



CADTH Health Technology Review

Review of Guidelines on Second-Line Therapy for Patients With Relapsing- Remitting Multiple Sclerosis: A 2024 Update

Key Messages

What Is the Issue?

- Multiple sclerosis is a chronic autoimmune disorder that causes damage to central nervous system cells. Relapsing-remitting multiple sclerosis is characterized by relapses (episodes of new or worsening symptoms) followed by periods of partial or complete recovery (remission).
- First-line therapies for multiple sclerosis include interferons, glatiramer acetate, dimethyl fumarate, and teriflunomide. Second-line therapies include natalizumab, alemtuzumab, and fingolimod.
- The considerations for switching from a first-line to a second-line therapy for patients with relapsing-remitting multiple sclerosis are unclear.

What Did We Do?

- To inform decisions around switching patients with relapsing-remitting multiple sclerosis from a first-line to a second-line therapy, we sought to identify and summarize recommendations from evidence-based guidelines.
- We searched key resources, including journal citation databases, and conducted a focused internet search for relevant evidence published since 2019. One reviewer screened articles for inclusion based on predefined criteria, critically appraised the included guidelines, and narratively summarized the findings.

What Did We Find?

- We identified 2 evidence-based guidelines that included recommendations around switching from a first-line to a second-line therapy in patients with relapsing-remitting multiple sclerosis.
- One guideline from Spain classified therapies as moderate-efficacy (interferons, glatiramer acetate, dimethyl fumarate, and teriflunomide) and high-efficacy (fingolimod, cladribine, ocrelizumab, natalizumab, and alemtuzumab). The guideline recommends that patients switch from a moderate-efficacy disease-modifying therapy to a high-efficacy disease-modifying therapy for a variety of reasons including suboptimal response, adverse events, comorbidities, pregnancy plans, confirmed progression of disability, and tolerability issues. The guideline also included several recommendations specific to switching to natalizumab as well as washout periods when switching from a moderate-efficacy therapy.

Key Messages

- One guideline from France included recommendations regarding washout periods for switching from a first-line therapy. The guideline recommends that when switching from a first-line therapy, a second-line therapy or an induction therapy could be started without a washout period if the patient has normal biological results. The guideline also recommends validating the indication, timing, and washout period of a switch to a second-line therapy or induction therapy with a multiple sclerosis expert centre or in a multidisciplinary consensus meeting. The guideline also included specific considerations for washout periods for dimethyl fumarate and teriflunomide.

What Does It Mean?

- The considerations for switching from a first-line to a second-line therapy in patients with relapsing-remitting multiple sclerosis – including the timing of a switch, choice of second-line therapy, and washout periods – depend on treatment response, individual patient characteristics, and the specific first-line therapy being used.
- Additional evidence-based guidelines that use comprehensive methods for identifying evidence and include clear links between identified evidence and recommendations will help to reduce uncertainty around considerations for switching from first-line to second-line therapies in patients with relapsing-remitting multiple sclerosis.

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Abbreviations

CDEC	Canadian Drug Expert Committee
JCV	John Cunningham virus

Context and Policy Issues

What Is Relapsing–Remitting Multiple Sclerosis?

Multiple sclerosis is a chronic autoimmune disorder of the central nervous system that causes demyelination (damage to the protective cover [myelin sheath] around nerve cells) and neurodegeneration (damage and/or death of nerve cells).^{1,2} Symptoms of multiple sclerosis can include constant fatigue, vision deficit, intense pain, sensory dysfunction, gait disturbances, cognitive impairment, urinary incontinence, and spasticity.^{1,3} The diagnosis of multiple sclerosis is based on clinical symptoms, cerebrospinal fluid analysis, and MRI.³ It is estimated that more than 77,000 people older than 20 live with multiple sclerosis in Canada and almost 75% are women.⁴ The cause of multiple sclerosis is unknown, and the age of onset is typically 20 to 40 years.³ Relapsing–remitting multiple sclerosis, the most common form of the disease, is characterized by relapses (episodes of new or worsening symptoms) followed by periods of partial or complete recovery (remission).^{1,5}

What Is the Current Practice?

There is no known cure for multiple sclerosis. However, treatments can decrease inflammation and reduce symptoms and the accumulation of disability.⁶ Treatment of multiple sclerosis includes disease-modifying therapies, acute relapse treatment, comorbidity management, symptom control, psychological support, rehabilitative strategies, and lifestyle modifications.² The goal of disease-modifying therapies in relapsing–remitting multiple sclerosis is to decrease the frequency of relapses and reduce short-term disability.² Disease-modifying therapies for multiple sclerosis include injectable medications (e.g., interferons, glatiramer acetate), oral medications (e.g., fingolimod, fumarates, teriflunomide), and monoclonal antibodies (e.g., natalizumab, ocrelizumab, alemtuzumab).²

What Are Second–Line Therapies for Relapsing–Remitting Multiple Sclerosis?

Disease-modifying therapies for relapsing–remitting multiple sclerosis can be classified as first-line or second-line therapies. First-line therapies include interferons, glatiramer acetate, dimethyl fumarate, and teriflunomide.⁷ Second-line therapies include (but are not limited to) natalizumab, alemtuzumab, and fingolimod.⁷

Natalizumab is indicated for the treatment of patients with relapsing–remitting multiple sclerosis to reduce the frequency of clinical exacerbations, decrease the number and volume of brain lesions, and delay the progression of physical disability.⁸ Natalizumab is generally recommended in patients who had an inadequate response to, or are unable to tolerate, other therapies for multiple sclerosis.⁸ The recommended dose of natalizumab is a 300 mg IV infusion every 4 weeks.⁸ In 2009, the Canadian Drug Expert Committee (CDEC) recommended that natalizumab (Tysabri) be listed for patients with a diagnosis of multiple sclerosis established according to current clinical criteria and MRI evidence.⁹

Alemtuzumab is indicated for the treatment of adults with relapsing–remitting multiple sclerosis with highly active disease defined by clinical and imaging features, despite treatment with at least 2 other disease-modifying therapies, or where any other disease-modifying therapy is contraindicated or otherwise unsuitable.¹⁰ The recommended dose of alemtuzumab is 12 mg/day IV infusion for 2 treatment courses.¹⁰

The initial course is 12 mg/day for 5 consecutive days (60 mg total) and the second course is 12 mg/day for 3 consecutive days (36 mg total) administered 12 months after the initial course.¹⁰ In 2015, CDEC recommended that alemtuzumab (Lemtrada) be listed for the treatment of adults with relapsing-remitting multiple sclerosis, with active disease defined by clinical and imaging features, who have had an inadequate response to interferon beta or other disease-modifying therapies.¹¹

Fingolimod is indicated for the treatment of patients with relapsing-remitting multiple sclerosis to reduce the frequency of clinical exacerbations and delay the progression of physical disability.¹² Fingolimod is generally recommended for patients who had an inadequate response to, or are unable to tolerate, 1 or more other therapies for multiple sclerosis.¹² Fingolimod is available as capsules for oral administration and the recommended dose of fingolimod for adults is 0.5 mg once daily.¹² In 2011, CDEC recommended that fingolimod (Gilenya) be listed for the treatment of patients with relapsing-remitting multiple sclerosis.¹³

Why Is It Important to Do This Review?

The current report is an update to our previous report published in 2019.¹⁴ The 2019 report identified 1 evidence-based guideline that included recommendations on switching from a first-line to a second-line therapy for patients with relapsing-remitting multiple sclerosis.¹⁴ The guideline included a strong recommendation in favour of switching to a more efficacious drug for patients currently treated with interferon or glatiramer acetate who show evidence of disease activity.¹⁴ The guideline also included a consensus statement indicating that the decision on which drug to switch to should consider patient characteristics and comorbidities, drug safety profile, and disease severity and activity.¹⁴ Since only 1 guideline was identified, the report concluded that additional guidelines could help reduce uncertainty around considerations for switching from first-line to second-line therapies for patients with relapsing-remitting multiple sclerosis.¹⁴

Objective

The purpose of this report is to summarize and critically appraise evidence-based guidelines regarding switching from first-line to second-line therapies for patients with relapsing-remitting multiple sclerosis.

Research Question

What are the evidence-based guidelines regarding switching to a second-line therapy in patients with relapsing-remitting multiple sclerosis?

Methods

Literature Search Methods

The literature search strategy used in this report is an update of 1 developed for a previous CADTH report.¹⁴ For the current report, an information specialist conducted a literature search on key resources including MEDLINE, the Cochrane Database of Systematic Reviews, the International HTA Database, Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The initial search was limited to English-language documents published between January 1, 2014, and August 26, 2019. For the current report, database searches were rerun on May 31, 2024, to capture any articles published or made available since the initial search date. The search of major health technology agencies was also updated to include documents published since August 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. As an update to our previous report, articles were included if they were made available since the previous search date and were not included in the 2019 report.¹⁴ The final selection of full-text articles was based on the inclusion criteria presented in [Table 1](#).

Table 1: Selection Criteria

Criteria	Description
Population	Adults with RRMS who are currently treated with a first-line treatment Exclude: patients with clinically isolated syndrome, primary progressive MS, secondary progressive MS
Intervention	Second-line treatments: Lemtrada (alemtuzumab) Gilenya (fingolimod) Tysabri (natalizumab)
Comparator	NA
Outcomes	Evidence-based guidelines and recommendations on considerations for switching to second-line treatment (e.g., patient characteristics/clinical features/other circumstances, such as clinical relapses and lesions detected by MRI)
Study designs	Evidence-based guidelines

MS = multiple sclerosis; NA = not applicable; RRMS = relapsing-remitting multiple sclerosis.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in [Table 1](#) or they were duplicate publications. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument¹⁵ as a guide. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 50 citations were identified in the literature search. Following screening of titles and abstracts, 39 citations were excluded and 11 potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 13 publications were excluded for various reasons, and 2 evidence-based guidelines met the inclusion criteria and were included in this report. [Appendix 1](#) presents the PRISMA¹⁶ flow chart of the study selection. Additional references of potential interest are provided in [Appendix 2](#).

Summary of Guideline Characteristics

Additional details regarding the characteristics of included publications are provided in [Appendix 3](#).

The Spanish Society of Neurology (2022)¹⁷ guideline development group were from Spain. The French Multiple Sclerosis Society (2021)¹⁸ guideline development group were from France.

To inform the Spanish Society of Neurology (2022)¹⁷ guideline, a subgroup of 2 experts conducted a literature search using PubMed between January 16, 2019, and October 19, 2019. Based on the evidence identified, the subgroup formulated the recommendation statements to submit to the guideline expert panel for critical evaluation.¹⁷ Consensus on the recommendations was reached using a modified Delphi method.¹⁷ Recommendation statements underwent 2 rounds of assessment by the guideline panel and required 80% agreement from the panel to be accepted.¹⁷ The quality of evidence and strength of recommendations in the guideline were not assigned ratings.¹⁷

The recommendations for the French Multiple Sclerosis Society (2021)¹⁸ guideline were developed by a steering committee of 7 experts based on a systematic analysis of the literature, the product characteristics published by the European Medicines Agency and by relevant French authorities, and their own experience. Based on the limited evidence identified, the level of evidence supporting the guideline was graded as level C (low level of evidence). The steering committee submitted the recommendations to a rating group who had to decide on their level of agreement with each recommendation on a scale from 1 (totally disagree) to 10 (totally agree). After 2 rounds of rating, recommendations were classified as appropriate if the median score was greater than or equal to 7, "with strong agreement" if the range of rating was greater than or equal to 7 and "with relative agreement" if the minimum score was less than 7. Recommendations were classified as

inappropriate if more than 2 raters disagreed and justified their position even if the median score was greater than or equal to 7.

The target populations of both guidelines are broader than the relevant population for the current report (i.e., adults with relapsing-remitting multiple sclerosis who are currently treated with a first-line treatment). Specifically, the target population for the Spanish Society of Neurology (2022)¹⁷ guideline is patients with relapsing multiple sclerosis and the target population for the French Multiple Sclerosis Society (2021)¹⁸ guideline is patients with multiple sclerosis. Only recommendations relevant to the current report are included. The intended users are health care practitioners for the Spanish Society of Neurology (2022)¹⁷ guideline and physicians for the French Multiple Sclerosis Society (2021)¹⁸ guideline.

The interventions considered in the Spanish Society of Neurology (2022)¹⁷ guideline were disease-modifying therapies. The interventions considered in the French Multiple Sclerosis Society (2021)¹⁸ guideline were interferon beta-1a, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, natalizumab, ocrelizumab, alemtuzumab, cladribine, and mitoxantrone.

Summary of Critical Appraisal

Additional details regarding the appraisal of the included guidelines are provided in [Appendix 4](#).

The objective, target population, and intended users of the guideline were clearly described in both guidelines. The recommendations were specific and clear in both guidelines. In the French Multiple Sclerosis Society (2021)¹⁸ guideline, only the names of the guideline development group were provided and not their affiliations or areas of expertise. A list of the guideline development group members was not provided in the Spanish Society of Neurology (2022)¹⁷ guideline. Providing this information helps to determine whether the guideline development group includes individuals from all relevant professional groups (e.g., clinicians, content experts, methodology experts, and so forth). Neither of the guidelines state whether the views and preferences of people with multiple sclerosis were sought. Perspectives of people with multiple sclerosis should inform the development of guidelines that may impact them. The literature search for the Spanish Society of Neurology (2022)¹⁷ guideline was only conducted in 1 database and may have missed relevant evidence due to lack of a comprehensive search strategy. The French Multiple Sclerosis Society (2021)¹⁸ guideline states that a systematic analysis of the literature was conducted; however, no details of the search strategy were reported. Neither of the guidelines reported their inclusion and exclusion criteria for selecting evidence. Both guidelines include some limited discussion around how the recommendation statements link to the evidence identified in the literature search. The Spanish Society of Neurology (2022)¹⁷ guideline states that the recommendations are based on expert opinion and that they reflect the current levels of evidence as well as expert experience. The French Multiple Sclerosis Society (2021)¹⁸ guideline states that the proposed washout periods before starting new disease-modifying therapies are based on expert experience due to the poor available literature. The quality of evidence supporting the recommendations in the Spanish Society of Neurology (2022)¹⁷ guideline was not rated, and the recommendations were not assigned a strength. Without these elements, it is difficult to determine the risk of bias in the evidence that informed the development of the recommendations. The quality of evidence and strength of recommendations were rated in the French Multiple Sclerosis Society (2021)¹⁸ guideline. The Spanish Society of Neurology (2022)¹⁷ guideline and

medical writing assistance for the guideline were funded by Merck, and this may have influenced the content of the guideline. Additionally, the competing interests of the authors were reported; however, there was no discussion of how they were managed. Therefore, we cannot determine whether the authors' competing interests had an impact on the development of the guideline and the recommendations. The French Multiple Sclerosis Society (2021)¹⁸ guideline did not receive funding and the authors stated that they had no competing interests.

Summary of Recommendations

[Appendix 5](#) presents the relevant recommendations from the included guidelines.

Guidelines Regarding Switching to a Second-Line Therapy in Patients With Relapsing-Remitting Multiple Sclerosis

Spanish Society of Neurology (2022)¹⁷

The Spanish Society of Neurology (2022)¹⁷ guideline did not report the strength of recommendations or quality of evidence informing the recommendations.

The guideline recommends that the concept of treatment lines should no longer be used for multiple sclerosis and that disease-modifying therapies be classified into moderate-efficacy disease-modifying therapies (interferons, glatiramer acetate, dimethyl fumarate, and teriflunomide) and high-efficacy disease-modifying therapies (fingolimod, cladribine, ocrelizumab, natalizumab, and alemtuzumab).

The guideline includes several recommendations on when to switch patients from moderate- to high-efficacy disease-modifying therapies:

- Patients should switch from a moderate-efficacy disease-modifying therapy to a high-efficacy disease-modifying therapy due to suboptimal response, which is based on a combination of clinical activity (presence of relapses and/or increase in disability) and radiological activity (more than 2 active lesions).
- Escalation from moderate- to high-efficacy disease-modifying therapies should be considered in certain cases (e.g., adverse events, comorbidities, or pregnancy plans) regardless of prior clinical response.
- Escalation from moderate- to high-efficacy disease-modifying therapies could be a valid strategy in the case of confirmed progression of disability even in the absence of clinical and/or radiological activity.
- A switch within the same efficacy group should be considered in the case of tolerability issues with a moderate-efficacy disease-modifying therapy, whereas the switch to a high-efficacy disease-modifying therapy would be a secondary option.
- Tolerability issues with a moderate-efficacy disease-modifying therapy could entail a switch to a high-efficacy disease-modifying therapy in some cases (e.g., comorbidities, pharmacological interactions, and so forth).

The guideline also includes several recommendations specific to switching to natalizumab:

- In the case of a need for a switch to a high-efficacy disease-modifying therapy, a different treatment than natalizumab would be used in patients who are positive for John Cunningham virus (JCV).
- In the case of a need for a switch to a high-efficacy disease-modifying therapy, the use of natalizumab is only recommended for 2 years in patients who are positive for JCV considering the risk/benefit balance on a case-by-case basis.
- In the case of a need for a switch to a high-efficacy disease-modifying therapy, even if natalizumab is safe for use for 2 years, another therapeutic option would be preferred for patients who are positive for JCV patients to avoid rebound issues.
- In the case of a need for a switch to a high-efficacy disease-modifying therapy, natalizumab can be assessed as a potential option in patients who are negative for JCV.

The guideline includes several recommendations specific to washout periods when switching from a moderate-efficacy disease-modifying therapy:

- In the case of dimethyl fumarate, it is necessary to wait until a normal lymphocyte count is reached before switching to another disease-modifying therapy.
- In the case of dimethyl fumarate and persistent lymphopenia, switching to another therapy will depend on the benefit-risk balance for each patient.
- The washout period for dimethyl fumarate must be determined by normalization of the lymphocyte count.
- In the case of teriflunomide, an accelerated elimination procedure with cholestyramine is recommended before switching to another therapy.
- The washout period for teriflunomide must be determined in line with drug levels in the blood and normalization of the lymphocyte count.
- No washout period is needed for different formulations of interferon beta.
- No washout period is needed for glatiramer acetate.

French Multiple Sclerosis Society (2021)¹⁸

The French Multiple Sclerosis Society (2021)¹⁸ guideline rated the quality of evidence supporting all the recommendations as level C (low level of evidence).

The French Multiple Sclerosis Society (2021)¹⁸ guideline classified therapies as first-line (interferon beta-1a, glatiramer acetate, teriflunomide, and dimethyl fumarate), second-line (fingolimod, natalizumab, and ocrelizumab), and induction (mitoxantrone, cladribine, and alemtuzumab).

The guideline recommends that, in the case of first-line therapy discontinuation, another first-line therapy, a second-line therapy, or an induction therapy could be started without a washout period if the patient has normal biological results (appropriate with relative agreement). The guideline recommends waiting for a lymphocyte count greater than or equal to 800/mm (unless otherwise validated by a multiple sclerosis expert centre or multidisciplinary consensus meeting) in the case of dimethyl fumarate discontinuation

and lymphopenia (appropriate with relative agreement). The guideline recommends initiating a washout for teriflunomide discontinuation if the patient is intending to become pregnant or in the case of early pregnancy (appropriate with strong agreement). The guideline recommends validating the indication, timing, and washout period of a switch to a second-line therapy or induction therapy with a multiple sclerosis expert centre or in a multidisciplinary consensus meeting (appropriate with relative agreement).

Limitations

This report is limited by the quantity and quality of guidelines identified. Only 2 guidelines were identified, 1 of which only included recommendations around washout periods when switching disease-modifying therapies. Both guidelines had multiple important limitations, as discussed in the critical appraisal section. The literature searches conducted to inform the guidelines may not have been comprehensive because 1 guideline only searched a single database and details of the literature search were not reported in the other guideline. Additionally, the links between supporting evidence and recommendations were unclear in both guidelines and some of the recommendations were based on expert opinion. The French Multiple Sclerosis Society (2021)¹⁸ guideline noted that there was a lack of evidence on disease-modifying therapy switching and rated the level of evidence used to inform the guidelines as low. The Spanish Society of Neurology (2022)¹⁷ guideline did not rate the quality of evidence informing the guideline.

Additionally, there were inconsistencies between how the 2 guidelines classified drugs used for relapsing-remitting multiple sclerosis. The Spanish Society of Neurology (2022)¹⁷ guideline classified drugs as moderate-efficacy or high-efficacy disease-modifying therapies. The French Multiple Sclerosis Society (2021)¹⁸ guideline classified drugs as first-line, second-line, or induction therapies. The moderate-efficacy therapies in the Spanish Society of Neurology (2022)¹⁷ guideline were the same drugs classified as first-line in the French Multiple Sclerosis Society (2021)¹⁸ guideline (i.e., interferons, glatiramer acetate, dimethyl fumarate, and teriflunomide).

Finally, neither of the included guidelines were from Canada. All the guideline panel members for the French Multiple Sclerosis Society (2021)¹⁸ guideline were from France and the Spanish Society of Neurology (2022)¹⁷ guideline did not include a list of the guideline panel members.

Conclusions and Implications for Decision- or Policy-Making

We identified 2 evidence-based guidelines^{17,18} that included recommendations on switching to a second-line therapy for patients with relapsing-remitting multiple sclerosis.

The Spanish Society of Neurology (2022)¹⁷ guideline classified therapies as moderate-efficacy (interferons, glatiramer acetate, dimethyl fumarate, and teriflunomide) and high-efficacy (fingolimod, cladribine, ocrelizumab, natalizumab, and alemtuzumab). The guideline recommends that patients switch from a moderate-efficacy disease-modifying therapy to a high-efficacy disease-modifying therapy for a variety

of reasons including suboptimal response, adverse events, comorbidities, pregnancy plans, confirmed progression of disability, and tolerability issues. The guideline also recommends that patients who are positive for JCV switch to a different treatment than natalizumab. Additionally, the guideline includes several recommendations around washout periods when switching from a moderate-efficacy disease-modifying therapy.

The French Multiple Sclerosis Society (2021)¹⁸ guideline classified therapies as first-line (interferon beta-1a, glatiramer acetate, teriflunomide, and dimethyl fumarate), second-line (fingolimod, natalizumab, and ocrelizumab), and induction (mitoxantrone, cladribine, and alemtuzumab). The guideline includes several recommendations on washout periods for switching from a first-line therapy. The guideline recommends that when switching from a first-line therapy, a second-line therapy or an induction therapy could be started without a washout period if the patient has normal biological results. The guideline recommends validating the indication, timing, and washout period of a switch to a second-line therapy or induction therapy with a multiple sclerosis expert centre or in a multidisciplinary consensus meeting.

The guideline identified in our 2019 report on this topic included a strong recommendation that patients with relapsing-remitting multiple sclerosis and evidence of disease activity who are taking interferon or glatiramer acetate should switch to a second-line therapy.¹⁴ This recommendation is consistent with the recommendation in the Spanish Society of Neurology (2022) guideline that patients with a suboptimal response to a moderate-efficacy therapy should switch to a high-efficacy therapy.¹⁷

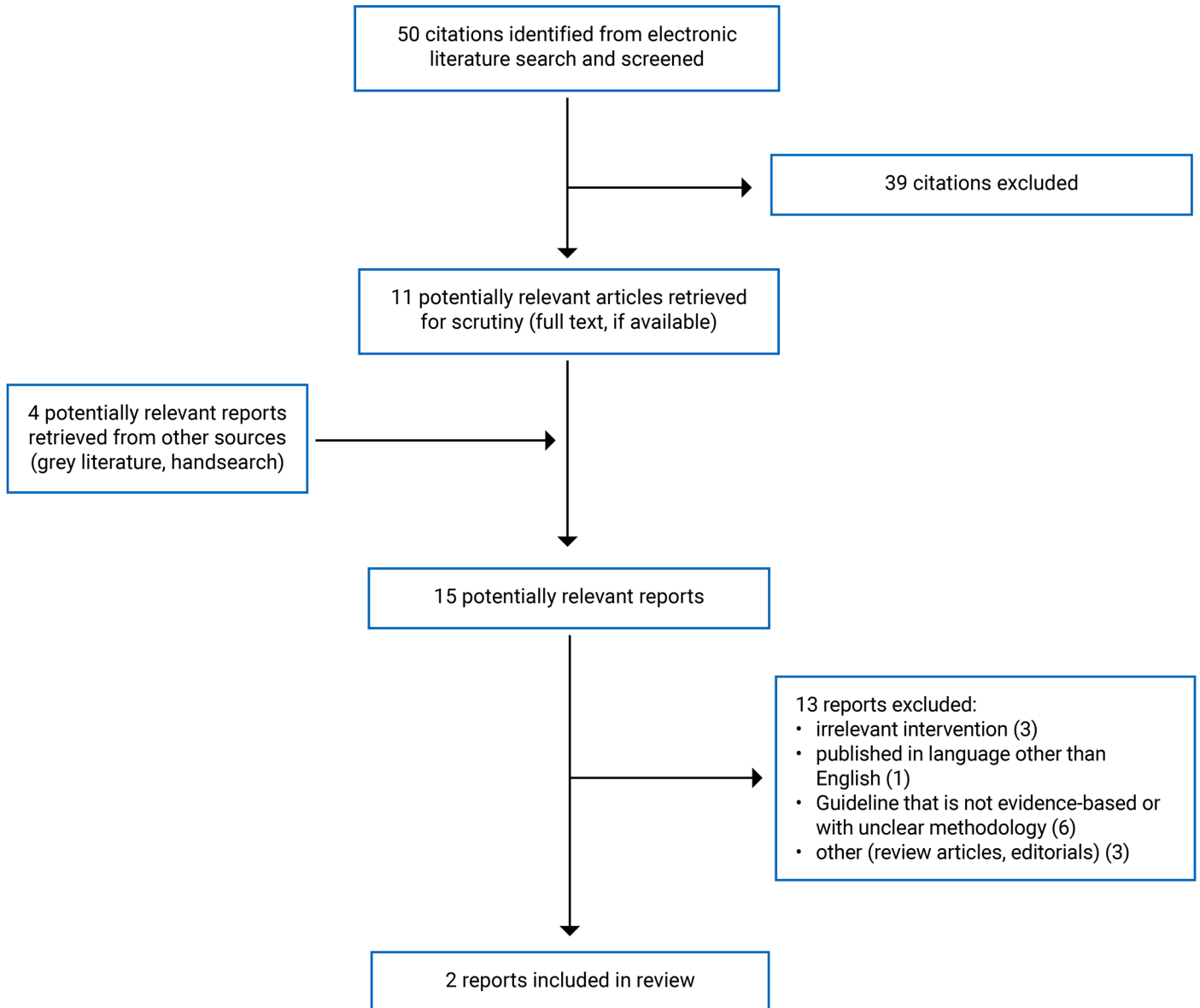
The considerations for switching from a first-line to a second-line therapy in patients with relapsing-remitting multiple sclerosis including the timing of a switch, choice of second-line therapy, and washout periods depend on treatment response, individual patient characteristics, and the specific first-line therapy being used. Evidence-based guidelines with comprehensive literature searches and explicit links between supporting evidence and recommendations would help to reduce uncertainty around considerations for switching from first-line to second-line therapies for patients with relapsing-remitting multiple sclerosis.

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Appendix 1: Selection of Included Studies

Figure 1: PRISMA¹⁶ Flow chart of Study Selection



Appendix 2: References of Potential Interest

Note that this appendix has not been copy-edited.

Previous CADTH Reports

Alemtuzumab, Cladribine, Fingolimod, and Natalizumab as First-Line Treatments in Adult Patients With Highly Active Relapsing Multiple Sclerosis. *Can J Health Technol.* 2024;4(5): <https://www.cadth.ca/alemtuzumab-cladribine-fingolimod-and-natalizumab-first-line-treatments-adult-patients-highly>. Accessed 2024 Jun 12.

Guidelines – Consensus-Based or Unclear Methodology

Hassoun HK, Hatem AO, Al-Mahdawi A, et al. Iraqi experts consensus on the management of relapsing remitting multiple sclerosis in adults. *Curr Med Res Opin.* 2024:1-9.

Yamout B, Al-Jumah M, Sahraian MA, et al. Consensus recommendations for diagnosis and treatment of Multiple Sclerosis: 2023 revision of the MENACTRIMS guidelines. *MS Relat Disord.* 2024;83(105435).

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Bayas A, Berthele A, Hemmer B, Warnke C, Wildemann B. Controversy on the treatment of multiple sclerosis and related disorders: positional statement of the expert panel in charge of the 2021 DGN Guideline on diagnosis and treatment of multiple sclerosis, neuromyelitis optica spectrum diseases and MOG-IgG-associated disorders. *Neurol Res Pract.* 2021;3(45).

Freedman MS, Devonshire V, Duquette P, et al. Treatment Optimization in Multiple Sclerosis: Canadian MS Working Group Recommendations. *Can J Neurol Sci.* 2020;47(4):437-455.

Appendix 3: Characteristics of Included Publications

Note that this appendix has not been copy-edited.

Table 2: Characteristics of Included Guidelines

Intended users, target population	Interventions considered	Evidence collection, synthesis, and quality assessment	Recommendations development and evaluation	Guideline validation
Spanish Society of Neurology (2022)¹⁷				
Intended users: health care practitioners Target population: patients with relapsing multiple sclerosis	Disease-modifying therapies	A search for the latest evidence on disease-modifying therapy switching in relapsing multiple sclerosis was carried out. A subgroup of 2 experts selected potentially relevant articles and formulated the statements to submit to the expert panel for critical evaluation. Details on evidence quality assessment were not provided.	Recommendations were established by consensus which was reached using a modified Delphi method. Statements underwent 2 rounds of assessment and required 80% agreement from the panel to be accepted. At the second meeting, statements that did not have 80% agreement were discussed and either reformulated or discarded.	Not reported.
French Multiple Sclerosis Society (2021)¹⁸				
Intended Users: physicians Target Population: patients with multiple sclerosis	Interferon beta-1a, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, natalizumab, ocrelizumab, alemtuzumab, cladribine, and mitoxantrone	A systematic analysis of the literature was conducted, and the product characteristics published by the European Medicines Agency and relevant French authorities were reviewed. The methods used to appraise the quality of the evidence were not described; however, the level of evidence was graded as level C (low level of evidence).	The recommendations were established by consensus. Each rater decided on their level of agreement with each recommendation on a scale from 1 (totally disagree) to 10 (totally agree). After 2 rounds of rating, recommendations were then classified as 'appropriate' if the median score was ≥ 7 , 'with strong agreement' if the range of rating was ≥ 7 and 'with relative agreement' if the minimal score was < 7 . Recommendations were classified as 'inappropriate' if > 2 raters disagreed and justified their position, even if the median score was ≥ 7 .	Not reported.

Appendix 4: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 3: Strengths and Limitations of Guidelines Using AGREE II¹⁵

Item	Spanish Society of Neurology (2022) ¹⁷	French Multiple Sclerosis Society (2021) ¹⁸
Domain 1: scope and purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes
Domain 2: stakeholder involvement		
4. The guideline development group includes individuals from all relevant professional groups.	Unclear	Unclear
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Unclear	Unclear
6. The target users of the guideline are clearly defined.	Yes	Yes
Domain 3: rigour of development		
7. Systematic methods were used to search for evidence.	Partially	Partially
8. The criteria for selecting the evidence are clearly described.	No	No
9. The strengths and limitations of the body of evidence are clearly described.	No	Partially
10. The methods for formulating the recommendations are clearly described.	Yes	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	No	Partially
13. The guideline has been externally reviewed by experts before its publication.	Unclear	Unclear
14. A procedure for updating the guideline is provided.	No	No
Domain 4: clarity of presentation		
15. The recommendations are specific and unambiguous.	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes

Item	Spanish Society of Neurology (2022) ¹⁷	French Multiple Sclerosis Society (2021) ¹⁸
Domain 5: applicability		
18. The guideline describes facilitators and barriers to its application.	No	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	No	No
20. The potential resource implications of applying the recommendations have been considered.	No	No
21. The guideline presents monitoring and/or auditing criteria.	No	No
Domain 6: editorial independence		
22. The views of the funding body have not influenced the content of the guideline.	No	Yes
23. Competing interests of guideline development group members have been recorded and addressed.	Partially	Yes

AGREE II = Appraisal of Guidelines for Research and Evaluation II; NA = not applicable.

Appendix 5: Summary of Recommendations

Note that this appendix has not been copy-edited.

Table 4: Summary of Recommendations in Included Guidelines

Recommendations	Quality of evidence and strength of recommendations
Spanish Society of Neurology (2022)¹⁷	
<p>“At present, the concept of treatment lines in MS is obsolete. The different treatments (DMTs) can be classified into 2 broad groups: 1) moderate-efficacy DMTs (interferons, glatiramer acetate, dimethyl fumarate and teriflunomide) and 2) high-efficacy DMTs (fingolimod, cladribine, ocrelizumab, natalizumab and alemtuzumab) (p. 5)¹⁷”</p>	Not reported
<p>“A suboptimal response* in a patient with a moderate-efficacy DMT must be managed by switching to a high-efficacy DMT (*based on a combination of clinical activity [presence of relapses and/or increase in disability] and radiological activity [>2 active lesions]) (p. 5)¹⁷”</p>	Not reported
<p>“In certain cases (such as adverse events, comorbidities or pregnancy plans), escalation from moderate- to high-efficacy DMTs should be considered, regardless the prior clinical response (p. 5)¹⁷”</p>	Not reported
<p>“Escalation from moderate- to high-efficacy DMTs could be a valid strategy in the case of confirmed progression of disability, even in the absence of clinical and/or radiological activity (p. 5)¹⁷”</p>	Not reported
<p>“In the event of tolerability issues with a moderate-efficacy DMT, a switch within the same efficacy group should be considered, whereas the switch to a high-efficacy DMT would be a secondary option (p. 6)¹⁷”</p>	Not reported
<p>“In some cases (comorbidities, pharmacological interactions, etc.), tolerability issues with a moderate-efficacy DMT could entail switching to a high-efficacy DMT (p. 6)¹⁷”</p>	Not reported
<p>Recommendations for use of natalizumab:</p> <ul style="list-style-type: none"> • “In case of need for change to a high-efficacy DMT, a different treatment from natalizumab would be used in JCV+ patients • In case of need for change to a high-efficacy DMT, the use of natalizumab is only recommended for 2 years in JCV+ patients, always assessing case by case the risk/ benefit balance • In case of need for change to a high-efficacy DMT, even if natalizumab is safe for using during 2 years, another therapeutic option would be preferable in JCV+ patients to avoid rebound issues • In case of need for change to a high-efficacy DMT in JCV- patients, natalizumab can be assessed as part of the different approaches (p. 6)¹⁷” 	Not reported
<p>Washout periods:</p> <ul style="list-style-type: none"> • “In the case of DMF (elimination in approx. 1 day), it is necessary to wait before switching to another DMT until a normal limit lymphocyte count is reached 	Not reported

Recommendations	Quality of evidence and strength of recommendations
<ul style="list-style-type: none"> • In the case of DMF (elimination in approx. 1 day) and persistent lymphopenia, switching to another drug will depend on the benefit/risk balance for each patient • In the case of teriflunomide (natural elimination in > 2 years), an accelerated elimination procedure with cholestyramine is recommended before switching to another therapy • No washout period is needed for different formulations of IFN-beta • No washout period is needed for GA • The washout period for teriflunomide must be determined in line with drug levels in blood and normalization of the lymphocyte count • The washout period for DMF must generally be determined by lymphocyte count recovery (p. 6)¹⁷ 	
French Multiple Sclerosis Society (2021)¹⁸	
<p>“In the case of first-line therapy discontinuation, another first-line therapy, a second-line therapy or an induction therapy could be started without a washout period if the patient’s biological results are normal (p. 2).”¹⁸</p>	<p>Quality of evidence: level C (low level of evidence) Strength of recommendation: appropriate with relative agreement</p>
<p>“In the case of dimethyl fumarate discontinuation and if there is a lymphopenia, it is recommended to wait for a lymphocyte count ≥ 800/ mm, or unless otherwise validated by the MS expert centre or by a multidisciplinary consensus meeting (p. 2).”¹⁸</p>	<p>Quality of evidence: level C (low level of evidence) Strength of recommendation: appropriate with relative agreement</p>
<p>“In the case of teriflunomide discontinuation, a washout must be initiated in the case of a patient intending to become pregnant or in the case of early pregnancy (p. 2).”¹⁸</p>	<p>Quality of evidence: level C (low level of evidence) Strength of recommendation: appropriate with strong agreement</p>
<p>“It is recommended to validate the indication and the timing of the switch to a second-line therapy or induction therapy and the washout time with the MS expert centre or in a multidisciplinary consensus meeting (p. 2).”¹⁸</p>	<p>Quality of evidence: level C (low level of evidence) Strength of recommendation: appropriate with relative agreement</p>

DMF = dimethyl fumarate; DMT = disease-modifying therapy; GA = glatiramer acetate; IFN = interferon; JCV = John Cunningham virus; MS = multiple sclerosis.

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