

Comprehensive systematic review summary: 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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Abstract

Objective

To review evidence on starting, switching, and stopping disease-modifying therapies (DMTs) for multiple sclerosis (MS) in clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), and progressive MS forms.

Methods

Relevant, peer-reviewed research articles, systematic reviews, and abstracts were identified (MEDLINE, CENTRAL, EMBASE searched from inception to November 2016). Studies were rated using the therapeutic classification scheme. Prior published Cochrane reviews were also used.

Results

Twenty Cochrane reviews and an additional 73 full-text articles were selected for data extraction through an updated systematic review (completed November 2016). For people with RRMS, many DMTs are superior to placebo (annualized relapses rates [ARRs], new disease activity [new MRI T2 lesion burden], and in-study disease progression) (see summary and full text publications). For people with RRMS who experienced a relapse on interferon- β (IFN- β) or glatiramer acetate, alemtuzumab is more effective than IFN- β -1a 44 μ g subcutaneous 3 times per week in reducing the ARR. For people with primary progressive MS, ocrelizumab is probably more effective than placebo (in-study disease progression). DMTs for MS have varying adverse effects. In people with CIS, glatiramer acetate and IFN- β -1a subcutaneous 3 times per week are more effective than placebo in decreasing risk of conversion to MS. Cladribine, immunoglobulins, IFN- β -1a 30 μ g intramuscular weekly, IFN- β -1b subcutaneous alternate day, and teriflunomide are probably more effective than placebo in decreasing risk of conversion to MS. Suggestions for future research include studies considering comparative effectiveness, usefulness of high-efficacy treatment vs stepped-care protocols, and research into predictive biomarkers.

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Glossary

AAN = American Academy of Neurology; AE = adverse effect; ARR = annualized relapse rate; CIS = clinically isolated syndromes; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; HYP = high-yield process; IFN- β = interferon- β ; IM = intramuscular; MS = multiple sclerosis; PPMS = primary progressive multiple sclerosis; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

This article summarizes the findings and conclusions of an American Academy of Neurology (AAN) practice guideline on the efficacy and safety of disease-modifying therapies (DMTs) in multiple sclerosis (MS). References e1 through e49, cited here, are available at links.lww.com/WNL/A374 as a data supplement to this summary article.

A companion article presents the recommendations and suggestions for future research.¹ The complete practice guideline (systematic review, recommendations, and suggestions for future research) is available at links.lww.com/WNL/A429 as a data supplement to the companion recommendations article. This guideline, although not a formal update to the 2002 AAN guideline on DMTs,² replaces that earlier guideline. The complete guideline includes full details of the methodology used, including risk of bias classification for each study, confidence in the evidence determinations, and rationales for recommendation strength; space restrictions precluded more detailed description in this article.

MS affects more than 400,000 people in the United States and more than 2.3 million people worldwide.³ Since 1993, DMTs have been approved in the United States for treating relapsing forms of MS; most of these therapies are approved for use in other countries. Many additional medications have been used off-label for MS disease modification.

Multiple new DMTs have become available since publication of the 2002 AAN practice guideline on DMTs in MS.² Clinicians and people with MS may now choose from several medications, with differing mechanisms of action, risk profiles, and monitoring requirements. 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.

The new practice guideline,¹ based on the systematic review summarized here, provides guidance concerning current issues surrounding DMT for MS prescribing, specifically addressing

the following questions pertinent to clinically isolated syndromes of demyelination (CIS), relapsing-remitting MS (RRMS), and progressive forms of MS (secondary progressive MS [SPMS] and primary progressive MS [PPMS]):

1. In people with RRMS, are DMTs superior to placebo or other DMTs as measured by annualized relapse rates (ARRs) and the relative risk of relapse at 2 years?
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 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?
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 adverse effects (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?

Description of the analytic process

In May 2015, the AAN guideline subcommittee recruited a multidisciplinary panel to develop the guideline on which this systematic review is based. The panel consists of 12 AAN physician and nurse members, 2 representatives from the Consortium of Multiple Sclerosis Centers, and 3 patient representatives. Two AAN staff representatives were also appointed to the panel. Conflicts of interest were reviewed by the panel leadership; panelists with conflicts did not participate in systematic review development.

The 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.⁴ Institute of Medicine standards for systematic review and clinical practice guideline development were adhered to throughout the

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development process, including posting of the protocol and draft document with recommendations for public review and active solicitation of patient input.^{5,6} For the systematic review, the panel used appropriate Cochrane reviews (assessed by 2 panelists working independently of each other and using A Measurement Tool to Assess Systematic Reviews quality)⁷ in addition to treatment-specific systematic reviews. Two non-conflicted panelists working independently reviewed abstracts for article inclusion. From their review, full-text articles were obtained for data extraction, and risk of bias was established by 2 panelists rating articles independently of each other. Data extraction was performed by the AAN staff guideline methodologist and confirmed by panel members. The panel considered data for efficacy outcomes from randomized controlled trials (RCTs). For harms, the panel considered data from RCTs, cohort studies, case reports, and case series. Meta-analyses were performed when appropriate. Before data analysis, the panel completed an anonymous survey to establish the minimal clinically meaningful difference for measures of DMT efficacy and AEs; this information was used in the analytic portion of the guideline. Conclusions were developed using a modified Grading of Recommendations, Assessment, Development and Evaluation process.⁸

Analysis of evidence

Twenty Cochrane systematic reviews were identified and used in the evidence review process. These systematic reviews included data from 70 RCTs, which were included in the panel's evidence synthesis. For the update of the Cochrane reviews and de novo systematic review (completed November 2016), the combined searches yielded 4,301 abstracts. Each abstract was reviewed for relevance by at least 2 panel members, who deemed 284 as relevant. The corresponding articles were obtained for full-text review 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 was usually between 50 and 60 years. Most studies were 2 years in length (range 6 months–3 years). Trials occurred in multiple countries worldwide. Twenty-three DMTs were systematically reviewed: methotrexate, cyclophosphamide, pulsed corticosteroids for disease modification, interferon- β (IFN- β) (4 types: IFN- β -1b subcutaneous alternate day, IFN- β -1a intramuscular [IM] subcutaneous, pegylated IFN subcutaneous every other week, IFN- β -1a subcutaneous 3 times per week), glatiramer acetate (3 types: proprietary daily 20-mg subcutaneous form, proprietary 3-day-per-week 40-mg subcutaneous form, generic 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.

Safety note: After US Food and Drug Administration (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.^{8a}

The results of the systematic review support the following evidence-based conclusions. All recommendations are provided in the companion publication.¹

1. In people with RRMS, are DMTs superior to placebo or other DMTs as measured by ARRs and the relative risk of relapse at 2 years?

For this question, figure 1 presents the data regarding ARRs, and figure 2 presents the data on the relative risk of relapse at 2 years. The table shows the findings and conclusions for both the ARRs and the relative risk of relapse at 2 years.

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?

Risk of new or enlarging T2 lesions

The following DMTs are more effective than placebo in reducing the risk of MRI-detected new or enlarging T2 lesions (high confidence): fingolimod,^{9,10} IFN- β -1a 44 μ g subcutaneous 3 times weekly,¹¹ and natalizumab.¹²

Ocrelizumab¹³ is more effective than IFN- β -1a subcutaneous 3 times per week in reducing the risk of new or enlarging T2 lesions detected by MRI (high confidence).

Cladribine¹⁴ is probably more effective than placebo in reducing the risk of new or enlarging T2 lesions detected by MRI (moderate confidence).

The following DMTs are probably more effective than other DMTs in reducing the risk of MRI-detected new or enlarging T2 lesions (moderate confidence): alemtuzumab (vs IFN- β -1a subcutaneous 3 times per week),¹⁵ fingolimod (vs IFN- β -1a IM once weekly),¹⁶ IFN- β -1a 44 μ g subcutaneous 3 times weekly (vs IFN- β -1a IM once weekly).¹⁷

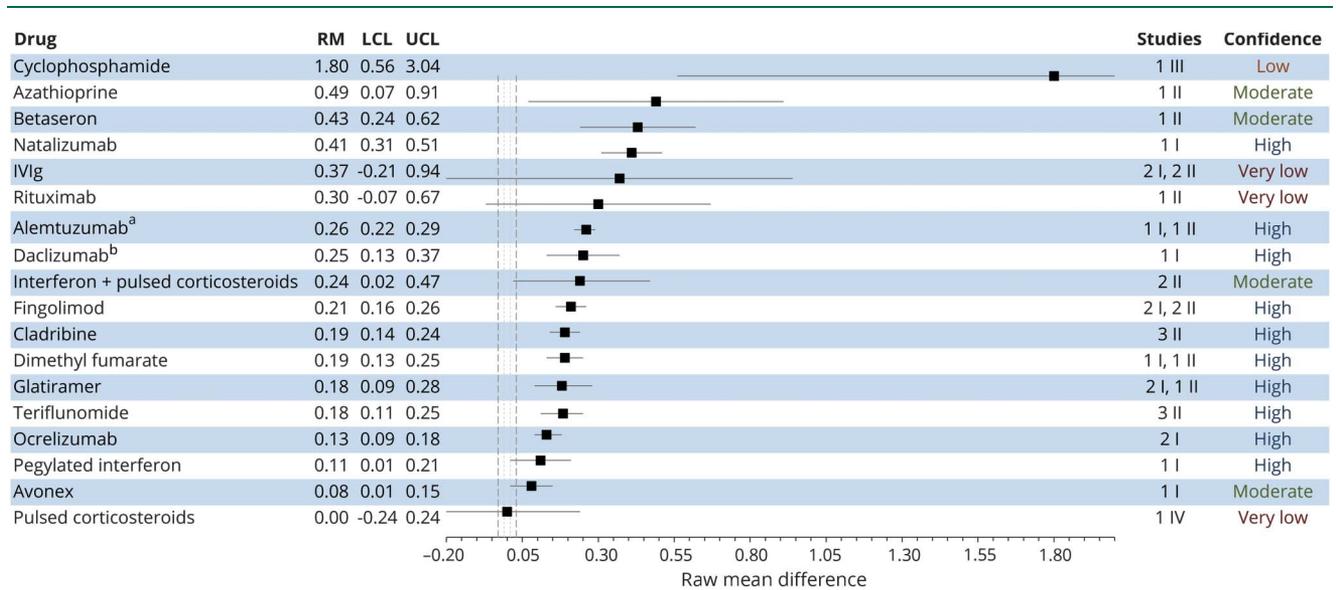
IFN- β -1a subcutaneous 3 times per week is possibly no more effective than glatiramer acetate in decreasing the risk of MRI-detected new or enlarging T2 lesions (low confidence).¹⁸

There is insufficient evidence to determine the efficacy of azathioprine compared with IFN- β ¹⁹ in reducing the risk of MRI-detected new or enlarging T2 lesions (very low confidence).

Reducing the volume or number of T2 lesions

The following DMTs are more effective than placebo in reducing the volume or number of MRI-detected T2 lesions (high confidence): daclizumab high-yield process (HYP),²⁰ dimethyl fumarate,^{18,21} glatiramer acetate,¹⁸ IFN- β -1a 30 μ g IM weekly,²² mitoxantrone,²³ natalizumab,¹² and pegylated IFN.²⁴ See the safety note on this page.^{8a}

Figure 1 Outcome: Annualized relapse rate, relapsing-remitting multiple sclerosis

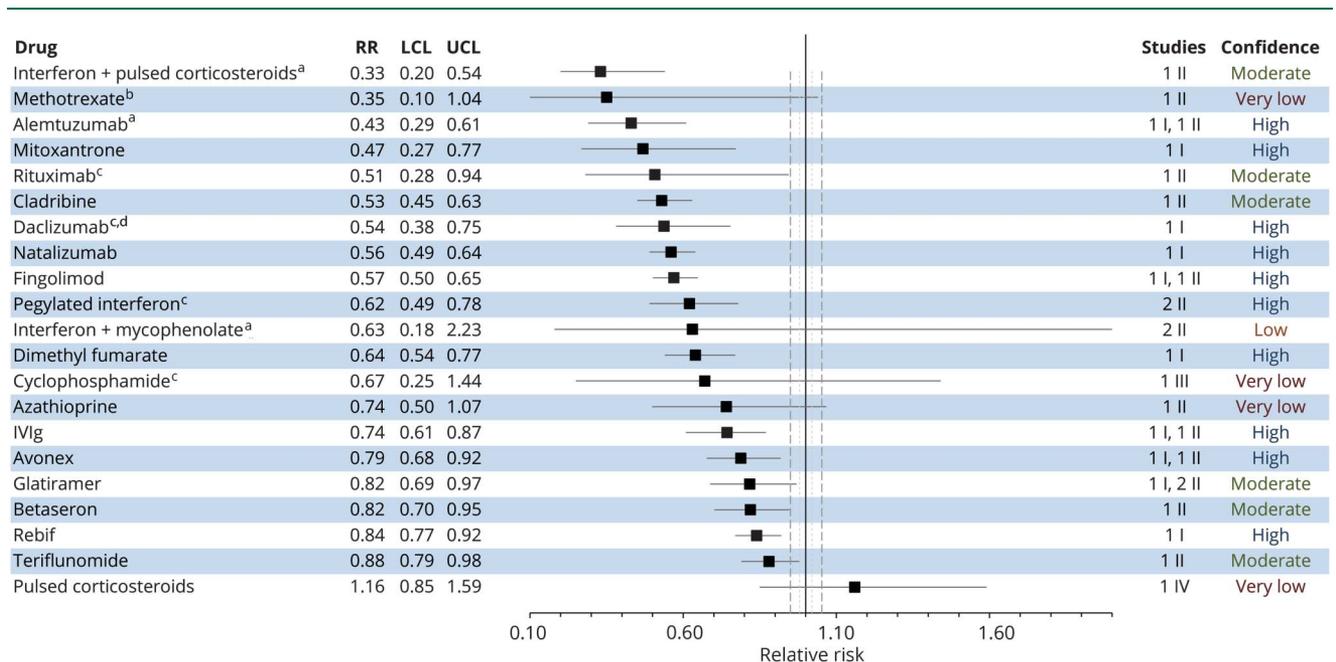


IVIg = IV immunoglobulin; LCL = lower confidence limit; RM = raw mean difference; UCL = upper confidence limit. ^aVersus interferon- β -1a 44 μ g 3 times per week subcutaneously. ^bSee safety note on page 791.^{8a}

Rituximab²⁵ and teriflunomide²⁶ are probably more effective than placebo in reducing the volume or number of MRI-detected T2 lesions (moderate confidence).

The following DMTs are probably more effective than other DMTs in reducing the volume or number of MRI-detected T2 lesions (moderate confidence): alemtuzumab

Figure 2 Outcome: Relative risk of relapse at 2 years, relapsing-remitting multiple sclerosis



IVIg = IV immunoglobulin; LCL = lower confidence limit; RR = risk ratio; UCL = upper confidence limit. ^aRelative to interferon alone. ^bOutcome assessed at 18 months. ^cOutcome assessed at 1 year. ^dSee safety note on page 791.^{8a}

Table Efficacy of disease-modifying therapies (DMTs) for reducing the annualized relapse rate (ARR) and risk of relapse at 2 years

Confidence strength	Reduction of the ARR		Reduction of risk of relapse at 2 y	
	Compared with placebo	Compared with other DMTs	Compared with placebo	Compared with other DMTs
High	Cladribine ^{14,e34} more effective	Alemtuzumab more effective than IFN-β-1a subcutaneous 3 times per wk ^{15,29}	Daclizumab HYP ³ more effective (outcome measured at 1 y) ²⁰	Alemtuzumab ^{15,29} more effective than IFN-β-1a subcutaneous 3 times per wk
	Daclizumab HYP ³ more effective ²⁰	Azathioprine more effective than β-interferons ^{19,e35}	Dimethyl fumarate ^{18,21} more effective	—
	Dimethyl fumarate ^{18,21} more effective ^b	Fingolimod more effective than IFN-β-1a IM once per wk ¹⁶	Fingolimod ^{9,10} more effective	—
	Fingolimod ^{9,10,e36} more effective	Ocrelizumab more effective than IFN-β-1a subcutaneous 3 times per wk ¹³	Immunoglobulins ^{39,40} more effective	—
	Glatiramer acetate ^{18,34,e37} more effective	—	IFN-β-1a IM once per wk ^{22,32} more effective	—
	Natalizumab ¹² more effective	—	IFN-β-1a subcutaneous 3 times per wk ¹¹ more effective	—
	Pegylated IFN ²⁴ more effective	—	Mitoxantrone ²³ more effective	—
	Teriflunomide ^{26,e38,e39} more effective	—	Natalizumab ¹² more effective	—
	—	—	Pegylated IFN more effective (outcome measured at 1 y) ²⁴	—
	Moderate	Azathioprine probably more effective ^{e40}	—	Cladribine probably more effective ¹⁴
IFN-β-1a IM once per wk ²² probably more effective		—	Glatiramer acetate probably more effective ^{18,34,35}	—
IFN-β-1b subcutaneous alternate day ^{e1} probably more effective		—	IFN-β-1b subcutaneous alternate day probably more effective ^{e1}	—
Pulsed corticosteroids added to IFN-β-1a ^{36,e41} probably more effective		—	Pulsed corticosteroids added to IFN-β-1a ^{e41} probably more effective	—
—		Daclizumab HYP ²⁷ IFN-β-1a once per wk probably more effective ^a	Rituximab probably more effective (outcome measured at 1 y) ²⁵	—
—		—	Teriflunomide ²⁶ probably more effective	—
Low		Cyclophosphamide ^{e42} possibly more effective	—	—
	—	—	—	Complex nonbiologic generic glatiramer acetate (Glatopa) ^{e44} possibly no more effective than glatiramer acetate (Copaxone)
	—	—	—	IFN-β-1a IM once weekly ³⁷ possibly no more effective than glatiramer acetate (Copaxone)
	—	—	—	IFN-β-1a subcutaneous 3 times weekly ^{e45} possibly no more effective than glatiramer acetate (Copaxone)
	—	—	—	—

Continued

Table Efficacy of disease-modifying therapies (DMTs) for reducing the annualized relapse rate (ARR) and risk of relapse at 2 years (continued)

Confidence strength	Reduction of the ARR		Reduction of risk of relapse at 2 y	
	Compared with placebo	Compared with other DMTs	Compared with placebo	Compared with other DMTs
	—	—	—	IFN-β-1b subcutaneous alternate day ^{e46,e47} possibly no more effective than glatiramer acetate (Copaxone)
Very low	Azathioprine insufficient to support or refute ^{e40}	—	Azathioprine insufficient to support or refute ^{e40}	—
	Immunoglobulins insufficient to support or refute ^{39,40,e48,e49}	—	Cyclophosphamide insufficient to support or refute (outcome measured at 12 mo) ^{e42}	—
	Pulsed corticosteroids insufficient to support or refute ³⁰	—	Methotrexate insufficient to support or refute ^{e2}	—
	Rituximab insufficient to support or refute ²⁵	—	Pulsed corticosteroids insufficient to support or refute ³⁰	—

Abbreviations: HYP = high-yield process; IFN-β = interferon-β; IM = intramuscular.

^a See safety note on page 791.^{8a}

^b Glatiramer acetate included as a reference comparator in a dimethyl fumarate study and not powered for study of noninferiority or superiority; required by regulatory agency.

(vs IFN-β-1a subcutaneous 3 times per week)¹⁵ and daclizumab (vs IFN-β-1a IM once weekly).²⁷ See safety note on page 791.^{8a}

There is insufficient evidence to determine the efficacy of mycophenolate mofetil vs IFN-β-1a once weekly for reducing the volume or number of MRI-detected T2 lesions (very low confidence).²⁸

There is insufficient evidence to determine the efficacy of pulsed corticosteroids²⁹ relative to placebo for reducing the volume or number of MRI-detected T2 lesions (very low confidence).

Reducing loss of parenchymal volume

Ocrelizumab¹³ is more effective than IFN-β-1a 44 μg subcutaneous 3 times weekly in reducing loss of parenchymal volume (high confidence).

Alemtuzumab is probably more effective than IFN-β-1a 44 μg subcutaneous 3 times weekly²⁹ in reducing loss of parenchymal volume (moderate confidence).

Pulsed corticosteroids³⁰ are probably more effective than placebo in reducing loss of parenchymal volume (moderate confidence).

There is insufficient evidence to determine the efficacy of the following DMTs relative to placebo in reducing loss of parenchymal volume (very low confidence): IFN-β-1a 30 μg IM weekly²² and mycophenolate mofetil added to IFN-β-1a 30 μg IM weekly.³¹

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?

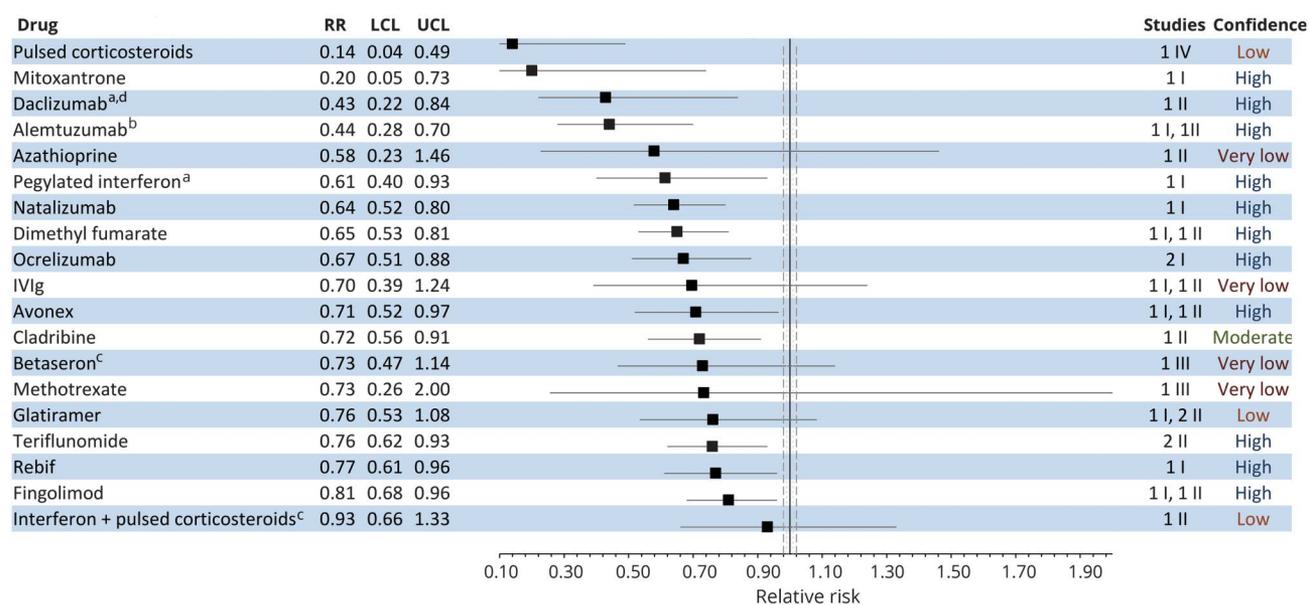
The most consistently reported measure for in-study disability progression was the proportion of people with MS with disability progression. Disability progression was defined by an increase in the Expanded Disability Status Scale (EDSS) of 1 point in those with a baseline EDSS score of 5.0 or lower, or an increase of 0.5 point in those with a baseline EDSS score of 5.5 or higher, sustained for 3 or 6 months, and detected over a 2-year study period (figure 3).

The following DMTs are more effective than placebo in reducing the risk of disability progression in people with RRMS (high confidence): daclizumab HYP,²⁰ dimethyl fumarate,^{18,21} fingolimod,^{9,10} IFN-β-1a 30 μg IM weekly,^{22,32} IFN-β-1a 44 μg subcutaneous 3 times weekly,¹¹ mitoxantrone,²³ natalizumab,¹² pegylated IFN,²⁴ and teriflunomide.^{26,33} See safety note on page 791.^{8a}

The following DMTs are more effective than other DMTs in reducing the risk of disability progression in people with RRMS (high confidence): alemtuzumab (vs IFN-β-1a 44 μg subcutaneous 3 times weekly)^{15,29} and ocrelizumab (vs IFN-β-1a 44 μg subcutaneous 3 times weekly).¹³

Cladribine¹⁴ is probably more effective than placebo in reducing the risk of disability progression in people with RRMS (moderate confidence).

Figure 3 Outcome: Relative risk (RR) of in-study disability progression at 2 years, relapsing-remitting multiple sclerosis



IVIg = IV immunoglobulin; LCL = lower confidence limit; UCL = upper confidence limit. ^aOutcome measured at 1 year. ^bVersus interferon- β -1a. ^cOutcome measured at 3 years. ^dSee safety note on page 791.^{8a}

Daclizumab is probably more effective than IFN- β -1a 30 μ g IM²⁷ in reducing the risk of disability progression in people with RRMS (moderate confidence). See safety note on page 791.^{8a}

Pulsed corticosteroids³⁰ are possibly more effective than placebo in reducing the risk of disability progression in people with RRMS (low confidence).

The following DMTs are possibly no more effective than placebo in reducing the risk of disability progression in people with RRMS (low confidence): glatiramer acetate^{18,34,35} and pulsed corticosteroids added to IFN- β -1a IM once weekly.³⁶

Fingolimod is possibly no more effective than IFN- β -1a IM weekly in reducing the risk of disability progression over 1 year (low confidence).¹⁶ See safety note on page 791.^{8a}

IFN- β -1a is possibly no more effective than glatiramer acetate in reducing the risk of disability progression over 3 years (low confidence).³⁷

There is insufficient evidence to determine the efficacy of the following DMTs compared with placebo in reducing the risk of disability progression in people with RRMS (very low confidence): azathioprine,³⁸ immunoglobulins,^{39,40} IFN- β -1b subcutaneous alternate day,^{e1} and methotrexate.^{e2}

IFN- β -1b alternate day is probably less effective than glatiramer acetate in reducing the risk of disability progression over 2 years (moderate confidence).^{e1}

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?

For individuals with RRMS who experienced a relapse on IFN- β or glatiramer acetate, alemtuzumab is more effective than IFN- β -1a 44 μ g subcutaneous 3 times per week in reducing the ARR, the relapse risk, disability progression, and risk of new or enlarging T2 lesions over 2 years (high confidence).¹⁵

In individuals with RRMS who experience 1 or more relapses in the preceding 12 months on IFN- β , 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).^{e3}

In individuals with RRMS who experienced one 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).^{e4}

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).^{e4}

Note that natalizumab is not presently approved/recommended as an add-on therapy to other DMTs owing to potential safety concerns associated with combined use of this medication.

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

Risk of relapse

Figure 4 presents these data regarding risk of relapse. IFN- β -1b subcutaneous alternate day (SPMS) is more effective than placebo in reducing the risk of relapse in people with progressive MS (high confidence).^{e5,e6}

The following DMTs are probably more effective than placebo in reducing the risk of relapse in people with progressive MS (moderate confidence): IFN- β -1a 60 μ g IM weekly (SPMS)^{e7} and mitoxantrone (worsening RRMS and SPMS).^{e8}

There is insufficient evidence to determine the efficacy of the following DMTs compared with placebo in reducing the risk of relapse in people with progressive MS (very low confidence): azathioprine,³⁸ immunoglobulins,^{e9,e10} and methotrexate (chronic progressive MS, older terminology that is undefined but included present PPMS and SPMS disease types).^{e11} There is insufficient evidence to determine the efficacy of high-dose corticosteroids compared with low-dose corticosteroids^{e12} in reducing the risk of relapse in people with SPMS (very low confidence).

Disability progression

The following DMTs are probably more effective than placebo in reducing the risk of in-study disability progression in people with progressive MS (RRMS or SPMS; moderate confidence): mitoxantrone (worsening RRMS and SPMS)^{e13} and ocrelizumab (PPMS).^{e14}

The following DMTs are possibly no more effective than placebo in reducing the risk of in-study disability progression in people with progressive MS (low confidence): cladribine (SPMS),^{e15} fingolimod (PPMS),^{e16} glatiramer acetate (progressive forms of MS^{e17} and PPMS^{e18}), IFN- β -1a 30 μ g IM weekly (SPMS^{e7} and PPMS^{e19}), IFN- β -1a subcutaneous 3 times per week (SPMS),^{e20} IFN- β -1b subcutaneous alternate day (SPMS^{e5,e6} and PPMS^{e21}), and rituximab (PPMS).^{e22}

There is insufficient evidence to determine the efficacy of the following DMTs relative to placebo in reducing the risk of in-study disability progression in people with progressive MS (very low confidence): azathioprine,³⁸ corticosteroids added to mitoxantrone,^{e23} cyclophosphamide,^{e24,e25} immunoglobulins,^{e9,e10} and methotrexate (CPMS [PPMS]).^{e11}

There is insufficient evidence to determine the efficacy of high-dose corticosteroids relative to low-dose corticosteroids^{e26} in reducing the risk of in-study disability progression in people with progressive MS (very low confidence).

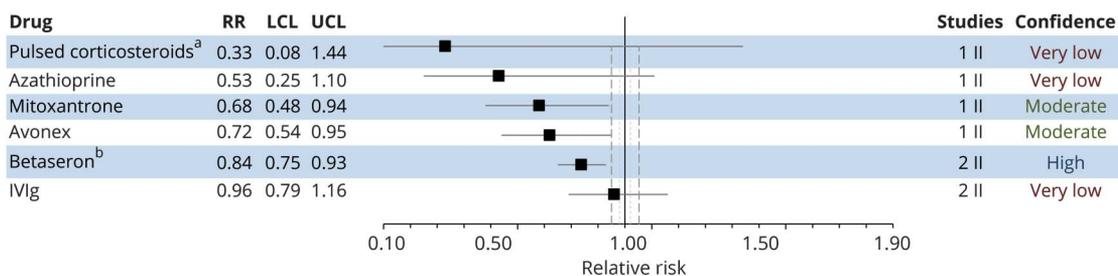
6. What are the AEs of DMTs in people with MS compared with placebo (AE-related discontinuation and serious or life-threatening AEs)?

A comprehensive review of adverse effects associated with DMTs is included in the full-text document (data supplement to the companion recommendations article, links.lww.com/WNL/A429) and table.

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

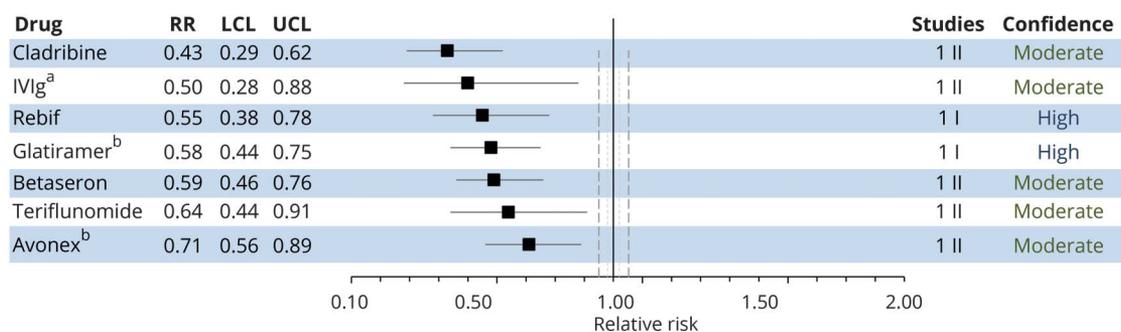
Figure 5 presents the data regarding risk of conversion to MS in people with CIS. For individuals with CIS, the following DMTs are more effective than placebo in reducing the proportion of individuals converting to MS (high confidence): glatiramer acetate^{e27} and IFN- β -1a subcutaneous 3 times weekly.^{e28}

Figure 4 Outcome: Relative risk (RR) of relapse at 2 years secondary progressive multiple sclerosis



IVIg = IV immunoglobulin; LCL = lower confidence limit; UCL = upper confidence limit. ^aHigh-dose corticosteroids vs low-dose corticosteroids. ^bOutcome measured at 3 years.

Figure 5 Outcome: Relative risk (RR) of conversion to multiple sclerosis over 2 years



IVIg = IV immunoglobulin; LCL = lower confidence limit; UCL = upper confidence limit. ^aOutcome measured at 1 year. ^bOutcome measured at 3 years.

For individuals with CIS, the following DMTs are probably more effective than placebo in reducing the proportion of individuals converting to MS (moderate confidence): cladribine,^{e29} immunoglobulins,^{e30} IFN- β -1a 30 μ g IM weekly,^{e31} IFN- β -1b subcutaneous alternate day,^{e32} and teriflunomide.^{e33}

Discussion

Multiple DMTs are now approved for use in CIS or MS, allowing people with MS and clinicians to consider DMT mechanism of action, efficacy, and AE profile in the decision-making process. This systematic review was used to develop a practice guideline for the use of DMT for MS, acknowledging the limits of current evidence. Measures of efficacy such as long-term disability, patient satisfaction, quality of life, and effects on MS symptoms may be important to the decision-making process but ultimately remain inadequately studied. Similarly, there is a dearth of high-quality evidence pertaining to the comparative efficacy of specific DMTs or various treatment strategies (e.g., high-efficacy treatment vs stepped-care treatment protocols). Future studies addressing these and other questions are needed to further inform treatment recommendations, particularly those pertaining to when to switch or stop DMTs.

Author contributions

Dr. Rae-Grant: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revision of the manuscript, critical revision of the manuscript for important intellectual content, study supervision. Dr. Day: study concept and design, analysis or interpretation of data, drafting/revision of the manuscript, critical revision of the manuscript for important intellectual content. Dr. Marrie: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revision of the manuscript, critical revision of the manuscript for important intellectual content. Dr. Rabinstein: analysis or interpretation of data, drafting/revision of the manuscript. Dr. Cree: study concept and design, drafting/revision

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Conflict of interest statement

The American Academy of Neurology (AAN) is committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least 3 AAN committees, a network of neurologists, *Neurology*[®] peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at aan.com. For complete information on this process, access the 2011 AAN process manual, as amended.⁴

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References

- Rae-Grant A, Day GS, Marrie RA, et al; for the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2018;90:777–788.
- Goodin DS, Frohman EM, Garmany GP, et al; on behalf of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Disease-modifying therapies in multiple sclerosis: subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology* 2002;58:169–178.
- 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.
- American Academy of Neurology. Clinical Practice Guideline Process Manual, 2011 ed. [online]. St. Paul: The American Academy of Neurology; 2011. Available at: aan.com/policy-and-guidelines/guidelines/about-guidelines/. Accessed March 12, 2016.
- Institute of Medicine; Eden J, Levit L, Berg A, Morton S, editors. Committee on Standards for Systematic Reviews of Comparative Effectiveness Research. Washington, DC: National Academies Press; 2011.
- Institute of Medicine, Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. Clinical Practice Guidelines We Can Trust. Washington, DC: National Academies Press; 2011.
- Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007;7:10.
- Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the *Journal of Clinical Epidemiology*. *J Clin Epidemiol* 2011;64:380–382.
- Biogen and AbbVie announce the voluntary worldwide withdrawal of marketing authorizations for ZINBRYTA[®] (daclizumab) for relapsing multiple sclerosis [press release]. Available at: <http://media.biogen.com/press-release/autoimmune-diseases/biogen%20and-abbvie-announce%20voluntary%20worldwide-withdrawal-market>. Issued March 2, 2018. Accessed March 5, 2018.
- Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010;362:387–401.
- Calabresi P, Radue EW, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014;13:545–556.
- PRISMS (Prevention of Relapses and Disability by Interferon Beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. *Lancet* 1998;352:1498–1504.
- Polman C, O'Connor PW, Havdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006;354:899–910.
- Hauser SL, Bar-Or A, Comi G, et al; for the OPERA I and OPERA II Clinical Investigators. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med* 2017;376:221–234.
- Giovannoni G, Comi G, Cook S, et al; on behalf of the CLARITY Study Group. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N Engl J Med* 2010;362:416–426.
- Cohen J, Coles AJ, Arnold DL, et al; CARE-MS I Investigators. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet* 2012;380:1819–1828.
- Cohen J, 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.
- Panitch H, Goodin DS, Francis G, et al; or the University of British Columbia MS/MRI Research Group. Randomized, comparative study of interferon beta-1a treatment regimens in MS the EVIDENCE Trial. *Neurology* 2002;59:1496–1506.
- Fox R, Miller DH, Phillips JT, et al; on behalf of the CONFIRM Study Investigators. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med* 2012;367:1087–1097.
- Massacesi L, Tramacere I, Amoroso S, et al. Azathioprine versus beta interferons for relapsing-remitting multiple sclerosis: a multicentre randomized non-inferiority trial. *PLoS One* 2014;9:e113371.
- Gold R, Giovannoni G, Selmaj K, et al; on behalf of the SELECT Study Investigators. Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomised, double-blind, placebo-controlled trial. *Lancet* 2013;381:2167–2175.
- Gold R, Kappos L, Arnold DL, et al; on behalf of the DEFINE Study Investigators. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med* 2012;367:1098–1107.
- Vollmer T, Sorensen PS, Selmaj K, et al; on behalf of the BRAVO Study Group. A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis. *J Neurol* 2014;261:773–783.
- Millefiorini E, Gasperini C, Pozzilli C, et al. Randomized placebo-controlled trial of mitoxantone in relapsing-remitting multiple sclerosis: 24-month clinical and MRI outcome. *J Neurol* 1997;244:153–159.
- Calabresi P, Kieseier BC, Arnold DL, et al; for the ADVANCE Study Investigators. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. *Lancet Neurol* 2014;13:657–665.
- Hauser SL, Waubant E, Arnold DL, et al; for the HERMES Trial Group. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Engl J Med* 2008;358:676–688.
- O'Connor P, Wolinsky JS, Confavreux C, et al; for the TEMSO Trial Group. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med* 2011;365:1293–1303.
- Kappos L, Wiendl H, Selmaj K, et al. Daclizumab HYP versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med* 2015;373:1418–1428.
- Frohman EM, Cutter G, Remington G, et al. A randomized, blinded, parallel-group, pilot trial of mycophenolate mofetil (CellCept) compared with interferon beta-1a (Avonex) in patients with relapsing-remitting multiple sclerosis. *Ther Adv Neurol Disord* 2010;3:15–28.
- 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;80:1829–1839.
- Zivadinov R, Rudick RA, De Masi R, et al. Effects of IV methylprednisolone on brain atrophy in relapsing-remitting MS. *Neurology* 2001;57:1239–1247.
- Remington GM, Treadaway K, Frohman T, et al. A one-year prospective, randomized, placebo-controlled, quadruple-blinded, phase II safety pilot trial of combination therapy with interferon beta-1a and mycophenolate mofetil in early relapsing-remitting multiple sclerosis (TIME MS). *Ther Adv Neurol Disord* 2010;3:3–13.
- Jacobs L, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. *Ann Neurol* 1996;39:285–294.
- Confavreux C, O'Connor P, Comi G, et al; for the TOWER Trial Group. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014;13:247–256.
- Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial: Copolymer 1 Multiple Sclerosis Study Group. *Neurology* 1995;45:1268–1276.

35. Bornstein MB, Miller A, Slagle S, et al. A pilot trial of COP 1 in exacerbating-relapsing multiple sclerosis. *N Engl J Med* 1987;317:408–414.
36. Ravnborg M, Sorensen PS, Andersson M, et al. Methylprednisolone in combination with interferon beta-1a for relapsing-relapsing multiple sclerosis (MECOMBIN study): a multicentre, double-blind, randomized, placebo-controlled, parallel-group study. *Lancet Neurol* 2010;9:672–680.
37. Lublin FD, Cofield SS, Cutter GR, et al; on behalf of the CombiRx Investigators. Randomized study combining interferon and glatiramer acetate in multiple sclerosis. *Ann Neurol* 2013;73:327–340.
38. Ellison G, Myers LW, Mickey MR, et al. A placebo-controlled, randomized, double-masked, variable dosage, clinical trial of azathioprine with and without methylprednisolone in multiple sclerosis. *Neurology* 1989;39:1018–1026.
39. Fazekas F, Deisenhammer F, Stasser-Fuchs S, Nahler G, Mamoli B. Randomised placebo-controlled trial of monthly intravenous immunoglobulin therapy in relapsing-relapsing multiple sclerosis: Austrian Immunoglobulin in Multiple Sclerosis Study Group. *Lancet* 1997;349:598–593.
40. Achiron A, Gabbay U, Gilad R, et al. Intravenous immunoglobulin treatment in multiple sclerosis, effect on relapses. *Neurology* 1998;50:398–402.

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Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

Alexander Rae-Grant, Gregory S. Day, Ruth Ann Marrie, et al.

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Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

Editors' note: Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

In the special article “Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis,” Rae-Grant et al. reported the findings of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology based on reviewing the evidence on starting, switching, and stopping disease-modifying therapies for clinically isolated syndrome, relapsing-remitting MS, and progressive forms of MS. In response, Dr. Tran, on behalf of Genentech, argues that the report did not make it clear that data on annualized relapse rate reduction and relative risk of in-study disability progression for ocrelizumab (presented along with other therapies in figures 1 and 3) were from direct comparisons with subcutaneous interferon- β -1a 44 μ g 3 times weekly in 2 phase 3 randomized, double-blind, double-dummy trials. In response, Dr. Rae-Grant agrees that this information should have been included, but notes that statements in the text of the summary and in a key accompanying table acknowledged the superior efficacy of ocrelizumab compared with interferon- β -1a 3 times weekly. Dr. Rae-Grant also notes that data on subgroup analysis of treatment of highly active MS with ocrelizumab were not available at the time of publication of the systematic review.

Aravind Ganesh, MD, DPhil, and Steven Galetta, MD
Neurology® 2019;93:764. doi:10.1212/WNL.0000000000008365

Reader response: Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

Katherine R. Tran (San Francisco)
Neurology® 2019;93:764–765. doi:10.1212/WNL.0000000000008366

Genentech recognizes that high-quality and trustworthy guidelines, such as those published by the American Academy of Neurology, are important both for providers to optimize patient care and for payers to manage appropriate utilization of multiple sclerosis (MS) treatments. We appreciate the opportunity to provide the following corrections to inform accurate recommendations for health care decision makers.

The Comprehensive Systematic Review Summary omits key information regarding ocrelizumab in figures 1 and 3.¹ Figure 1 lists disease-modifying therapies (DMTs) by annualized relapse rate (ARR) reductions from highest to lowest; figure 3 lists DMTs by relative risk of in-study disability progression at 2 years. The figures do not include a footnote indicating that the ARR and disability progression for ocrelizumab are relative to subcutaneous interferon- β -1a 44 μ g 3 times weekly, although there is such a note included for alemtuzumab.

Author disclosures are available upon request (journal@neurology.org).

The efficacy and safety of ocrelizumab compared with subcutaneous interferon- β -1a 44 μ g 3 times weekly in RMS was evaluated in 2 identical, phase 3, randomized (1:1), double-blind, double-dummy, head-to-head comparative trials.^{2,3} Readers may infer indirect treatment comparisons using these figures, and the omission of this fundamental detail misrepresents the relative efficacy of MS DMTs.

1. Rae-Grant A, Day GS, Marrie RA, et al. Comprehensive systematic review summary: disease-modifying therapies for adults with multiple sclerosis: Report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. *Neurology* 2018;90:789–800.
2. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med* 2017;376:221–234.
3. Genentech, Inc Highlights of prescribing information: ocrevus (ocrelizumab) injection, for intravenous use: full prescribing information. Available at: gene.com/download/pdf/ocrevus_prescribing.pdf. Accessed: December 12, 2018.

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Author response: Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

Alex D. Rae-Grant (Cleveland)

Neurology® 2019;93:765. doi:10.1212/WNL.0000000000008376

I thank Dr. Tran for the comment on our comprehensive systematic review summary for the American Academy of Neurology guideline on disease-modifying therapy for adults with multiple sclerosis (MS).¹

In regard to figures 1 and 3,¹ Dr. Tran correctly points out that critical information related to the ocrelizumab findings should have been included in each figure to indicate that the ocrelizumab findings are in comparison with interferon- β -1a (IFN- β -1a). We regret missing this in our proofing of this set of long and complex articles.

The text of the summary, a key accompanying table, and the full-text guideline document reflect the active comparator using IFN- β -1a subcutaneous 3 times per week.¹ The following language was used for conclusions about ocrelizumab: “Ocrelizumab¹³ is more effective than IFN- β -1a subcutaneous 3 times per week ... (high confidence);” “Ocrelizumab¹³ is more effective than IFN- β -1a 44 μ g subcutaneous 3 times weekly... (high confidence).”

In addition, a key table of efficacy for reducing the annualized relapse rate for relapsing MS documented the active comparator status in the summary¹ as follows: “Ocrelizumab more effective than IFN- β -1a subcutaneous 3 times per wk.”

This information should have been included in the published article, and we will notify the *Neurology* journal of this error as quickly as feasible.

We further appreciate your comments about subgroup analysis of treatment of highly active MS with ocrelizumab. Unfortunately, these data were not published when we completed our systematic review.

Medicine is a constantly evolving process; we noted this in our summary. How payers use guidelines to make decisions about access to care is beyond the scope and control of guideline development.

1. Rae-Grant A, Day GS, Marrie RA, et al. Comprehensive systematic review summary: disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2018;90:789–800.

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Editors' note: High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy

In the article “High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy,” Albrecht et al. investigated the prevalence of neutralizing antibodies (NABs) against botulinum neurotoxin type A (BoNT/A) in a monocentric, observational cross-sectional study of 596 outpatients treated with BoNT/A over a mean of 5.3 years for different indications and found that 13.9% had measurable NABs. The probability of developing NABs increased with the single and cumulative dose of treatment and was associated with the BoNT/A formulation used, leading the authors to recommend avoiding booster injections and reducing the individual injected doses. In response, Dr. Jankovic notes that the authors did not mention other studies that showed a much lower frequency of NABs, although after shorter periods of observation, and indicates that no data were provided regarding any correlation between the presence of NABs and clinical response. In this regard, Dr. Jankovic notes that none of the patients in a previous study with blocking antibodies identified by the mouse protection assay (MPA) had any clinical response, suggesting that the MPA may be more clinically meaningful. In their reply, Albrecht et al. postulate that lower rates of NABs in previous studies may relate to lower sensitivity of the MPA, lower BoNT doses used, and substantially shorter duration of treatment. In contrast to Dr. Jankovic’s findings, they report that all their patients with NABs opted to continue treatment and reported ongoing subjective benefit. Both the authors and Dr. Jankovic agree on the need for novel assays with higher sensitivity and specificity that are (ideally) not animal based. In another response, Mulroy et al. caution that the authors’ conclusions may mislead readers into thinking that long-term treatment with frequent or repeated BoNT injections can result in clinical treatment failure. Like Dr. Jankovic, they too highlight the absence of data on clinical effectiveness in this study and note that NAB serostatus did not always correlate with clinical response in previous studies. They also seek to clarify the authors’ disclosures, given that the study was funded by Merz Pharmaceuticals, which manufactures one of the BoNT formulations studied. Replying to these comments, Albrecht et al. argue that there is consensus that the induction of NABs should be avoided, as they are associated with reduced treatment response in several studies. They acknowledge that they do not have information about NAB induction with treatment intervals shorter than 10 weeks in their study, note the difficulty of comparing treatment efficacy across different indications, and concede that efficacy data were not available for all patients. They also state that pharmaceutical funding had no influence on the interpretation or analysis of their data. This correspondence highlights enduring uncertainty in the field regarding the clinical implications of NABs as detected by existing animal-based assays.

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Neurology® 2019;93:766. doi:10.1212/WNL.00000000000008375

Reader response: High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy

Joseph Jankovic (Houston)
Neurology® 2019;93:766–767. doi:10.1212/WNL.00000000000008379

In the article by Albrecht et al.,¹ the authors reported nearly 14% prevalence of neutralizing antibodies, determined by mouse hemidiaphragm assay (MHDA), among 596 patients treated with botulinum neurotoxin type A (BoNT/A), mostly with abo-BoNT/A (n = 324). They cited similar

prevalence of neutralizing antibodies based on their own study,² but they failed to mention other studies showing much lower frequency of such antibodies, albeit after a shorter observation period. For example, in a prospective study of 326 patients with cervical dystonia treated with BoNT/A, only 1.2% tested positive for antibodies detected by the mouse protection assay (MPA).³ Albrecht et al.¹ provided no data on the correlation between the presence of antibodies detected by MHDA and clinical response, although they stated that their patients were “still responding.”

In contrast, none of our patients with positive titers for blocking antibodies tested by MPA had any clinical response, indicative of true immunoresistance.⁴ Therefore, the latter assay is more clinically meaningful as it correlates well with clinical response, which may explain the differences in the reports of secondary unresponsiveness among various studies using different assays and BoNT products.⁵ More sensitive and specific assays that are not animal based are needed to monitor the emergence of blocking antibodies, particularly in patients treated chronically with high doses of BoNT.

1. Albrecht P, Jansen A, Lee JI, et al. High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy. *Neurology* 2019;92:e48–e54.
2. Hefter H, Rosenthal D, Moll M. High botulinum toxin-neutralizing antibody prevalence under long-term cervical dystonia treatment. *Mov Disord Clin Pract* 2016;3:500–506.
3. Brin MF, Comella CL, Jankovic J, et al. Long-term treatment with botulinum toxin type A in cervical dystonia has low immunogenicity by mouse protection assay. *Mov Disord* 2008;23:1353–1360.
4. Hanna PA, Jankovic J. Mouse bioassay versus Western blot assay for botulinum toxin antibodies: correlation with clinical response. *Neurology* 1998;50:1624–1629.
5. Bellows S, Jankovic J. Immunogenicity Associated with Botulinum Toxin Treatment. *Toxins (Basel)*. 2019;Aug 26;11(9).

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Author response: High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy

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We thank Dr. Jankovic for his valuable comments on our article.¹ The study by Brin et al.,² which, along with similar studies, is analyzed in a review referenced in our article,³ reported lower rates of neutralizing antibodies (NABs) (1.4% at a mean treatment duration of 2.5 years and maximum duration of 4 years) in cervical dystonia. Reasons may be a lower sensitivity of the mouse protection assay (MPA) compared with our mouse hemidiaphragm test, the lower doses applied, and the fact that the treatment duration was substantially shorter than in our study (mean 5.3 years and maximum 23 years). We completely agree that the clinical relevance of the observed NABs should be investigated by assessing the clinical response. These investigations are underway and will be the subject of a following publication. However, we can already state that we do not share Dr. Jankovic’s impression that all patients with detectable NABs display complete unresponsiveness. All our patients were on continued treatment by choice and reported at least some subjective benefit of therapy.¹ This is in line with previous studies using the MPA that also reported responsiveness in some patients despite positive NABs.^{2,4} We agree that novel, ideally not animal-based, assays with high sensitivity and specificity should be established and validated.

1. Albrecht P, Jansen A, Lee JI, et al. High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy. *Neurology* 2019;92:e48–e54.

Author disclosures are available upon request (journal@neurology.org).

2. Brin MF, Comella CL, Jankovic J, et al. Long-term treatment with botulinum toxin type A in cervical dystonia has low immunogenicity by mouse protection assay. *Mov Disord* 2008;23:1353–1360.
3. Naumann M, Boo LM, Ackerman AH, Gallagher CJ. Immunogenicity of botulinum toxins. *J Neural Transm (Vienna)* 2013;120:275–290.
4. Naumann M, Carruthers A, Carruthers J, et al. Meta-analysis of neutralizing antibody conversion with onabotulinumtoxinA (BOTOX®) across multiple indications. *Mov Disord* 2010;25:2211–2218.

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Reader response: High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy

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We read with interest the article by Albrecht et al.,¹ which demonstrated that 14% of 596 patients treated with various botulinum toxin (BoNT) preparations over 2–5 years developed neutralizing antibodies (Nabs). Although the study clearly focuses on the presence of Nabs and not on the clinical effect, the conclusions by Albrecht et al.¹ that “... avoiding booster injections and providing short intervals between injections... may diminish the risk of NAb induction...” and that “... the dose per injection session should be kept as low as possible to avoid clinically relevant immunization...” could mislead readers into believing that long-term treatment with frequent or repeated BoNT injections can result in clinical treatment failure.

The authors stated that “... patients were still responding (at least partially)...,”¹ but do not include data on clinical effectiveness. Most prior studies in this area have done so, as this greatly impacts on patient management.² It would be useful to know whether these data were not collected or have been omitted from publication intentionally. As previously demonstrated, Nab serostatus does not necessarily correlate with clinical response to repeated injections.^{2,3}

Last, the authors reported no disclosures related to the study,¹ yet the study was funded by a pharmaceutical company that manufactures one of the BoNTs included in the study. This needs clarification.

1. Albrecht P, Jansen A, Lee JI, et al. High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy. *Neurology* 2019;92:e48–e54.
2. Fabbri M, Leodori G, Fernandes RM, et al. Neutralizing antibody and botulinum toxin therapy: a systematic review and meta-analysis. *Neurotox Res* 2016;29:105–117.
3. Brin MF, Comella CL, Jankovic J, Lai F, Naumann M. Long-term treatment with botulinum toxin type A in cervical dystonia has low immunogenicity by mouse protection assay. *Mov Disord* 2008;23:1353–1360.

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Author response: High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy

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We thank Mulroy et al. for their comment on our article.¹ The association of neutralizing antibodies (NABs) against botulinum neurotoxin A and a reduced treatment response has been reported in several publications.^{2,3} It is, therefore, consensus that the induction of NABs should be avoided if possible. Given the constant treatment intervals >10 weeks in our study,¹ we do

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not have information about NAB induction with shorter treatment intervals. With these regimens, an impact was reported in previous studies.^{4,5} Our investigation was directed to identify other factors relevant for the induction of NABs and the prevalence in a large sample of treatment responsive patients across different indications. As comparing treatment efficacy across different indications is challenging and efficacy data was not available for all patients, we chose to not focus on treatment response.

Funding by Merz Pharmaceuticals was transparently reported at the bottom of the manuscript and all unrelated disclosures are listed on the journal webpage. As this funding had no influence on the interpretation or analysis of the data, it was not additionally listed as a relevant disclosure.

1. Albrecht P, Jansen A, Lee JI, et al. High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy. *Neurology* 2019;92:e48–e54.
2. Greene P, Fahn S, Diamond B. Development of resistance to botulinum toxin type A in patients with torticollis. *Mov Disord* 1994;9:213–217.
3. Göschel H, Wohlfarth K, Frevert J, Dengler R, Bigalke H. Botulinum A toxin therapy: neutralizing and nonneutralizing antibodies—therapeutic consequences. *Exp Neurol* 1997;147:96–102.
4. Naumann M, Boo LM, Ackerman AH, Gallagher CJ. Immunogenicity of botulinum toxins. *J Neural Transm (Vienna)* 2013;120:275–290.
5. Lange O, Bigalke H, Dengler R, et al. Neutralizing antibodies and secondary therapy failure after treatment with botulinum toxin type A: much ado about nothing? *Clin Neuropharmacol* 2009;32:213–218.

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CORRECTION

Comprehensive systematic review summary: 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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In the special article “Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology,” by Rae-Grant et al.,¹ there are errors in figures 1 and 3. In figure 1, a superscript “a” is missing from “Ocrelizumab” to indicate the comparator intervention (interferon- β -1a 44 μ g 3 times per week subcutaneously); in figure 3, a superscript “b” is missing from “Ocrelizumab,” also to indicate the comparator intervention (interferon- β -1a). Additionally, in the table “Efficacy of disease modifying therapies (DMTs) for reducing the annualized relapse rate (ARR) and risk of relapse at 2 years,” there should not be an entry for “very low” confidence for azathioprine under “Reduction of the ARR.” The entry for very low confidence for azathioprine under “Reduction of risk of relapse at 2 y” appears correctly. The authors regret the errors.

Reference

1. Rae-Grant A, Day GS, Marrie RA, et al. Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2018;90:789-800.

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