Authors’ Response to Commentary from Sutliff et al on the Comprehensive Systematic Review: Rehabilitation in Multiple Sclerosis

Jodie K. Haselkorn, MD, MPH; Christina Hughes, MD; Alex Rae-Grant, MD; Lily Jung Henson, MD, MMM; Christopher T. Bever, MD, MBA; Albert C. Lo, MD, PhD; Theodore R. Brown, MD, MPH; George H. Kraft, MD, MS; Gary Gronseth, MD; Melissa J. Armstrong, MD, MSc; Pushpa Narayanaswami, MBBS, DM

We thank Sutliff et al.\textsuperscript{1} for their commentary on our systematic review, “Rehabilitation in Multiple Sclerosis.”\textsuperscript{2} When the American Academy of Neurology (AAN) undertook this systematic review (SR), and several other MS topics\textsuperscript{2-4} in 2007, we knew that physicians had been receiving questions from their patients regarding the most appropriate and efficacious rehabilitation therapies for MS. The MS society was extensively involved in discussions regarding the need for these systematic reviews.

Sutliff et al.\textsuperscript{1} mention that the composition of our SR author panel\textsuperscript{2} “lacked specialist diversity.” During the panel selection meeting in November 2007, the Guideline Development Subcommittee leadership strived to balance the panel and include MS experts, rehabilitation experts with national and international recognition, non-MS expert neurologists, and guideline development methodologists. We acknowledge that physical and occupational therapists, speech and language therapists and exercise physiologists were not included on the panel. Sutliff et al.\textsuperscript{1} mention that addition of these specialists would have contributed to input regarding the use of clinically accessible outcomes in the inpatient (instead of the outpatient) arena and the utility of an occupational therapist in improving upper arm dexterity. However, this was an SR,\textsuperscript{2} not a
clinical practice guideline (CPG). This nuance is very important because the CPG process lends itself to some degree of expert opinion and formal consensus, whereas the SR does not. Therefore, the conclusions of our SR\textsuperscript{2} would have been the same even with the inclusion of other experts because SR conclusions are based on the AAN risk of bias assessment of each study and not on expert opinion. The strength of the evidence is a key criterion for AAN SRs and CPGs. If the evidence is a case series or cohort study without a comparison group, it does not rise to the level of inclusion because of the low confidence in the results. This is transparently discussed and serves as a stimulus for better quality research.

We agree that finding high-level evidence is more difficult in rehabilitation strategies compared to therapeutic agents. We also agree that evidence-based medicine is more than just the conclusions of a SR or recommendations of a CPG. Sutliff et al.\textsuperscript{1} suggest that we could have highlighted methodologic issues; we have extensively highlighted the shortcomings of the MS rehabilitation research in the recommendations for research section of our SR.\textsuperscript{2} We do not think, as Sutliff et al.\textsuperscript{1} suggest, that it is appropriate to blame the risk of bias assessment for failure to identify high-level studies in our SR.\textsuperscript{2} This approach would suggest that we are willing to settle for weaker evidence in rehabilitation to inform practice as compared to the evidence for therapeutic agents. This approach does not serve our patients, who deserve the highest level of evidence that informs their care. Hence, the field of rehabilitation should also be challenged to develop study protocols that are robust, instead of setting a lower bar for the quality of these studies.
During the development of the manuscript, the AAN process requires broad review and expert stakeholder input. AAN staff work with the guideline author panel to identify and target relevant organizations, patient advocacy groups, and AAN sections to review the draft and provide critical feedback to improve the clarity of the document, the timeliness of the topic, the importance and comprehensiveness of the clinical questions and the search, and the accuracy of the information provided. Our SR of rehabilitation in MS was sent twice to the MS section of the AAN. No comments were received in the first round. In the second round, we received 8 comments, including one regarding the non-inclusion of an article (Hebert et al.) quoted in table e-1 from Sutliff et al. We responded to all comments, including the non-inclusion of this study, explaining that this is an excellent study that would probably have been classified as Class I evidence. It was identified in the literature search but was excluded because vestibular rehabilitation was not included in our SR (along with cognitive rehabilitation and a number of other types of rehabilitation interventions as noted in the inclusion criteria and questions). This response was conveyed to the MS section. Several other issues brought up by Sutliff et al. were addressed in that response by the author panel and the Guideline Development, Dissemination and Implementation (GDDI) subcommittee. (Table 1 provides all comments received and the responses; names have been omitted for anonymity.)

As is the case with all AAN SRs, the authors of this SR worked with a professional medical librarian to search all appropriate terms that would yield sensitive and specific published citations that pertained to the clinical questions and met the inclusion criteria. The search dates are clearly and transparently mentioned in the SR. We recognize the lag time between the updated search in 2013 and the SR published in 2015. Although we ideally prefer to update the
literature search as close as possible to publication, this is not always feasible. In addition, based on the quality of studies identified in previous 2 extensive searches, the possibility of finding literature that would be of good enough quality to drive recommendations was not high.

Sutliff et al.\textsuperscript{1} provide a table of studies that were “not included” in our SR.\textsuperscript{2} This is not accurate. Of these “not included” studies, at least 5 studies\textsuperscript{6–10} are included in the full SR online.\textsuperscript{2} These studies were reviewed, summarized and referenced in the extensive and comprehensive SR online.\textsuperscript{2} The executive summary is limited to 3500 words and 40 references per \textit{Neurology} journal guidelines. Therefore, only those studies that drove conclusions were discussed in the executive summary, and the references after number 40 are provided online as e-references. As mentioned earlier, Hebert et al.\textsuperscript{5} was excluded because it evaluated a treatment not included in the SR\textsuperscript{2} questions. Some studies\textsuperscript{11} that Sutliff et al.\textsuperscript{1} mention evaluate strategies (cognitive behavioral therapies) that were beyond the scope of our SR.\textsuperscript{2} Several others were published in 2015 or later, after the publication of our SR\textsuperscript{2} and therefore could not have been included in the SR,\textsuperscript{2} even if the literature was updated just before publication.\textsuperscript{11–23} Finally, several others were narrative reviews,\textsuperscript{13,14,21,24,25} which are not included in AAN SRs or CPGs except to cross check references. We have included 3 original studies from the authors of one of these reviews.\textsuperscript{24} Therefore, upper extremity rehabilitation, contrary to the statement by Sutliff et al.,\textsuperscript{1} was not excluded in this SR.

Sutliff et al.\textsuperscript{1} also raise a concern regarding reimbursement due to a misinterpretation of this review. Although we understand their concern, we would like to emphasize that this is a SR, not a CPG with recommendations for management. This is also a concern with many other CPGs
where evidence is not available to drive recommendations. As Sutliff et al.\(^1\) state, educating payers that lack of evidence is not evidence of ineffectiveness is a responsibility that all of us bear. We have consistently urged members to bring any denials by payers to the attention of the AAN. Many recent SRs and CPGs have a payer summary or companion piece directed to the payers. If there is concern regarding payer denials for rehabilitation in MS, such a summary is a consideration.

We would like to thank Sutliff et al.\(^1\) for their helpful comments. However, a process to engage the author panel of this SR\(^2\) and the leadership of the AAN GDDI subcommittee in the pre-publication phase of this commentary would have conclusively clarified several of their concerns, especially with respect to the literature search and inclusion of relevant studies, which, in contradistinction to table e-1 provided in their commentary,\(^1\) were either already included, not relevant, reviews, or published after the publication of our SR.\(^2\) A dialogue about the process of guideline development and specifics of this SR\(^2\) may have been useful.

Since the time of this SR,\(^2\) the AAN guideline development methodology has evolved and now seeks to include a number of perspectives on the writing panel, in addition to the specialists with expertise regarding the disease(s) in question. AAN, when possible, seeks representation from specialty societies to include these perspectives outside the field of neurology including patients, family members, and caregivers and other relevant healthcare professionals. The AAN also engages in a number of public comment periods with the intention of obtaining constructive comments and novel information relevant to the SR/CPG. The penultimate drafts of SRs and CPGs are posted for public comment prior to their submission to *Neurology* for consideration of
publication and approval, with the purpose of improving the process and the final product, making it useful for the clinical and lay communities. The GDDI process requires the committee to review all CPGs/SRs every 3 years to determine if there is new literature that will change the published conclusions and recommendations. When this process is undertaken for the MS Rehabilitation SR, if committee review delineates the need for a revision, the new guideline development methodology will be utilized and will include several of the specialists and experts that Sutliff et al. mention. In the new process, we also include a formal search update as close as possible to publication but this obviously cannot include studies published just before publication of the SR/CPG.

Finally, the AAN will continue to collaborate, review, endorse, and promote materials developed externally that meet or exceed the high quality of the AAN that can fill an immediate need and/or complement existing AAN CPGs/SRs. We applaud the Consortium of MS Centers (CMSC) and the International Organization of Multiple Sclerosis Rehabilitation Therapists (IOMSRT) for developing timely material to meet a need in the MS community. We also encourage organizations like CMSC and the IOMSRT to build on our SRs recommendations for future research and design studies that will provide an evidence base of high quality to obtain funding from government agencies and other organizations. We, the MS rehabilitation field, will progress faster when we develop priorities for funding, meet with possible funding organizations, and encourage Congress for research funding. Our patients deserve the highest quality of evidence to inform their care.
Table 1: AAN MS Section Review Comments to the Draft SR on Rehabilitation in Multiple Sclerosis, and Responses from Author Panel (February 2015)

<table>
<thead>
<tr>
<th>#</th>
<th>Comments</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reviewers</td>
<td>1. <strong>Overall value:</strong> 2 2. <strong>Clarity:</strong> 1 1. A glossary of abbreviations, definitions, outcome measures, and the significant differences for treated and control populations with respect to these outcomes is needed if the neurological community is to benefit from the labors of the authors. Units should be given and explained. 2. In most cases it’s not clear from this review what type of therapy was given to patients, especially with respect to upper extremity therapy. 3. <strong>Timeliness:</strong> 1 The period of publication review is inappropriately old and 2014 references are excluded. Of possibly use to future investigators and clinicians in my opinion would be an annotation of recently published papers (possibly after 2000). Much interesting work is currently addressing the use of functional electrical stimulation and the selection of patients most like to respond to therapy. The annotation would group papers by some of the more interesting areas of clinical and applied physical therapy research such as: 1. the potentiating beneficial effects of functional electrical stimulation when added to traditional physical therapy,</td>
<td>This information is given in Table 1 of the full manuscript and the online table of outcome measures. We have added a statement early in the executive summary indicating this. Units that were left off have been added. See above. This is a common problem in evidence based reviews because of the time involved in development. While the issues raised are interesting and important, they were not those selected by the working group for review. Papers reporting on these interventions were Class III and</td>
</tr>
</tbody>
</table>
2. sensory augmentation of recovery of neurologic function, the timing of rehabilitation with regard to CNS insult,  
3. whether neurological reserve can be assessed as a factor determining the suitability for rehabilitation, and  
Whether genes influence rehabilitation potential.  
4. The role of pragmatic, functional therapy in achieving relevant functional outcomes as emphasized in the neuroplasticity literature.  

4. Importance of clinical questions:  
1. This is a somewhat valuable document if used properly, but it needs to be carefully presented so that the information is not used abusively by third party payers.  

The questions the authors propose to answer remain unanswered and are presumably unanswerable at this time. They fail to point out that this is not unexpected and could be anticipated for the following reasons:  

1. Clinical trials including rehabilitation are rarely funded by government or private entities except when testing pharmacological therapies funded by drug companies.  
2. Many physical therapy interventions are supported for limited times or not at all by insurance carriers. The effect of such reimbursement is that treatment time and long-term observations are limited to small numbers of patients or cannot be performed.  

IV and were therefore not included in the review.  

Points 3 and 4 are worthy topics, but were not part of the scope of this review.  

All AAN guidelines contain a disclaimer related to this issue.  

We agree that there are relatively few trials. Clinical trials including rehabilitation are funded by the NIDRR and the VA.  

Thank you. We agree.
3. As the authors point out, the cohort of patients undergoing physical therapy is quite heterogeneous and therefore the “signal to noise” inherent in current single center or multi-center trial with few sites is large. Studies targeting experimental subjects who are disparate in their level of disability or who are not stabilized to the extent possible by pharmacologic management may open studies to variability that could conceal significant results relative to cohort.

5. Comprehensiveness of lit review: 2
Smaller studies are excluded which in this limited literature may be important. Much interesting work is currently addressing the use of functional electrical stimulation, robotic support, combinations of robotics, FES and dynamic body weight support, and the selection of patients most like to respond to therapy. (see above comments)

6. Clarity and conciseness of recommendations: 1
The authors should avoid making recommendations where data does not exist. The task of establishing guidelines is beyond the reach of the authors, and in my opinion, this paper should never be used in that manner (as it will be unless the futility of such use is clearly stated by the authors).

7. Accuracy: 2
The most important aspects of modern physical therapy have been ignored.

8. Format: 3

Thank you. We agree.

We followed the AAN methodology for evidence based reviews on this and agree that it limits the conclusions. We would point out that one of the included studies, Beer et al. did include robotics.

Because this was an evidence based review rather than a clinical practice guideline the authors drew conclusions but did not make recommendations.

If that is true it is due to the studies in the literature and the methodology for EBRs.
The format would be acceptable if data existed that could be assessed. The authors have shown that there is a paucity of well-designed clinical trials of rehabilitation in MS. They identify only one 8-week Class I study to address the questions they pose!

**Additional comments:**
Very few clinical neurologists will gain anything from this paper after reading the abstract. It does not serve the purpose it proposes to serve.

The recommendations for future research section is well thought out with the following exception:

The crucial paragraph in the report reads: "The available evidence precludes making recommendations with regard to the effectiveness of rehabilitation therapy in specific MS subtypes or in milder disability from progressive MS, or immediately after MS relapse. Also, the benefit of rehabilitation interventions is unknown beyond 12 weeks in moderate disability from progressive MS. Studies either excluded individuals who had a recent exacerbation or failed to mention timing of relapse in relation to the rehabilitation technique."

It should read: "The available evidence as judged by the criteria applied to this review precludes making recommendations with regard to the effectiveness of rehabilitation therapy in MS."

The abstract reflects the conclusions drawn from the review.

The authors have only the published literature to work with.

We have modified this sentence to address this concern.
| 2. | **1. Overall value:** 3  
**2. Clarity:** 4  
Please clarify what parts of the disability scales are improved with Inpatient rehab (3 weeks) followed by home exercises (15) weeks. Like gait versus upper extremity dexterity or strength.  
**3. Timeliness:** 5  
Very timely and speedy turnover to the reviewers.  
**4. Importance of clinical questions:** 5  
**5. Comprehensiveness of lit review:** 5  
Very good and broad literature review and good use of class 1 and 11 studies.  
**6. Clarity and conciseness of recommendations:** 4  
**7. Accuracy:** 4  
**8. Format:** 4  
**Additional comments:**  
Just provide more clarity on what measures are affected instead of saying there was improvement in disability scales. This is because clinicians need to specifically know what symptoms may improve so that the patient is better informed and also this therapy is expensive.  
A very good and well written manuscript. | EDSS was not described. FIM information was given as a composite of self-care, locomotion and transfer subscales was added.  
Thank you.  
Thank you.  
This is given in Table 1 of the full manuscript. |
1. Overall value: 5
2. Clarity: 4
These AAN guidelines are very dull to read, but this is a function of the format of the literature reviews. The articles are an excellent objective review of the literature. The number and type of articles reviewed leads to similar and rather repetitious data. This can't be avoided. The comprehensiveness of the reviews is excellent and this leads to unavoidable length and articles that are rather dull to read.

3. Timeliness: 5
This article should be published without delay.

4. Importance of clinical questions: 5
The clinical questions addressed were appropriate.

5. Comprehensiveness of lit review: 5
The review is very comprehensive. The authors are to be commended.

6. Clarity and conciseness of recommendations: 5
The comments and recommendations for future studies are very good. It does address the problem of controls in these rehabilitation studies.

7. Accuracy: 5

8. Format: NR

Additional comments:
There are some minimal suggestions/correction.

pp 37, top: suggest adding a comma: '1 Class II study each, except...'

Thank you

This correction has been made.
pp. 60 top: the word 'assistive' is misspelled twice near the top of the table. Also, this table is a bit difficult to read. The lines are somewhat difficult to decipher from each other. Perhaps some color breaks could help. Often shading is used, although I don't favor this.

| 4. | 1. **Overall value:** 2  
|    | 2. **Clarity:** 1  
|    | The systematic review is limited to studies on physical therapy, physical exercise programs, balance training, pulmonary rehabilitation and cooling. It does not address upper extremity function, energy conservation, speech/swallowing problems, cognitive rehab, falls prevention, reaction time, and fatigue management. The CMSC has a journal with many more articles that are research in nature and much more relevant to rehabilitation in MS than those selected.  
|    | 3. **Timeliness:** 5  
|    | Timing is good; selection of articles was poor. Articles should have been more widely representative and come from rehabilitation sources, the CMSC, RIMS, and other journals.  
|    | 4. **Importance of clinical questions:** 1  
|    | Very limited in scope.  
|    | 5. **Comprehensiveness of lit review:** 2  
|    | see above  
|    | 6. **Clarity and conciseness of recommendations:** 2  
|    | see above  

The literature search followed the AAN guidelines for evidence based reviews which are based on the Institute of Medicine guidelines. Energy conservation studies that met the criteria were included. See above.
<table>
<thead>
<tr>
<th>7. Accuracy: 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>see above</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8. Format: 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Many comments refer to the outcomes on disability which needs to be defined. In MS, maintenance of function and safety are important rehab goals whereas prevention of disability is a multi-faceted concept based on a team approach using pharmacotherapeutic and non-pharmacotherapeutic management. The conclusions of the paper are sound but stand on very thin ice in terms of evidence.</td>
</tr>
</tbody>
</table>

**Additional comments:**
There were no rehab clinicians involved (PT, OT, SLP) or rehab nursing professionals. There is a huge variability in the types of exercise programs studied with inconsistent measurement and outcome parameters. The studies did not reflect real-life rehabilitation problems in MS. A position paper or a white paper based on a live summit including all MS professionals would be more relevant and helpful than this systematic review of poorly selected papers.

<table>
<thead>
<tr>
<th>5.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Overall value: 2</td>
</tr>
<tr>
<td>2. Clarity: 2</td>
</tr>
<tr>
<td>The document is titled Rehabilitation in MS but the review is limited to studies on physical therapy, physical exercise and balance interventions (with a few studies on pulmonary rehabilitation and cooling); it does not address many aspects of rehabilitation (such as cognitive rehab, speech, swallowing, motor planning, coordination, etc.); the document should either be re-titled to be accurate</td>
</tr>
</tbody>
</table>

| This is given in the full manuscript in the text and particularly in Table 1. |

| The members of the evidence based review group were selected based on the AAN criteria in force at the time that the work was begun. |

| This is an evidence-based review not a guidance document. |

| Question 4 did examine more than physical rehabilitation. |

| The development group did start with a larger group of candidate questions but did limit the number to the four included based on making the scope achievable. |
or at the very least, the authors should clearly define the scope of the review - that it is limited to certain areas.

3. **Timeliness:** 4

4. **Importance of clinical questions:** 1

The document has very limited value for clinicians. Although the review of literature is good, the paucity of strong evidence necessitates further discussion on the specific limitations found and to make recommendations to guide clinicians and researchers in the development of stronger evidence of treatment value for all rehabilitation interventions that may be accessed/utilized for people living with MS.

A much more valuable pursuit would be the development of a white paper that outlines the current state of science with regard to rehabilitation in MS, recommends best practices and guides healthcare professionals in how best to utilize rehab services and how to assess benefits of the interventions.

5. **Comprehensiveness of lit review:** 3

There is huge variability in the types of exercise programs studied (some with no historical evidence of treatment benefit), the interval durations of both treatment episodes and study length, the types of exercise or activities studied and huge variability in the types of patients or individuals studied, making any comparisons dangerous. The review included many non-US studies and there is great variation in the practices included.

---

Thank you for your comments.

This may be correct but what was done was an evidence-based review.

These issues are dealt with in the full manuscript and particularly in Table 1.

The heterogeneity of interventions was one of the reasons given in the full manuscript for not making recommendations (but only conclusions).
of rehabilitation between the US and other countries. These points should be addressed [further] in the document.

6. Clarity and conciseness of recommendations: 2

7. Accuracy: 3

Many comments refer to the effectiveness of interventions on 'disability'--this is a broad umbrella term that needs to be clearly defined for the purposes of this document. The term disability covers impairments, activity limitations and participation restrictions. At times, the authors refer to disability as a global measure of functioning (as with the FIM scale, for example) and at other times, it appears to refer to mobility or locomotion only. The authors need to be clear and consistent in the meaning and use of this term.

8. Format: 4

Additional comments:

Table 1 and the text in the full manuscript lists the actual outcomes used in each study.

| 6. | 1. Overall value: 5 |
|    | 2. Clarity: 4 |
|    | 3. Timeliness: 5 |
|    | 4. Importance of clinical questions: 5 |
|    | 5. Comprehensiveness of lit review: 4 |

We feel the authors have missed an important Class I/II 3-arm, examiner blinded, randomized controlled trial. This study conducted and authored by Drs. Hebert and Corboy. The study: Effects of vestibular rehabilitation on multiple sclerosis-related fatigue and upright postural control: a randomized controlled trial. Phys Ther. 2011 Aug;91(8):1166-83. PMID: 21680771.

This is an excellent study that would probably have been classified as Class I evidence. The article was identified in early searches but was excluded because the panel did not include vestibular rehabilitation in the review (along with cognitive rehabilitation and a number of
We believe this study fits the criteria for this review, specifically in the section: Gait and balance training, based on the following details of the study and results:

The vestibular rehabilitation program in this study was comprised of multi-faceted balance and eye movement/stability exercises, conducted 2 times per week under supervision along with a daily home-based program comprised of these exercises. The effects on balance (computerized dynamic posturography), fatigue (modified fatigue impact scale), dizziness (dizziness handicap inventory) were found to be largely significant; to a lesser degree the effects on depression (BDI-II) and walking capacity (6MWT) were also reported.

Abstract

BACKGROUND:
Fatigue and impaired upright postural control (balance) are the 2 most common findings in people with multiple sclerosis (MS), with treatment approaches varying greatly in effectiveness.

OBJECTIVES:
The aim of this study was to investigate the benefits of implementing a vestibular rehabilitation program for the purpose of decreasing fatigue and improving balance in patients with MS.

DESIGN:
The study was a 14-week, single-blinded, stratified blocked randomized controlled trial.

SETTING:
Measurements were conducted in an outpatient clinical setting, and interventions were performed in a human performance laboratory.

PATIENTS:
Thirty-eight patients with MS were randomly assigned to an experimental group, an exercise control group, or a wait-listed control group.

INTERVENTION:
The experimental group underwent vestibular rehabilitation, the exercise control group underwent bicycle endurance and stretching exercises, and the wait-listed control group received usual medical care.

MEASUREMENTS:
Primary measures were a measure of fatigue (Modified Fatigue Impact Scale), a measure of balance (posturography), and a measure of walking (Six-Minute Walk Test). Secondary measures were a measure of disability due to dizziness or disequilibrium (Dizziness Handicap Inventory) and a measure of depression (Beck Depression Inventory-II).

RESULTS:
Following intervention, the experimental group had greater improvements in fatigue, balance, and disability due to dizziness or disequilibrium compared with the exercise control group and the wait-listed control group. These results changed minimally at the 4-week follow-up. Limitations The study was
limited by the small sample size. Further investigations are needed to determine the underlying mechanisms associated with the changes in the outcome measures due to the vestibular rehabilitation program.

CONCLUSION:
A 6-week vestibular rehabilitation program demonstrated both statistically significant and clinically relevant change in fatigue, impaired balance, and disability due to dizziness or disequilibrium in patients with MS.

Including this study in the current study/review will also require adding computerized dynamic posturography to the list of objective measures of balance, and the MFIS to the list of non-objective measures."

6. Clarity and conciseness of recommendations: 5
7. Accuracy: 4
We feel the authors have missed an important Class I/II 3-arm, examiner blinded, randomized controlled trial. This study conducted and authored by Drs. Hebert and Corboy (reviewers submitting this form). The study: Effects of vestibular rehabilitation on multiple sclerosis-related fatigue and upright postural control: a randomized controlled trial. Phys Ther. 2011 Aug;91(8):1166-83. PMID: 21680771.
We believe this study fits the criteria for this review, specifically in the section: Gait and balance training, based on the following details of the study and results:

The vestibular rehabilitation program in this study was comprised of multi-
faceted balance and eye movement/stability exercises, conducted 2 times per week under supervision along with a daily home-based program comprised of these exercises. The effects on balance (computerized dynamic posturography), fatigue (modified fatigue impact scale), dizziness (dizziness handicap inventory) were found to be largely significant; to a lesser degree the effects on depression (BDI-II) and walking capacity (6MWT) were also reported.

Abstract
BACKGROUND:
Fatigue and impaired upright postural control (balance) are the 2 most common findings in people with multiple sclerosis (MS), with treatment approaches varying greatly in effectiveness.

OBJECTIVES:
The aim of this study was to investigate the benefits of implementing a vestibular rehabilitation program for the purpose of decreasing fatigue and improving balance in patients with MS.

DESIGN:
The study was a 14-week, single-blinded, stratified blocked randomized controlled trial.

SETTING:
Measurements were conducted in an outpatient clinical setting, and interventions were performed in a human performance laboratory.

PATIENTS:
Thirty-eight patients with MS were randomly assigned to an experimental group, an exercise control group, or a wait-listed control group.

INTERVENTION:
The experimental group underwent vestibular rehabilitation, the exercise control group underwent bicycle endurance and stretching exercises, and the wait-listed control group received usual medical care.

MEASUREMENTS:
Primary measures were a measure of fatigue (Modified Fatigue Impact Scale), a measure of balance (posturography), and a measure of walking (Six-Minute Walk Test). Secondary measures were a measure of disability due to dizziness or disequilibrium (Dizziness Handicap Inventory) and a measure of depression (Beck Depression Inventory-II).

RESULTS:
Following intervention, the experimental group had greater improvements in fatigue, balance, and disability due to dizziness or disequilibrium compared with the exercise control group and the wait-listed control group. These results changed minimally at the 4-week follow-up. Limitations: The study was limited by the small sample size. Further investigations are needed to determine the underlying mechanisms associated with the changes in the outcome measures due to the vestibular rehabilitation program.

CONCLUSION:
A 6-week vestibular rehabilitation program demonstrated both
statistically significant and clinically relevant change in fatigue, impaired balance, and disability due to dizziness or disequilibrium in patients with MS.

Including this study in the current study/review will also require adding computerized dynamic posturography to the list of objective measures of balance, and the MFIS to the list of non-objective measures.

8. **Format: 5**

**Additional comments:**
Please contact us at any time for further clarification of our recommendations.

| 7. | 1. **Overall value:** 3  
   2. **Clarity:** 3  
   It is not clear whether the benefits of different interventions are sustained over time, for e.g., on disability, if yes, over what time period.  
   Also, the measures employed in different studies are too varied and the patient population heterogeneous to draw any firm conclusions about their efficacy  
   3. **Timeliness:** 3  
   4. **Importance of clinical questions:** 3  
   5. **Comprehensiveness of lit review:** 4  
   6. **Clarity and conciseness of recommendations:** 4  
   Could have included less number of studies focusing on limited and more define measures, such as only outpatient physical therapy or the studies including a more homogeneous | 10. **The review group narrowed the questions addressed from 14 initial questions in order to make the review feasible.**  
   **The full manuscript gives durations.**  
   That is the reason for our guarded conclusions. |
group of patients, e.g., only primary and secondary progressive patients

7. **Accuracy:** 4
8. **Format:** 3

Could have been more concise, currently, it is too extensive, not necessarily all the data reviewed is useful

**Additional comments:**
Overall, it is a good review, it is a bit challenging to read through it, partly attributable to the multitude of rehab measures studied and also relevance to the practicing neurologists

| 8. | **1. Overall value:** 4  
**2. Clarity:** 3  
I believe that a systemic review of rehabilitation interventions is a valuable document. However, I believe rehabilitation consists of a multidisciplinary approach and isn't limited to physical rehabilitation. This particular document only covers physical rehabilitation and I believe the document should clearly state that it is specific to physical rehabilitation interventions (e.g. does not include cognitive, vocational, psychotherapy, etc.). In addition, the document is unclear in some sections when providing a review of some of the data. Examples of this are on page 14 line 4 where it appears that two mean differences are displayed and it is difficult to interpret. Another example is page 15 lines 19-21 where the numbers are expressed for improvement in 6MW and 9HPT, but it is unclear what the improvement is (I'm guessing it is seconds, but it could be made clearer either in the document text or the table). Also page 19 line 15, | See above.  
Thank you.  
The review committee did limit the types of studies reviewed, as indicated in the full manuscript, in order to make the review feasible.  
Thank you. Units have been added and all abbreviations are now defined on first use.  
Question 4 did go beyond physical rehabilitation. |
MWT should be defined either in the text of the table to better understand the calculation.

3. **Timeliness: 5**

4. **Importance of clinical questions: 4**

I believe the questions are pertinent and applicable to the care of people with MS. As stated earlier, I would clarify, particularly in question 3 that the interventions being reviewed are physical rehabilitation methods. I think is particularly important related to question 3 because there is the not the inclusion of other types of rehabilitation which may impact impairment and QOL/

5. **Comprehensiveness of lit review: 3**

I am concerned that the review did not incorporate a complete review of the literature as the search did not incorporate some of the most extensive rehab databases such as CIRRIE and CINAHL. For example, there are no articles cited from the Journal of Physical Therapy, the journal of the American Physical Therapy Association or Medicine and Science in Sports and Exercise through the American College of Sports Medicine which have many articles related to physical therapy interventions for MS and exercise for people with MS.

6. **Clarity and conciseness of recommendations: 3**

I thought the conclusions sections following each question could have been structured differently. In the

CIRRIE was not included but CINAHL, was. The manuscript has been corrected to include this.

Any journal listed in one of the searched databases would have been included.
initial portion of the conclusions, I think it would be helpful to include a statement such as is done in the second portion of the conclusion statement. In the second part of the conclusion it is stated 'Data are inadequate to support or refute...' I think a similar statement would be helpful in the first portion. 'Based on the data reviewed.' and then include that various treatments are 'probably effective' or 'may be effective.' It is already stated that there is a paucity of well-designed studies, so I think it may be clearer to restate that as part of the conclusions so the reader doesn't assume that something may be or probably is effective since there may not be adequate data.

7. Accuracy: 3
See comments on comprehensiveness of the review above.

8. Format: 4
Overall I thought the format was fine with the exception of some of the comments above.

Additional comments:
I applaud the AAN for taking on this topic to provide a systematic review of rehabilitation in MS. I am concerned about whether the review has provided a complete review of rehabilitation in MS given the review did not include common rehab databases.

Thank you for the opportunity to review this document.

9. 1. Overall value: 1
2. Clarity: 1
Clarity/readability is very poor. See a similar OT review: Yu, C.-H., &

3. **Timeliness:** 5
Timeliness is high but better document must be generated, no third-party insurance or health system reviewer will read through this. Major finding bullet points etc. would help

4. **Importance of clinical questions:** 5
Rehabilitation is not reviewed, PT, OT inpatient rehabilitation and "comprehensive outpatient rehabilitation" whatever it is, are reviewed and it should be communicated this way. I am to infer cognitive rehabilitation, dysphagia rehabilitation etc. have no data or role? Communicate what is being reviewed clearly in the title and throughout the text.

5. **Comprehensiveness of lit review:** 2
See above for style, for accuracy would get PT and OT input (we even have a few very expert ones who belong to AAN). See the OT review cited above for an estimate of studies missed for just fatigue management alone

6. **Clarity and conciseness of recommendations:** 1
Reviews were specifically excluded from the search based on the AAN process.

The findings do not lend themselves to that kind of summary.

The questions make clear that not all forms of rehabilitation were examined.

See the comments above.
see above

7. Accuracy: 2
8. Format: 2

Additional comments:
I would very insulted if the American Association of Physical therapists came out with their own review of the evidence that neurologists or even MS Specialist neurologists have any documented benefit for short or long term MS. We live in a multidisciplinary world and OT and PT practitioners are not our staff, they bring unique knowledge to the table.

The manuscript does not conclude that rehabilitation should not be done. It concludes that the evidence base is weak and further studies are needed to demonstrate effectiveness.

REFERENCES


15. Sandroff BM, Hillman CH, Benedict RHB, Motl RW. Acute effects of walking, cycling, and yoga exercise on cognition in persons with relapsing-remitting multiple sclerosis without


