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

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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 μg 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 μg 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 nonconflicted 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 μg subcutaneous 3 times weekly,[11] and natalizumab.[12]

Ocrelizumab[13] 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).

Cladribine[14] 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 μg 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]

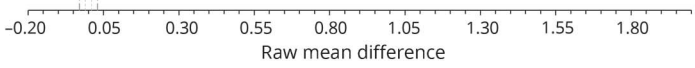
There is insufficient evidence to determine the efficacy of azathioprine compared with IFN-β[19] in reducing the risk of MRI-detected new or enlarging T2 lesions (very low confidence).

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 μg 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

Drug	RM	LCL	UCL	Studies	Confidence
Cyclophosphamide	1.80	0.56	3.04	1 III	Low
Azathioprine	0.49	0.07	0.91	1 II	Moderate
Betaseron	0.43	0.24	0.62	1 II	Moderate
Natalizumab	0.41	0.31	0.51	1 I	High
IVIg	0.37	-0.21	0.94	2 I, 2 II	Very low
Rituximab	0.30	-0.07	0.67	1 II	Very low
Alemtuzumab[a]	0.26	0.22	0.29	1 I, 1 II	High
Daclizumab[b]	0.25	0.13	0.37	1 I	High
Interferon + pulsed corticosteroids	0.24	0.02	0.47	2 II	Moderate
Fingolimod	0.21	0.16	0.26	2 I, 2 II	High
Cladribine	0.19	0.14	0.24	3 II	High
Dimethyl fumarate	0.19	0.13	0.25	1 I, 1 II	High
Glatiramer	0.18	0.09	0.28	2 I, 1 II	High
Teriflunomide	0.18	0.11	0.25	3 II	High
Ocrelizumab	0.13	0.09	0.18	2 I	High
Pegylated interferon	0.11	0.01	0.21	1 I	High
Avonex	0.08	0.01	0.15	1 I	Moderate
Pulsed corticosteroids	0.00	-0.24	0.24	1 IV	Very low



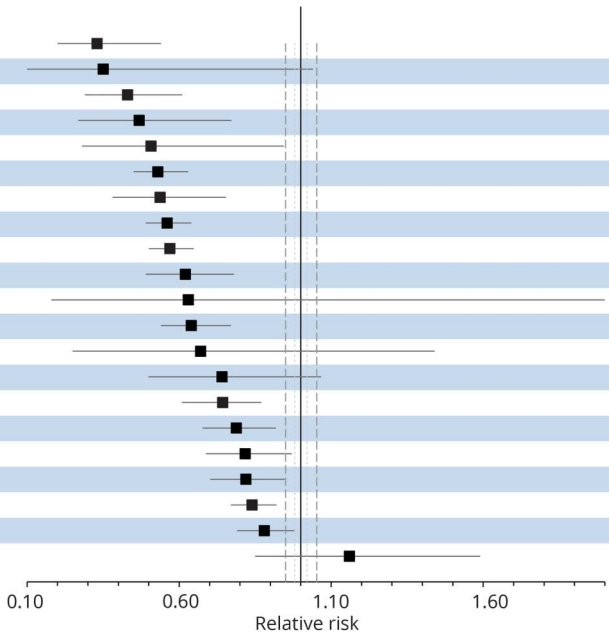
IVIg = IV immunoglobulin; LCL = lower confidence limit; RM = raw mean difference; UCL = upper confidence limit. [a]Versus interferon-β-1a 44 μg 3 times per week subcutaneously. [b]See safety note on page 791.[8a]

Rituximab[25] and teriflunomide[26] 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

Drug	RR	LCL	UCL	Studies	Confidence
Interferon + pulsed corticosteroids[a]	0.33	0.20	0.54	1 II	Moderate
Methotrexate[b]	0.35	0.10	1.04	1 II	Very low
Alemtuzumab[a]	0.43	0.29	0.61	1 I, 1 II	High
Mitoxantrone	0.47	0.27	0.77	1 I	High
Rituximab[c]	0.51	0.28	0.94	1 II	Moderate
Cladribine	0.53	0.45	0.63	1 II	Moderate
Daclizumab[c,d]	0.54	0.38	0.75	1 I	High
Natalizumab	0.56	0.49	0.64	1 I	High
Fingolimod	0.57	0.50	0.65	1 I, 1 II	High
Pegylated interferon[c]	0.62	0.49	0.78	2 II	High
Interferon + mycophenolate[a]	0.63	0.18	2.23	2 II	Low
Dimethyl fumarate	0.64	0.54	0.77	1 I	High
Cyclophosphamide[c]	0.67	0.25	1.44	1 III	Very low
Azathioprine	0.74	0.50	1.07	1 II	Very low
IVIg	0.74	0.61	0.87	1 I, 1 II	High
Avonex	0.79	0.68	0.92	1 I, 1 II	High
Glatiramer	0.82	0.69	0.97	1 I, 2 II	Moderate
Betaseron	0.82	0.70	0.95	1 II	Moderate
Rebif	0.84	0.77	0.92	1 I	High
Teriflunomide	0.88	0.79	0.98	1 II	Moderate
Pulsed corticosteroids	1.16	0.85	1.59	1 IV	Very low



IVIg = IV immunoglobulin; LCL = lower confidence limit; RR = risk ratio; UCL = upper confidence limit. [a]Relative to interferon alone. [b]Outcome assessed at 18 months. [c]Outcome assessed at 1 year. [d]See 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

	Reduction of the ARR		Reduction of risk of relapse at 2 y	
Confidence strength	**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[a] more effective (outcome measured at 1 y)[20]	Alemtuzumab[15,29] more effective than IFN-β-1a subcutaneous 3 times per wk
	Daclizumab HYP[a] 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]	Daclizumab HYP[a] probably more effective than IFN-β-1a IM once per wk (outcome measured at 3 y)[27]
	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	—	—	Mycophenolate mofetil plus IFN-β-1a IM weekly[31,e43] possibly no more effective than IFN plus placebo (outcome measured at 1 y)
	—	—	—	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 corticosteroids[29] relative to placebo for reducing the volume or number of MRI-detected T2 lesions (very low confidence).

Reducing loss of parenchymal volume

Ocrelizumab[13] 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 weekly[29] in reducing loss of parenchymal volume (moderate confidence).

Pulsed corticosteroids[30] 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 weekly[22] 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?

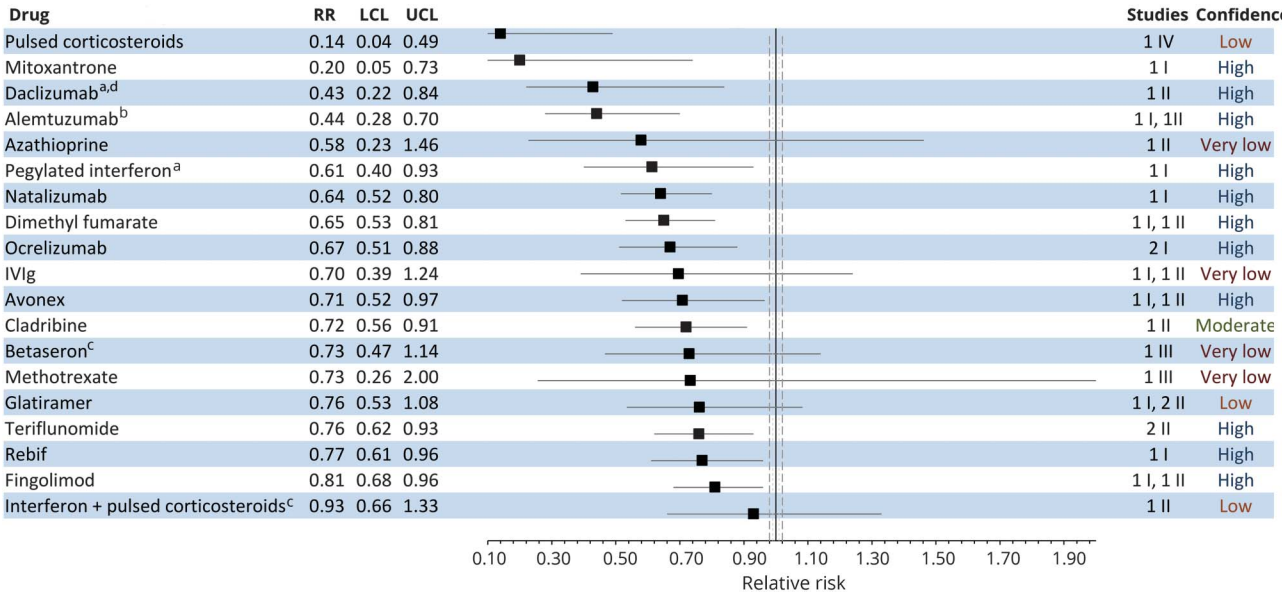
The most consistently reported measure for in-study disability progression was the proportion of people with MS with disability progression. Disability progression was defined by an increase in the Expanded Disability Status Scale (EDSS) of 1 point in those with a baseline EDSS score of 5.0 or lower, 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]

Cladribine[14] 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. [a]Outcome measured at 1 year. [b]Versus interferon-β-1a. [c]Outcome measured at 3 years. [d]See safety note on page 791.[8a]

Daclizumab is probably more effective than IFN-β-1a 30 μg IM[27] in reducing the risk of disability progression in people with RRMS (moderate confidence). See safety note on page 791.[8a]

Pulsed corticosteroids[30] 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 μg 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 μg 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 μg 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).

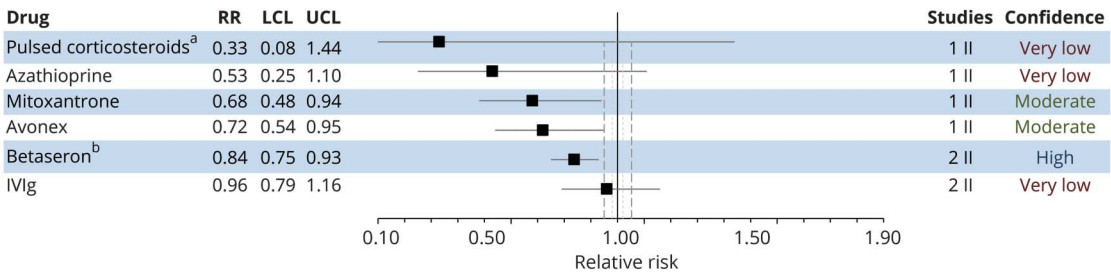
6. What are the AEs of DMTs in people with MS compared with placebo (AE-related discontinuation and serious or life-threatening AEs)?

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?

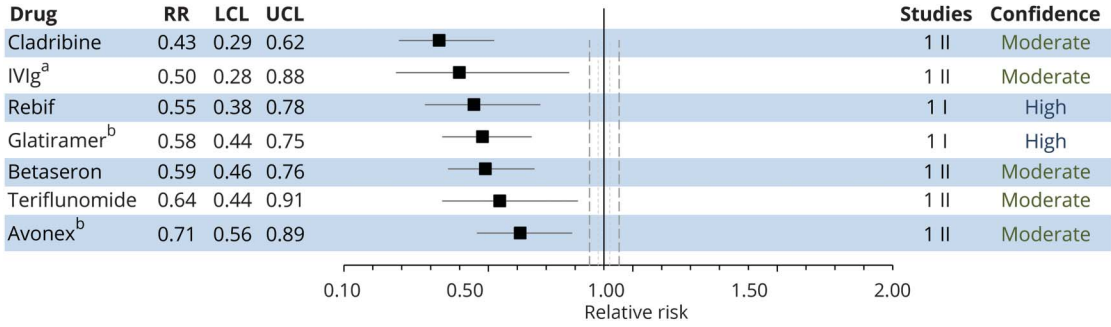
Figure 5 presents the data regarding risk of conversion to MS in people with CIS. For individuals with CIS, the following DMTs are more effective than placebo in reducing the proportion of individuals converting to MS (high confidence): glatiramer acetate[e27] and IFN-β-1a subcutaneous 3 times weekly.[e28]

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. [a]High-dose corticosteroids vs low-dose corticosteroids. [b]Outcome 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. [a]Outcome measured at 1 year. [b]Outcome 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 μg 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/revising 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/revising 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/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Rabinstein: analysis or interpretation of data, drafting/revising the manuscript. Dr. Cree: study concept and design, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Gronseth: analysis or interpretation of data, critical revision of the manuscript for important intellectual content, study supervision. Dr. Haboubi: study concept and design, analysis or interpretation of data, drafting/revising the manuscript. J. Halper: study concept and design, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Hosey: critical revision of the manuscript for important intellectual content. Dr. Jones: study concept and design, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Lisak: study concept and design, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Pelletier: study concept and design, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Potrebic: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision. C. Sitcov: study concept and design, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. R. Sommers: drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Stachowiak: study concept and design, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. T.S.D. Getchius: study supervision. S.A. Merillat: drafting/revising the manuscript, study supervision. Dr. Pringsheim: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision.

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