TITLE: Treatment of Patients with Multiple Sclerosis: A Review of Guidelines

DATE: 13 March 2013

CONTEXT AND POLICY ISSUES

Multiple sclerosis (MS) is an unpredictable, often disabling disease of the central nervous system. The disease attacks the myelin, which is a protective covering wrapped around the nerves of the central nervous system. There are four types of MS disease states: relapsing-remitting MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS), and progressive relapsing MS (PRMS). RRMS describes a course of MS characterized by an unpredictable but clearly defined episodes (or exacerbations) during which new symptoms appear or existing ones get worse affecting 85% of MS patients. The hallmark of RRMS is the recovery or remission that occurs between attacks. PPMS describes a course of MS which is characterized by a slow accumulation of disability, without relapses affecting 10% of patients. It may stabilize for periods of time, and even offer minor temporary improvement, but overall, there are not periods of remission in PPMS. SPMS follows on a course of RRMS. Over time, distinct relapses and remissions become less apparent and the disease begins to worsen steadily. About 50% of people with RRMS will develop SPMS within 10 years of diagnosis. PRMS, the rarest course of MS, affects about 5% of patients. People with this form of MS experience steadily worsening disease from the beginning, but also experience clear attacks of symptoms, with or without recovery.

MS medications are generally divided into three categories: immunomodulatory therapies, steroids, and medications for MS related symptoms such as fatigue or pain. The goals of MS treatment include improving the speed of recovery from attacks, reducing the number of attacks or the number of MRI lesions, and attempting to slow progression of the disease. However, choosing, initiating, stopping and changing treatments for patients remains a point of controversy among healthcare professionals. As a result, the purpose of this review is to examine the evidence-based guidelines for the treatment of MS and stopping or switching MS treatment.

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RESEARCH QUESTIONS

1. What are the evidence-based guidelines for treatment of patients with multiple sclerosis?
2. What are the evidence-based guidelines for stopping or switching treatment?

KEY MESSAGE

Limited evidence-based guidelines are available for the treatment of multiple sclerosis, and the stopping or switching of treatment. The available evidence has suggested plasmapheresis as an adjunctive or alternative treatment for MS, corticosteroids for the treatment of relapse, and natalizumab in cases of failure on other drugs or intolerance.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to guidelines. The search was also limited to English language documents published between January 1, 2008, and February 11, 2013.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for final article selection (see Table 1).

Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with Multiple Sclerosis (any type)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Treatment with drugs or non-pharmacological treatment</td>
</tr>
<tr>
<td>Comparator</td>
<td>N/A</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Guidelines and recommendations for treatment options, timing of treatment initiation, stopping rules, and guidance on switching treatment</td>
</tr>
<tr>
<td>Study Designs</td>
<td>Evidence-based guidelines</td>
</tr>
</tbody>
</table>

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications, methodology for guideline development was unclear (i.e. unclear if a systematic review of literature was conducted for evidence to support the guideline) or were published prior to 2008.
Critical Appraisal of Individual Studies

Evidence-Based Guidelines were assessed using the Appraisal of Guidelines for Research and Evaluation II (AGREE II). A numeric score for each study was not calculated, instead a narrative summary of study strengths and limitations was provided.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 133 citations. From these, 21 articles were selected for further examination. One additional guideline was identified from grey literature searching. Of the 22 articles, three evidence-based guidelines were identified. The study selection process is outlined in a PRISMA flowchart (Appendix 1).

Additional references of potential interest which did not meet the selection criteria are provided in Appendix 2.

Summary of Study Characteristics

Study Design

Three articles are included in this report. The three evidence-based guidelines were based on evidence from a systematic search of the literature. All three guidelines did not specify exclusion criteria based on study type.

Country of Origin

One of the evidence-based guidelines was generated in France, and two evidence-based guidelines were generated in the United States of America (USA).

Population

The French guideline was designed to provide treatment options for patients with MS experiencing a relapse. A 2011 guideline from a subcommittee of the American Academy of Neurology (AAN) was designed to assess treatments for neurological disorders including MS. Finally, a 2008 guideline from a subcommittee of the AAN was designed to assess treatments for any type of MS.

Intervention and Comparators

The French guideline provided recommendations for treatment with methylprednisolone, corticosteroids, plasma exchanges (or plasmapheresis), intravenous immunoglobulins. The 2011 AAN guideline provided recommendations around treatment with plasmapheresis. Finally, the 2008 AAN guideline provided recommendations about treatment with natalizumab.
Outcomes

The French guideline provided recommendations around the treatment of relapse addressing issues such as functional scores and disability. The 2011 AAN guideline provided recommendations around relapses and severe disease states. The 2008 AAN guideline provided recommendations concerning patients who have failed treatment or demonstrated intolerance and for situations where a treatment should not be used. Criteria for the grading of recommendations and levels of evidence are included in Appendix 4.

Summary of Critical Appraisal

A detailed summary of the critical appraisal of individual included reports can be found in Appendix 3.

An evidence-based guideline from the Multiple Sclerosis Think Tank in France was included. The strengths of the evidence-based guideline include a clear objective, explicitly predefined research questions developed a priori, a systematic search of the literature was conducted, the strength of the evidence and a grading scheme was described, and recommendations were clearly outlined. Limitations of the guideline include the lack of clarity around the specific target population (MS disease state), lack of information on the barriers and aids to implementing the recommendations, lack of information provided on how patients should be monitored during the recommended treatment periods and no information on if or how the guideline will be updated.

Cortese et al. (2011) created an evidence-based guideline developed from a subcommittee of the American Academy of Neurology (AAN). The strengths of the guideline include a clear objective, and a systematic literature search. Limitations of the guideline include the lack of specificity around the target patient population, no information provided on the barriers and aids to implementing the recommendations, no information provided on how patients should be monitored during the recommended treatment periods, and no information on if or how the guideline will be updated.

Goodin et al. (2008) generated an evidence-based guideline developed from a subcommittee of the AAN. The strengths of the guideline include a clear objective, explicit research questions, a systematic literature search, and an analysis of the strengths and limitations of the included literature that formed the basis of the recommendations. Limitations of the guideline include no description of the inclusion criteria, lack of clarity on whether patient input was considered, no information provided on the barriers and aids to implementing the recommendations, no information provided on how patients should be monitored during the recommended treatment periods and no information on if or how the guideline will be updated.

Summary of Findings

A summary of the guideline recommendations is provided in Appendix 5.

The Multiple Sclerosis Think Tank (MSTT) offered five recommendations relating to the treatment of MS relapses. Two of the recommendations suggested corticosteroids intravenously (IV) or orally, if the IV route cannot be used, as a treatment for a short duration (for example, methylprednisolone 500 mg to 1 g per day for 3 to 5 days). In cases of severe relapses, where
IV drug treatment is insufficient, a regimen of plasma exchanges (or plasmapheresis) was suggested. Rehabilitation was also recommended; it was suggested it should be adapted to the disability of patients from relapses and initiated as soon as possible. In addition, under no circumstances were IV immunoglobulins recommended in the treatment of MS relapses.

Cortese et al. (2011) from the subcommittee of the AAN provided three recommendations around plasmapheresis for neurological disorders including MS. Similar to the MSTT guideline, plasmapheresis was recommended as a treatment for individuals with severe CNS disease who fail on high-dose corticosteroids. In addition, it was recommended as an adjunctive treatment for exacerbations in relapsing types of MS. However, the final recommendation suggested against the use of plasmapheresis as a treatment for secondary progressive MS.

Goodin et al. (2008) from the subcommittee of the AAN provided two recommendations concerning treatment with natalizumab. Because of the potential for natalizumab being a cause of increased risk of progressive multifocal leukoencephalopathy (PML), natalizumab was recommended as a treatment for patients with RRMS after failure of other therapies due to disease activity or medication intolerance, or patients who have the disease progressing with an aggressive course. In addition, a recommendation against the combination of interferon beta and natalizumab was provided; this was due to an increased risk of PML.

Limitations

There were numerous limitations to the included guidelines. The guideline by the MSTT may be limited because only two of the five recommendations were evidence-based. Three of the five recommendations were based on “relative professional agreement” because of the absence of scientific evidence. Both of the recommendations from the subcommittee of the AAN provided grading of the recommendations with no explicit explanation of the level of evidence used to form the recommendations or outline of recommendation grading scheme. Furthermore, the AAN guidelines generally lack information around the duration of treatment with the recommended therapies. In addition, one of the recommendations concerning natalizumab suggested its use in cases where patients have failed other treatments. However, the recommendations do not specify which treatments should be failed before switching to this treatment option. Furthermore, none of the included guidelines provide a full treatment algorithm for MS. Instead, the included guidelines provide recommendations concerning treatment with one to three drug and non-drug treatments for MS.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

There are limited evidence-based guidelines concerning the starting, stopping, switching and selecting treatments for the various disease states of MS. The available evidence suggests plasmapheresis may be an option as an adjunctive therapy or alternative treatment for MS, corticosteroid may be used as a treatment or relapse, and natalizumab may be used as a treatment in cases of failure on other drugs or intolerance.

There is a general lack of an evidence-based treatment algorithm for MS. The result is there is little evidence for the basis of policy and decision making on MS treatment. In addition, in spite of some recommendations around the treatment of MS there is little information on the duration of treatment and monitoring. Although, there appears to be multiple guidelines in various
countries around the world to help with treatment decisions for MS, the majority do not appear to be evidence-based.\textsuperscript{8}

**PREPARED BY:**
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
[www.cadth.ca](http://www.cadth.ca)
REFERENCES


APPENDIX 1: Selection of Included Studies

133 citations identified from electronic literature search and screened

112 citations excluded

21 potentially relevant articles retrieved for scrutiny (full text, if available)

1 potentially relevant report retrieved from other sources (grey literature, hand search)

22 potentially relevant reports

19 reports excluded:
- expert opinion/consensus (6)
- methods unclear (4)
- irrelevant outcomes (2)
- non-randomized study (1)
- other (review articles, editorials) (6)

3 reports included in review
APPENDIX 2: Additional Information

Methods for Guidelines Development Unclear


# APPENDIX 3: Summary of Critical Appraisal

<table>
<thead>
<tr>
<th>Guideline Society, First Author, Publication, Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Multiple Sclerosis Think Tank Laplaud et al. (2012)France | ● Clinical questions determined a priori  
● Clear description of how recommendations were developed  
● Comprehensive search strategy including a list of mesh terms used to search for each research question | ● It is unclear how the guidelines will be updated  
● Not clear which recommendations are key  
● Guidelines provide little information around monitoring patients  
● Reports on only two treatment options for MS  
● It is unclear if patient input was considered |
| Therapeutics and Technology Assessment Subcommittee of the AAN Cortese et al. (2011)USA | ● Clear systematic review using multiple databases described in detail  
● Addresses the topic of MS adjunct therapy | ● Levels of evidence and recommendations are reported but no explanations of what these criteria are was provided  
● Does not provide full treatment algorithm reports on only a single treatment option for MS  
● The questions asked to generate the guideline are not described  
● It is unclear the strengths and limitations of the evidence used to generate the recommendations  
● Unclear how the guideline will be updated  
● It is unclear if patient input was considered |
| Therapeutics and Technology Assessment Subcommittee of the AAN Goodin et al. (2008)USA | ● Described the strengths and limitations of the evidence  
● Clear systematic search methods outlined  
● Clear clinical questions outlined and evidence reviewed specifically for each question | ● It is unclear how the recommendations were formed  
● Patient input was not considered in the guideline development  
● It is unclear how the guidelines will be updated  
● Recommendations do not specify which treatments should be failed before switching to natalizumab |

*AAN= American Academy of Neurology; MS=Multiple sclerosis; USA= United States of America*
## APPENDIX 4: Summary of Level of Recommendations and Evidence

<table>
<thead>
<tr>
<th>Guideline Society, First Author, Publication, Year</th>
<th>Level of Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multiple Sclerosis Think Tank</strong>&lt;sup&gt;6&lt;/sup&gt; Laplaud et al. (2012) France</td>
<td>Grade A= Level 1&lt;br&gt;Grade B= Level 2&lt;br&gt;Grade C= Level 3, 4, and 5&lt;br&gt;Professional agreement= absence of scientific proof</td>
<td><strong>Level 1</strong>: Randomized controlled trials with large sample size; meta-analysis&lt;br&gt;<strong>Level 2</strong>: Randomized controlled trials with small sample size&lt;br&gt;<strong>Level 3</strong>: Contemporary non-randomized controlled trials/ Cohort studies&lt;br&gt;<strong>Level 4</strong>: Controlled trials with historical controls&lt;br&gt;<strong>Level 5</strong>: Case series&lt;br&gt;Absence of scientific proof” (p.429)</td>
</tr>
<tr>
<td><strong>Therapeutics and Technology Assessment Subcommittee of the AAN</strong> Cortese et al. (2011)&lt;sup&gt;6&lt;/sup&gt; USA</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Therapeutics and Technology Assessment Subcommittee of the AAN</strong> Goodin et al. (2008)&lt;sup&gt;7&lt;/sup&gt; USA</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

*AAN= American Academy of Neurology; NR=Not reported*
### APPENDIX 5: Summary of Guidelines and Recommendations

<table>
<thead>
<tr>
<th>Guideline Society, First Author, Publication, Year</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| **Multiple Sclerosis Think Tank Laplaud et al. (2012)** 6 France | - “When treatment for MS relapse is required, it should include high doses of intravenous (IV) corticosteroids (if not contraindicated) for a short duration (for example, methylprednisolone 500 mg to 1 g per day 3 to 5 days) (grade A)  
- When the IV route cannot be used, oral treatment with the same dose and same duration is advised (for example, methylprednisolone 500 mg to 1 g per day 3 to 5 days) (relative professional agreement)  
- For severe relapse with insufficient clinical improvement after well-conducted IV drug treatment, 5 to 7 plasma exchanges can be done at a rate of one exchange every 2 days (grade C)  
- There are no indications for using IV immunoglobulins in the treatment of MS relapses (relative professional agreement)  
- Rehabilitation adapted to the disability resulting from the relapse should be instituted as soon as possible (relative professional agreement).” p.430-431 |
| **Therapeutics and Technology Assessment Subcommittee of the AAN (Cortese et al., 2011)** 6 | - “Plasmapheresis should be considered for the adjunctive treatment of exacerbations in relapsing forms of MS (Level B).  
- Plasmapheresis may be considered in the treatment of fulminant CNS demyelinating diseases that fail to respond to high-dose corticosteroid treatment (Level C).  
- Plasmapheresis should not be offered for chronic progressive or secondary progressive MS (Level A).” p. 297 |
| **Therapeutics and Technology Assessment Subcommittee of the AAN (Goodin et al., 2008)** 7 | - “Because of the possibility that natalizumab therapy may be responsible for the increased risk of PML, it is recommended that natalizumab be reserved for use in selected patients with relapsing remitting disease who have failed other therapies either through continued disease activity or medication intolerance, or who have a particularly aggressive initial disease course.  
- Similarly, because combination therapy with IFNβ and natalizumab may increase the risk of PML, it should not be used.” p.771 |

**AAN=** American Academy of Neurology; **MS=** multiple sclerosis; **IFNβ=** interferon beta; **IV=** intravenous; **PML=** progressive multifocal leukoencephalopathy