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**CADTH RAPID RESPONSE REPORT:**
**SUMMARY WITH CRITICAL APPRAISAL**

# Second-Line Therapy for Patients with Relapsing-Remitting Multiple Sclerosis: A Review of Guidelines


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## Abbreviations

| | |
|---|---|
| DMT | disease modifying therapies |
| EAN | European Academy of Neurology |
| ECTRIMS | European Committee of Treatment and Research in Multiple Sclerosis |
| GRADE | Grading of Recommendations, Assessment, Development and Evaluation |
| MS | multiple sclerosis |
| MRI | magnetic resonance imaging |
| RCT | randomized controlled trial |
| RRMS | relapsing-remitting multiple sclerosis |

## Context and Policy Issues

Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system characterized by widespread inflammation, demyelination and degenerative changes.[1,2] Patients may experience a wide range of symptoms such as dizziness, tingling sensations, or visual disturbances, bladder and bowel dysfunction, and cognitive impairment.[3] In 2017, it was estimated that there were 79,723 cases of MS in Canada.[4] From the onset of MS, eighty-five to ninety percent of the patients have relapses and remissions of symptoms that characterize the relapsing-remitting multiple sclerosis (RRMS).[2] The different symptoms are associated with different areas of central nervous system inflammation.[2] There is no curative treatment available for MS, and the current therapeutic strategy is aimed at reducing the risk of relapses and potentially disability progression.[2] Patients are treated with disease-modifying therapies (DMTs) approved by Health Canada including beta interferons, glatiramer acetate, teriflunomide, ocrelizumab, dimethyl fumarate, cladribine, as well as alemtuzumab, fingolimod, and natalizumab.[5-7] These DMTs have different mechanisms of action that aim to suppress or modulate the dysregulated immune system, limit CNS inflammation, and prevent relapses and new lesions.[6] The alemtuzumab, fingolimod, and natalizumab are newer drugs that are currently considered as second-line therapies, which are drugs given when the initial treatment has proven to be inadequate, in adult patients with RRMS.[8-10] There is uncertainty in clinical practice regarding how and when to switch from the first-line therapy to a second-line therapy.[11] This review seeks to report on the critically appraisal of the evidence-based guidelines regarding switching to a second-line therapy in patients with RRMS.

## Research Question

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

## Key Findings

One evidence-based guideline was identified with one strong recommendation regarding switching from an interferon or glatiramer acetate to a second-line therapy in patients with relapsing-remitting multiple sclerosis and evidence of disease activity. Consensus statements provided by the guideline suggest that there is insufficient evidence on patient factors or disease activity considerations to make more specific recommendations for switching to second-line treatments. The consensus statements presented in this report should be interpreted with caution based on the limitations and paucity of evidence.

## Methods

### Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE via Ovid, Embase via Ovid, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were second line therapy and multiple sclerosis. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and August 26, 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. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

**Table 1: Selection Criteria**

| | |
|---|---|
| **Population** | Adult patients with RRMS who are currently treated with a first-line treatment<br>Exclude: patients with Clinically Isolated Syndrome, primary progressive MS, secondary progressive MS |
| **Intervention** | Second-line treatments:<br>• Lemtrada (alemtuzumab)<br>• Gilenya (fingolimod)<br>• Tysabri (natalizumab) |
| **Comparator** | Not applicable |
| **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 magnetic resonance imaging) |
| **Study Designs** | Health technology assessments, systematic reviews, meta-analyses, guidelines |

MS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis.

### Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1**:** Selection Criteria or were duplicate publications. Guidelines with unclear methodology were also excluded.

### Critical Appraisal of Individual Studies

The included guideline was critically appraised using the AGREE II instrument.[12] Summary scores were not calculated for the included guideline; rather, a review of its strengths and limitations were described narratively.

## Summary of Evidence

### Quantity of Research Available

A total of 180 citations were identified in the literature search. Following screening of titles and abstracts, 175 citations were excluded and five potentially relevant reports from the electronic search were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, seven publications were excluded due to irrelevant outcomes or irrelevant study designs, and one evidence-based guideline met the inclusion criteria and was included in this report. Appendix 1 presents the PRISMA[13] flowchart of the study selection. Additional references of potential interest are provided in Appendix 5.

### Summary of Study Characteristics

Additional details regarding the characteristics of the included publication are provided in Appendix 2.

#### *Study Design*

The evidence-based guideline included in this review was developed by the European Committee of Treatment and Research in Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) and was published in 2018.[2] The guideline focuses on DMTs and poses several review questions for both therapeutic intervention and clinical management of MS.[2]

Eligible study designs for the systematic reviews done by the guideline authors included systematic reviews, randomized controlled trials (RCTs) and observational studies. The search timeframe was from inception to 2015 for one of the relevant guideline review questions (review question 6) and from 2014 to 2016 for the other relevant guideline review question (review question 4; updating an existing review from 2016).[14] The search timeframe for the last relevant question (review question 5) was not reported.[14] The quality of evidence was determined by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, incorporating study design, risk of bias, consistency, directness and precision.[2] The recommendations were made based on consensus by a panel according to a standard process using the modified nominal group technique following a two-stage process. In the first stage, panel experts evaluated the evidence and rated their agreement with draft recommendations, and in the second stage they redeveloped statements with low agreement until consensus was reached through voting.[2]

The strength of recommendations was assigned as strong or weak, which were based on the risk-benefit balance and the quality of evidence.[2] Consensus statements were formulated for those aspects for which there is no sufficient evidence to support a formal recommendation.[2]

#### *Country of Origin*

The evidence-based guideline for the pharmacological treatment of patients with MS included in this review is intended to be applied in Europe and worldwide.[2]

### *Patient Population*

The evidence-based guideline has the target population of adult patients with MS,[2] of which the RRMS population is relevant to the current report. The intended users of the guideline include physicians, health care providers, patients, and health-policy makers.[2]

### *Interventions and Comparators*

In the included evidence-based guideline, review question 6 aims to explore treatment strategies for patients with inadequate treatment response, and considers switching from interferon or glatiramer acetate to a "more efficacious drug",[2] including alemtuzumab, fingolimod or natalizumab, as relevant interventions. There is no applicable comparator.

### *Outcomes*

In the included guideline, the outcomes of interest are efficacy of the relevant DMTs, response criteria, strategies to address suboptimal response and safety concerns, and treatment strategies in MS.

## Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in .

The guideline clearly described the overall objective, health questions, the target population of the guideline, and the intended user group.[2] It is unclear whether the views and preferences of individuals from all relevant professional groups was sought.[2] The guideline was developed using rigorous systematic methodology and recommendations were based on a systematically reviewed and critically appraised body of clinical evidence, which gives more confidence that the recommendations are not only based on studies that support the expert opinions of the guideline groups.[2] Recommendations in the guideline were accompanied by a measure of strength of the recommendation.[2] However, the recommendations regarding the considerations or patient characteristics that makes patients eligible for switching to a second-line therapy are not very clear or specific.[2] Details regarding the facilitators and barriers for the application of the recommendations and information regarding external peer review were lacking.[2] Potential resource implications and implementation guidance or tools were not described in the guideline.[2] Conflicts of interest were addressed.[2]

## Summary of Findings

The ECTRIMS/EAN guideline development group produced a set of recommendations regarding switching from interferon or glatiramer acetate to a second-line therapy in patients with RRMS[2]. Appendix 4 presents a table of the main study findings and authors' conclusions.

In their evidence review, ECTRIMS/EAN evaluated strategies for switching, factors to consider when switching, monitoring safety, and considerations regarding disease evolution and treatment response.[2]

One "strong" recommendation relevant to this report was made; this recommendation followed review question 6, which asked about the benefit of switching from interferon or glatiramer acetate to "more efficacious drugs" in patients with inadequate treatment response.[2] The guideline strongly recommends that patients that are currently treated with

interferon or glatiramer acetate who show evidence of disease activity should be offered a more efficacious drug.[2] The authors did not specify which drugs were more efficacious in the recommendation section but reported that all analyzed studies in the guideline consistently showed a benefit in switching to natalizumab, fingolimod, or alemtuzumab compared with interferon or glatiramer acetate.[2]

Early disease activity was defined as "relapses and/or disability progression and/or MRI activity at 6/12 months", and related recommendations and consensus statements about monitoring treatment response (from review questions 4 and 5) were also provided.[2] The guideline authors made a relevant "weak" recommendation for combining MRI with clinical measures for monitoring disease evolution in patients who are on treatment.[2] When monitoring treatment response, the guideline authors provided a consensus statement for the MRI method that measures new or unequivocally enlarging T2 lesions, supplemented by GAD-enhancing lesions.[2] Standardized high-quality MRI scans and interpretation by highly qualified readers with experience in MS are required to evaluate the lesions.[2] For monitoring treatment safety, a consensus statement was reported regarding the frequency of performing a standardized reference brain MRI.[2]

Under review question 6, the guideline panel had consensus on the factors that influence which drug to switch to; these include patient characteristics and comorbidities, drug safety profile, and disease severity and activity.[2] However, no more specific information was provided, and this statement was classified as a consensus statement, as there was insufficient evidence to support a formal recommendation.

### Limitations

The guideline by ECTRIMS/EAN[2] presents the recommendation to switch to a second-line therapy when the patient has inadequate response to interferon or glatiramer acetate; however, no evidence-based guidelines were identified regarding the patient clinical features or other considerations to switch from other first-line agents such as teriflunomide, ocrelizumab, and dimethyl fumarate. Many recommendations in the guideline were made with a weak grade of recommendation or were categorized as a consensus statement because of the lack of evidence base and reported therapeutic effects.[2] Additionally, the generalizability of the recommendation of the European guideline[2] to the Canadian context is unknown.

## Conclusions and Implications for Decision or Policy Making

One evidence-based guideline[2] was identified that addressed the research question. A variety of recommendations and consensus statements were made regarding considerations for switching from a first-line therapy to a second-line therapy in adult patients with RRMS.

The authors of the guideline by ECTRIMS/EAN discuss strategies for switching, factors to consider when switching, monitoring safety, disease evolution, and treatment response.[2] One relevant "strong" recommendation was made.[2] The guideline strongly recommends that patients that are currently treated with interferon or glatiramer acetate who show evidence of disease activity should be offered a more efficacious drug.[2] The guideline authors made a relevant "weak" recommendation for combining MRI with clinical measures for monitoring disease evolution in patients who are on treatment.[2]

Further guidelines and recommendations on switching from teriflunomide, ocrelizumab, and dimethyl fumarate to a second-line agent may help to reduce uncertainty in this area. The publication considered in this CADTH review was not conducted in Canada.[2] The health care resources requirement, training requirements and budgetary implications may differ between countries. Therefore, the applicability of these findings to the Canadian health care setting may be limited.

## References


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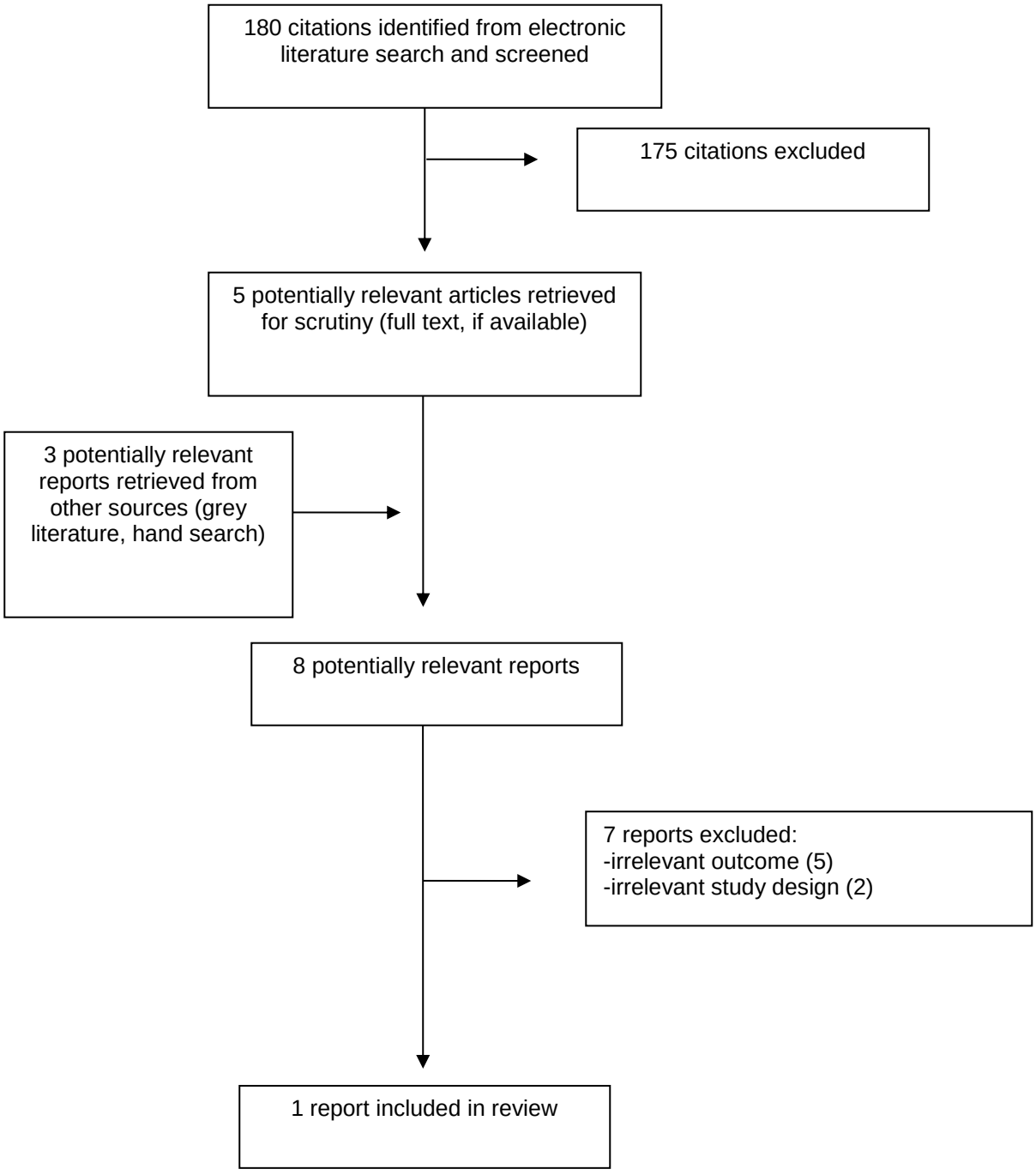
## Appendix 1: Selection of Included Studies



# Appendix 2: Characteristics of Included Publications

## Table 2: Characteristics of Included Guidelines

| Intended Users, Target Population | Intervention and Practice Considered | Major Outcomes Considered | Evidence Collection, Selection, and Synthesis | Evidence Quality Assessment | Recommendations Development and Evaluation | Guideline Validation |
|---|---|---|---|---|---|---|
| Montalban, 2018[2] | | | | | | |
| Physicians, healthcare providers, patients, and health-policy makers in Europe and worldwide<br><br>Adult population with MS, including RRMS | Disease-modifying treatment for MS, including all immunomodulatory and immunosuppressive drugs approved by the EMA | Treatment efficacy, response criteria, strategies to address suboptimal response and safety concerns, treatment strategies in MS and pregnancy | A search of the Cochrane Central Register of Controlled Trials (Central), Excerpta Medica Database (Embase), Medical Literature Analysis and Retrieval System Online (MEDLINE)/MEDLINE In-Process and Psychological Information Database (PsycINFO) for articles published since inception to 2015 for review question 6, from 2014 to 2016 for review question 4, timeframe NR for review question 5 SRs, RCTs with at least 1 year follow-up (48 weeks acceptable) and long-term extensions on included RCTs. 2 reviewers selected relevant articles. | GRADE approach<br><br>The quality of evidence incorporated: study design, risk of bias, inconsistency, indirectness and imprecision | Recommendations were developed by consensus by a panel according to a standard process using the modified nominal group technique following a two-stage process.<br><br>Panel member composition NR | NR |

EMA = European Medicine Agency; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; MS = multiple sclerosis; NR = not reported; RCT = randomized controlled trials; RRMS = relapsing-remitting multiple sclerosis; SR = systematic review.

# Appendix 3: Critical Appraisal of Included Publications

## Table 3: Strengths and Limitations of Guidelines using AGREE II[12]

| Item | Guideline |
|---|---|
| | Montalban, 2018[2] |
| 1. The overall objective(s) of the guideline is (are) specifically described. | Yes |
| 2. The health question(s) covered by the guideline is (are) specifically described. | Yes |
| 3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described. | Yes |
| 4. The guideline development group includes individuals from all relevant professional groups. | Unclear |
| 5. The views and preferences of the target population (patients, public, etc.) have been sought. | Yes |
| 6. The target users of the guideline are clearly defined. | Yes |
| 7. Systematic methods were used to search for evidence. | Yes |
| 8. The criteria for selecting the evidence are clearly described. | Yes |
| 9. The strengths and limitations of the body of evidence are clearly described. | Yes |
| 10. The methods for formulating the recommendations are clearly described. | Yes |
| 11. The health benefits, side effects, and risks have been considered in formulating the recommendations. | Yes |
| 12. There is an explicit link between the recommendations and the supporting evidence. | Yes |
| 13. The guideline has been externally reviewed by experts prior to its publication. | No |
| 14. A procedure for updating the guideline is provided. | Yes |
| 15. The recommendations are specific and unambiguous. | Unclear |
| 16. The different options for management of the condition or health issue are clearly presented. | Yes |
| 17. Key recommendations are easily identifiable. | Yes |
| 18. The guideline describes facilitators and barriers to its application. | Unclear |
| 19. The guideline provides advice and/or tools on how the recommendations can be put into practice. | No |
| 20. The potential resource implications of applying the recommendations have been considered. | No |
| 21. The guideline presents monitoring and/or auditing criteria. | Yes |
| 22. The views of the funding body have not influenced the content of the guideline. | Yes |
| 23. Competing interests of guideline development group members have been recorded and addressed. | Yes |

# Appendix 4: Main Study Findings and Authors' Conclusions

## Table 4: Summary of Recommendations in Included Guidelines

| Evidence and Quality of Evidence | Recommendations | Strength of Evidence and Recommendations |
|---|---|---|
| Montalban, 2018[2] | | |
| • **"Review question 6. In patients with relapsing MS treated with interferon or glatiramer acetate and evidence of early disease activity (relapses and/or disability progression and/or MRI activity at 6/12 months), what is the benefit of switching between interferon and glatiramer acetate versus moving to more efficacious drugs?" (pp106-107)** | | |
| "9 studies met the eligibility criteria for this review... Three of the studies were RCTs; five were retrospective cohorts; and one was a prospective cohort." (p107)<br><br>"All analysed studies were consistent in showing a benefit in switching to alemtuzumab, fingolimod or natalizumab compared with interferon or glatiramer acetate, depending on specific study comparators." (p107)<br><br>"Evidence obtained by RCTs was assessed for risk of bias using the 'Cochrane Risk of Bias tool'. There was a low risk of bias for sequence generation, allocation concealment, attrition and selective outcome reporting for all included trials. In two of the trials, there was a high risk of performance and detection bias since all patients, providers and assessors were aware of treatment allocation, whereas in the third trial,the risk of bias was low since all participants, providers and assessors were blinded to treatment allocation." (p107)<br><br>"The cohort studies were assessed using the Cochrane tool for 'ROBINS-I', three were judged as having a moderate risk of bias and three as having a serious risk of bias." (p107) | "R14. Offer a more efficacious drug to patients treated with interferon or glatiramer acetate who show evidence of disease activity assessed as recommended in questions 4 and 5 of this guideline." (p108) | The recommendation was classified as strong, as it was based on high-quality evidence. |
| | "R15. When deciding on which drug to switch to, in consultation with the patient, consider the following factors:<br>1. patient characteristics and comorbidities<br>2. drug safety profile<br>3. disease severity/activity" (p108) | The recommendation was classified as a consensus statement, as there was insufficient evidence to support a formal recommendation. |

## Table 4: Summary of Recommendations in Included Guidelines

| Evidence and Quality of Evidence | Recommendations | Strength of Evidence and Recommendations |
|---|---|---|
| • **"Review question 4. In patients with relapsing MS treated with DMDs, does the presence of early disease activity (relapses and/or disability progression and/or MRI activity at 6 months/12 months) predict an increased risk of future disability?" (p105)**<br>• **"Review question 5. In MS patients treated with DMDs, should a follow-up MRI be performed in a pre-specified time scheme to monitor treatment response and safety?" (p106)** | | |
| "Overall, criteria that included MRI or MRI combined with clinical measures had a higher predictive value than clinical criteria alone. When considering only MRI criteria, measures of new/newly enlarging T2 lesions outperformed those of GAD lesions. Of the 16 criteria evaluated in the SR by Rio et al., the following three were determined to have the best predictive value:<br>1. One or more new/newly enlarging T2 lesions;<br>2. Two or more new/newly enlarging T2 lesions;<br>3. Two or more criteria from the modified Rio<br>score." (p105)<br><br>"Using criteria from the AMSTAR tool, the SR was rated as low quality. This was due to the absence of reported information, namely, the study characteristics of included studies, an excluded studies list and a quality assessment of included studies. The primary studies were assessed with the Cochrane tool for 'ROBINS-I'. All four studies were judged as having a moderate risk of bias. This was mainly due to a lack of information about missing data and potential confounding factors." (p106) | "R10. Consider combining MRI with clinical measures when evaluating disease evolution in treated patients." (p106) | The recommendation was classified as weak, as it was based on low-quality evidence. |
| | "R11. When monitoring treatment response in patients treated with DMDs, perform a standardized reference brain MRI usually within 6 months of treatment onset and compare it with a further brain MRI performed typically 12 months after starting treatment. Adjust the timing of both MRIs, taking into account the following aspects:<br>1. the drug's mechanism of action (particularly the speed of action)<br>2. disease activity (including clinical and MRI measures)" (p106) | The recommendation was classified as a consensus statement, as there was insufficient evidence to support a formal recommendation. |
| | "R12. When monitoring treatment response in patients treated with DMDs, the measurement of new or unequivocally enlarging T2 lesions is the preferred MRI method supplemented by GAD enhancing lesions for monitoring treatment response. Evaluation of these parameters requires:<br>1. high quality, standardized MRI scans<br>2. interpretation by highly qualified readers with experience in MS" (p106) | The recommendation was classified as consensus statement, as there was insufficient evidence to support a formal recommendation. |
| | "R13. When monitoring treatment safety in patients treated with DMDs, perform a standardized reference brain MRI:<br>1. every year in low risk progressive multifocal leukoencephalopathy (PML) patients<br>2. more frequent MRIs (on a 3–6 monthly basis) in high risk PML patients (JC virus positive, natalizumab treatment duration over 18 months)<br>3. in patients with high risk of PML who switch drugs, at the time that the current treatment is discontinued and after the new treatment is started" (p106) | The recommendation was classified as consensus statement, as there was insufficient evidence to support a formal recommendation. |

DMD = disease modifying drug; GAD = gadolinium; JC virus = John Cunningham virus; MRI = magnetic resonance imaging; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy; R = recommendation.

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# Appendix 5: Additional References of Potential Interest

*Clinical Practice Guidelines – Unclear Methodology*

Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. *Pract Neurol.* 2015 Aug;15(4):273-9.