms of MS who have not had relapses in two 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.

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.

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.[18,19]

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

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.[20–25] Regular interactions and assessments by clinicians facilitate prompt identification and treatment of AEs, increased tolerability of the medication, and safety monitoring.[7,25] Some DMTs for MS have specific risk evaluation and mitigation strategies (REMS) with recommendations for follow-up frequency.[26–29]

Level B	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 REMs in people with MS on DMTs.

Starting: Recommendation 11

Rationale

DMTs have potential risks in pregnant women[30] 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.[31] In addition, because DMTs vary in terms of pregnancy risks,[30] DMT choice may be influenced by plans for pregnancy.

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.

Starting: Recommendation 12

Rationale

Chemotherapy, such as cyclophosphamide, may affect male fertility.[32] With teriflunomide treatment, there may be a risk of teratogenicity from male sperm, which could last for two years after treatment cessation if the patient is not treated with chelation therapy.[33]

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

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[34–37] associated with mitoxantrone use. Other effective medications with lower risk, which were unavailable at the time of US Food and Drug Administration (FDA) approval of mitoxantrone, are now available for treating MS.

Level B	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.

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.[38,39] 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.[40,e1] 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.[e2–e4] 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.[e5–e8] However, the risks and benefits of each treatment strategy need to be considered on a patient-by-patient basis.

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

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,[e9] 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.

Level C	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.

Starting: Recommendation 16

Rationale

People with MS with a positive John Cunningham virus (JCV) antibody test have a higher risk of developing progressive multifocal leukoencephalopathy (PML) while using natalizumab, particularly people with MS who have been treated for more than two 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.

Level C	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.

Starting: Recommendation 17

Rationale

Ocrelizumab is the only DMT shown to alter disease progression in individuals with primary progressive multiple sclerosis (PPMS) who are ambulatory. The randomized controlled trial (RCT) of rituximab in PPMS was promising but inconclusive.[e10] 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 three treatments.[e11–e13] 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.

Level B	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.

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.[e14–e17] 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.[e15,e17] 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.[e5,e6,e18–e21] Consequently, many clinicians obtain new baseline MRI three to six months after initiating DMTs to monitor from a treated baseline.[e22] 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.

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.

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.

Level B	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.

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.[e23] Injection fatigue (physical or emotional) or injection-related pain or discomfort may be a common reason for poor adherence.

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.

Switching: Recommendation 4

Rationale

Adherence to a DMT may also be affected by medication AEs.[13,25] All DMTs have common AEs that may affect adherence (see table e-2, links.lww.com/WNL/A376).

Level B	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.

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 (see table e-2, links.lww.com/WNL/A376).

Level B	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.

Switching: Recommendation 6

Rationale

PML is a serious safety concern[e24] that may affect compliance and necessitate consideration of a treatment switch. The PML risk is estimated at 4 per 1,000 overall with natalizumab[e25]; however, the presence and index level of JCV antibodies, longer duration use, and prior immunosuppression increase PML risk with natalizumab even further.[e24] 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 two years.[11] There are rare reports of PML with the use of both fingolimod and dimethyl fumarate.[e26–e29] There are reports of PML in people with MS who are HIV-negative and using rituximab for conditions other than MS.[e30] There is a potential risk of PML with ocrelizumab use, particularly with prior immunosuppressive therapies based on its similarity to other anti-CD20 antibodies.[e31]

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.

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.[e32] Herpes family virus infections have been reported with fingolimod and natalizumab use.[e33–e35] A potential increased risk of basal cell carcinoma was recently added to the fingolimod product label.[e29]

Level B	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.
	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).

Switching: Recommendation 8

Rationale

Neutralizing antibodies may be produced against natalizumab and have been associated with allergic reactions.[e36,e37] These antibodies may reduce the efficacy of the medication, especially if they are persistent.

Level B	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.

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 six months of discontinuation, with some people with MS having an increase in disease activity above their baseline activity, referred to as rebound activity.[e38] Data are limited for assessing the appropriate choice of an alternate DMT after natalizumab discontinuation. There is evidence that initiating fingolimod eight to 12 weeks after natalizumab discontinuation reduces new MRI-detected lesions compared with initiation 16 weeks after natalizumab discontinuation. Initiating fingolimod eight to 12 weeks after natalizumab discontinuation increases the proportion of people with MS who are relapse free compared with initiation after 16 weeks.[e39,e40] 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.[e41]

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.
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.

Switching: Recommendation 10

Rationale

Relapse risk is reduced during pregnancy and increases in the postpartum period.[e42] 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, links.lww.com/WNL/A376). 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.[e43]

Level B	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.
	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.

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 relapsing-remitting MS (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 secondary progressive multiple sclerosis (SPMS) if observed for long enough intervals, although disease course is highly variable.[e44] 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 one 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 percent of those continuing natalizumab use and in 15 percent to 29 percent 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 five 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 Expanded Disability Status Scale (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.

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.

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.[e45,e46] Among individuals with SPMS (those with and those without clinical relapses) for at least two years at the time of treatment withdrawal, an EDSS of 6 or greater was associated with a 50 percent 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.

Level B	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 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 (EDSS 7 or greater) for at least two years.

Stopping: Recommendation 3

Rationale

DMTs tested in people with CIS delay progression to MS onset. However, some people with CIS may not develop MS.[e47] Risks of active relapsing disease activity are higher in younger people with CIS.[17,e48,e49] 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.

Level B	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.

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.

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.

References

4. Schofield T, Elwyn G, Edwards A, Visser A. Shared decision making. Patient Educ Couns 2003;50:229–230.

5. Johnson J. On receiving the diagnosis of multiple sclerosis: managing the transition. Mult Scler 2003;9:82–88.

6. Ptacek JT, Eberhardt TL. Breaking bad news. A review of the literature. JAMA 1996;276:496–502.

7. Mohr DC, Goodkin DE, Likosky W, et al. Therapeutic expectations of patients with multiple sclerosis upon initiating interferon beta-1b: relationship to adherence to treatment. Mult Scler 1996;2:222–226.

8. Henze T, Rieckmann P, Toyka KV, Multiple Sclerosis Therapy Consensus Group of the German Multiple Sclerosis Society. Symptomatic treatment of multiple sclerosis. Multiple Sclerosis Therapy Consensus Group (MSTCG) of the German Multiple Sclerosis Society. Eur Neurol 2006;56:78–105.

9. Marrie RA, Horwitz RI. Emerging effects of comorbidities on multiple sclerosis. Lancet Neurol 2010;9:820–828.

10. Tettey P, Siejka D, Simpson S, Jr., et al. Frequency of comorbidities and their association with clinical disability and relapse in multiple sclerosis. Neuroepidemiology 2016;46:106–113.

11. EMA confirms recommendations to minimise risk of brain infection PML with Tysabri [press release]. London, UK: European Medicines Agency, 2016. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2016/02/WC500202389.pdf. Issued February 26, 2016.

12. Katsarava Z, Ehlken B, Limmroth V, et al.; C.A.R.E. Study Group. Adherence and cost in multiple sclerosis patients treated with IM IFN beta-1a: impact of the CARE patient management program. BMC Neurol 2015;15:170.

13. Irwin DE, Cappell KA, Davis BM, Wu Y, Grinspan A, Gandhi SK. Differences in multiple sclerosis relapse rates based on patient adherence, average daily dose, and persistence with disease-modifying therapy: observations based on real-world data. Value Health 2015;18:A764.

14. Miller D, Barkhof F, Montalban X, Thompson A, Filippi M. Clinically isolated syndromes suggestive of multiple sclerosis, part 2: non-conventional MRI, recovery processes, and management. Lancet Neurol 2005;4:341–348.

15. Abou Zeid N, Bhatti MT. Acute inflammatory demyelinating optic neuritis: evidence-based visual and neurological considerations. Neurolog 2008;14:207–223.

16. Optic Neuritis Study Group. Multiple sclerosis risk after optic neuritis: final optic neuritis treatment trial follow-up. Arch Neurol 2008;65:727–732.

17. Kuhle J, Disanto G, Dobson R, et al. Conversion from clinically isolated syndrome to multiple sclerosis: a large multicentre study. Mult Scler 2015;21:1013–1024.

18. Comi G, De Stefano N, Freedman MS, et al. Comparison of two dosing frequencies of subcutaneous interferon beta-1a in patients with a first clinical demyelinating event suggestive of multiple sclerosis (REFLEX): a phase 3 randomised controlled trial. Lancet Neurol 2012;11:33–41.

19. Miller A, Wolinsky JS, Kappos L, et al.; TOPIC Study Group. Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol 2014;13:977–986.

20. Girouard N, Soucy N. Patient considerations in the management of multiple sclerosis: development and clinical utility of oral agents. Patient Prefer Adherence 2011;5:101–108.

21. Brandes DW, Raimundo K, Agashivala N, Kim E. Implications of real-world adherence on cost-effectiveness analysis in multiple sclerosis. J Med Econ 2013;16:547–551.

22. Oleen-Burkey MA, Dor A, Castelli-Haley J, Lage MJ. The relationship between alternative medication possession ratio thresholds and outcomes: evidence from the use of glatiramer acetate. J Med Econ 2011;14:739–747.

23. Thomas NP, Curkendall S, Farr AM, Yu E, Hurley D. The impact of persistence with therapy on inpatient admissions and emergency room visits in the US among patients with multiple sclerosis. J Med Econ 2016;19:497–505.

24. Singer B, Lucas S, Kresa-Reahl K, Perrin Ross A, Blake P. Review: optimizing adherence to multiple sclerosis therapies. Int J MS Care 2008;10:113–126.

25. Treadaway K, Cutter G, Salter A, et al. Factors that influence adherence with disease-modifying therapy in MS. J Neurol 2009;256:568–576.

26. Gilenya [package insert]. Gp. Basel, Sweden: Novartis Pharmaceuticals Corp; 2014.

27. Ocrevus [package insert]. Cp. South San Francisco: Genentech; 2015.

28. Tysabri [package insert]. Tp. Cambridge, MA: Biogen; 2016.

29. Zinbryta [package insert]. Zp. Cambridge, MA: Biogen; 2016.

30. Bove R, Alwan S, Friedman JM, et al. Management of multiple sclerosis during pregnancy and the reproductive years: a systematic review. Obstet Gynecol 2014;124:1157–1168.

31. Coyle PK. Management of women with multiple sclerosis through pregnancy and after childbirth. Ther Adv Neurol Disord 2016;9:198–210.

32. Leroy C, Rigot JM, Leroy M, et al. Immunosuppressive drugs and fertility. Orphanet J Rare Dis 2015;10:136.

33. Cree BA. Update on reproductive safety of current and emerging disease-modifying therapies for multiple sclerosis. Mult Scler 2013;19:835–843.

34. Ellis R, Boggild M. Therapy-related acute leukaemia with mitoxantrone: what is the risk and can we minimise it? Mult Scler 2009;15:505–508.

35. Ellis R, Brown S, Boggild M. Therapy-related acute leukaemia with mitoxantrone: four years on, what is the risk and can it be limited? Mult Scler 2015;21:642–645.

36. Fleischer V, Salmen A, Kollar S, et al. Cardiotoxicity of mitoxantrone treatment in a German cohort of 639 multiple sclerosis patients. J Clin Neurol 2014;10:289–295.

37. Le Page E, Leray E, Edan G; French Mitoxantrone Safety Group. Long-term safety profile of mitoxantrone in a French cohort of 802 multiple sclerosis patients: a 5-year prospective study. Mult Scler 2011;17:867–875.

38. Lucchinetti C, Bruck W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. Ann Neurol 2000;47:707–717.

39. Confavreux C, Vukusic S. Natural history of multiple sclerosis: a unifying concept. Brain 2006;129:606–616.

40. Hutchinson M, Kappos L, Calabresi PA, et al.; AFFIRM and SENTINEL Investigators The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analyses of AFFIRM and SENTINEL. J Neurol 2009;256:405–415.

e1. Agency EM. Assessment report. Gilenya. International non-proprietary name: fingolimod. London, UK; 2014.

e2. Coles AJ, Fox E, Vladic A, et al. Alemtuzumab versus interferon beta-1a in early relapsing-remitting multiple sclerosis: post-hoc and subset analyses of clinical efficacy outcomes. Lancet Neurol 2011;10:338–348.

e3. Devonshire V, Havrdova E, Radue EW, et al.; FREEDOMS study group. Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomised, placebo-controlled FREEDOMS study. Lancet Neurol 2012;11:420–428.

e4. Hutchinson M. Predicting and preventing the future: actively managing multiple sclerosis. Pract 2009;9:133–143, discussion 144.

e5. Coles A, Twyman CL, Arnold DL, et al.; the CARE-MS II Investigators. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet 2012;380:1829–1839.

e6. Cohen JA, Barkhof F, Comi G, et al.; on behalf of the TRANSFORMS Study Group. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med 2010;362:402–415.

e7. Cohen J, Coles AJ, Arnold DL, et al.; CARE-MS I Investigators. Alemtuzumab versus interferon beta 1a as fi rst-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet 2012;380:1819–1828.

e8. Rudick R, Stuart WH, Calabresi PA, et al.; for the SENTINEL Investigators. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Engl J Med 2006;354:911–923.

e9. Browne P, Chandraratna D, Angood C, et al. Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. Neurology 2014;83:1022–1024.

e10. Hawker K, O'Connor P, Freedman MS, et al. Rituximab in Patients with Primary Progressive Multiple Sclerosis Results of a Randomized Double-Blind Placebo-Controlled Multicenter Trial. Ann Neurol 2009;66:460–471.

e11. Lublin F, Miller DH, Freedman MS, et al. Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet 2016;387:1075–1084.

e12. Wolinsky JS, Narayana PA, O'Connor P, et al. Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. Ann Neurol 2007;61:14–24.

e13. Montalban X, Sastre-Garriga J, Tintore M, et al. A single-center, randomized, double-blind, placebo-controlled study of interferon beta-1b on primary progressive and transitional multiple sclerosis. Mult Scler 2009;15:1195–1205.

e14. Fisniku LK, Brex PA, Altmann DR, et al. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. Brain 2008;131:808–817.

e15. Rio J, Rovira A, Tintore M, et al. Relationship between MRI lesion activity and response to IFN-beta in relapsing-remitting multiple sclerosis patients. Multiple Sclerosis 2008;14:479–484.

e16. Sormani MP, Rio J, Tintore M, et al. Scoring treatment response in patients with relapsing multiple sclerosis. Mult Scler 2013;19:605–612.

e17. Prosperini L, Gallo V, Petsas N, Borriello G, Pozzilli C. One-year MRI scan predicts clinical response to interferon beta in multiple sclerosis. Eur J Neurol 2009;16:1202–1209.

e18. Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging-measured disease activity and burden in patients with relapsing multiple sclerosis. Ann Neurol 2001;49:290–297.

e19. Confavreux C, O'Connor P, Comi G, et al. Oral terifl unomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol 2014;13:247–256.

e20. Johnson K, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis. Neurology 1995;45:1268–1276.

e21. PRISMS. Randomised double-blind placebo-controlled study of interferon -1a in relapsing/remitting multiple sclerosis. Lancet 1998;352:1498–1504.

e22. Traboulsee A, Simon JH, Stone L, et al. Revised Recommendations of the Consortium of MS Centers Task Force for a Standardized MRI Protocol and Clinical Guidelines for the Diagnosis and Follow-Up of Multiple Sclerosis. Am J Neuroradiol 2016;37:394–401.

e23. Devonshire V, Lapierre Y, Macdonell R, et al. The Global Adherence Project (GAP): a multicenter observational study on adherence to disease-modifying therapies in patients with relapsing-remitting multiple sclerosis. Eur J Neurol 2011;18:69–77.

e24. Clifford DB, De Luca A, Simpson DM, Arendt G, Giovannoni G, Nath A. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. Lancet Neurol 2010;9:438–446.

e25. US Food and Drug Administration. FDA Drug Safety Communication: New risk factor for Progressive Multifocal Leukoencephalopathy (PML) associated with Tysabri (natalizumab). Available at: https://www.fda.gov/drugs/drugsafety/ucm288186.htm. Published January 20, 2012. Accessed June 1, 2016.

e26. US Food and Drug Administration. FDA Drug Safety Communication: FDA warns about case of rare brain infection PML with MS drug Tecfidera (dimethyl fumarate). Available at: https://www.fda.gov/Drugs/DrugSafety/ucm424625.htm. Published November 25, 2014. Accessed June 1, 2016.

e27. Rosenkranz T, Novas M, Terborg C. PML in a patient with lymphocytopenia treated with dimethyl fumarate. N Engl J Med 2015;372:1476–1478.

e28. Nieuwkamp DJ, Murk JL, van Oosten BW. PML in patients treated with dimethyl fumarate. N Engl J Med 2015;373:584.

e29. US Food and Drug Administration. FDA Drug Safety Communication: FDA warns about cases of rare brain infection with MS drug Gilenya (fingolimod) in two patients with no prior exposure to immunosuppressant drugs. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm456919.htm. Published August 4, 2015. Accessed June 1, 2016.

e30. Carson KR, Evens AM, Richey EA, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. Blood 2009;113:4834–4840.

e31. Ocrevus [package insert]. In: Genentech, ed. South San Francisco, CA:2017.

e32. Huang D. Disseminated cryptococcosis in a patient with multiple sclerosis treated with fingolimod. Neurology 2015;85:1001–1003.

e33. Pelletier D, Hafler DA. Fingolimod for multiple sclerosis. N Engl J Med 2012;366:339–347.

e34. Ratchford JN, Costello K, Reich DS, Calabresi PA. Varicella-zoster virus encephalitis and vasculopathy in a patient treated with fingolimod. Neurology 2012;79:2002–2004.

e35. Fine AJ, Sorbello A, Kortepeter C, Scarazzini L. Central nervous system herpes simplex and varicella zoster virus infections in natalizumab-treated patients. Clin Infect Dis 2013;57:849–852.

e36. Krumbholz M, Pellkofer H, Gold R, Hoffmann LA, Hohlfeld R, Kumpfel T. Delayed allergic reaction to natalizumab associated with early formation of neutralizing antibodies. Arch Neurol 2007;64:1331–1333.

e37. Vennegoor A, Rispens T, Strijbis EM, et al. Clinical relevance of serum natalizumab concentration and anti-natalizumab antibodies in multiple sclerosis. Mult Scler 2013;19:593–600.

e38. Prosperini L, Annovazzi P, Capobianco M, et al. Natalizumab discontinuation in patients with multiple sclerosis: Profiling risk and benefits at therapeutic crossroads. Mult Scler 2015;21:1713–1722.

e39. Comi G, Gold R, Dahlke F, et al. Relapses in patients treated with fingolimod after previous exposure to natalizumab. Mult Scler 2015;21:786–790.

e40. Iaffaldano P, Lucisano G, Pozzilli C, et al. Fingolimod versus interferon beta/glatiramer acetate after natalizumab suspension in multiple sclerosis. Brain 2015;138:3275–3286.

e41. Alping P, Frisell T, Novakova L, et al. Rituximab versus fingolimod after natalizumab in multiple sclerosis patients. Ann Neurol 2016;79:950–958.

e42. Finkelsztejn A, Brooks JBB, Paschoal Jr FM, Fragoso YD. What can we really tell women with multiple sclerosis regarding pregnancy? A systematic review and meta-analysis of the literature. BJOG 2011;118:790–797.

e43. Lu E, Wang BW, Guimond C, Synnes A, Sadovnick D, Tremlett H. Disease-modifying drugs for multiple sclerosis in pregnancy: a systematic review. Neurology 2012;79:1130–1135.

e44. Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. Brain 1989;112 (Pt 1):133–146.

e45. Paz Soldan MM, Novotna M, Abou Zeid N, et al. Relapses and disability accumulation in progressive multiple sclerosis. Neurology 2015;84:81–88.

e46. Tremlett H, Zhao Y, Devonshire V. Natural history of secondary-progressive multiple sclerosis. Mult Scler 2008;14:314–324.

e47. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis. Ann Neurol 2011;69:292–302.

e48. Mowry EM, Pesic M, Grimes B, et al. Clinical predictors of early second event in patients with clinically isolated syndrome. J Neurol 2009;256:1061–1066.

e49. D'Alessandro, Roberto, et al. Risk of multiple sclerosis following clinically isolated syndrome: a 4-year prospective study. J Neurol 260.6:1583–1593.

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