Effects of Vestibular Rehabilitation on Multiple Sclerosis–Related Fatigue and Upright Postural Control: A Randomized Controlled Trial

Jeffrey R. Hebert, John R. Corboy, Mark M. Manago, Margaret Schenkman

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.
Fatigue and limited mobility are among the most common symptoms in people with multiple sclerosis (MS), with reports of fatigue ranging from 50% to 85%. The definition of MS-related fatigue is commonly understood as the self-reported perception of decreased physical or mental energy, often leading to limitations in daily activities or routines. Multiple sclerosis-related fatigue is strongly linked to impaired physical activity and quality of life.

The cause of fatigue in people with MS most likely is multifactorial, including both primary and secondary causes. Primary fatigue is directly related to the disease process involving the neuromuscular system in the form of demyelination or axonal degeneration. Secondary fatigue refers to fatigue indirectly caused by factors such as depression, physical inactivity, or sleep disorder.

Effective treatment of MS-related fatigue is limited. Drug therapies have been tested, with conflicting reports of efficacy. Studies of energy conservation education have had conflicting results. Exercise studies have demonstrated benefits in fitness level, quality of life, balance, and walking capacity in people with MS; however, no consistent effect on fatigue has been reported. Some multifaceted rehabilitation studies have shown improvements in fatigue, but others have shown no effect.

One possible cause of fatigue worthy of investigation is impairments of central sensory integration. Central sensory integration of the visual, somatosensory, and vestibular systems is the basis for effective upright postural control. Impaired central sensory integration can lead to reduced upright postural control, with resulting dizziness or vertigo. Impaired upright postural control has been linked to poor central sensory integration, as well as fatigue, in patients with MS.

The high prevalence of MS-related lesions in the brain stem and cerebellum, ranging from 34.7% to 50.9%, supports the possibility of impairments of central sensory processing, because the brain stem and cerebellum are vital to this process. Rates of peripheral deficit vestibulopathy as high as 85% also have been reported in patients with MS, further illustrating the importance of the vestibular system for central sensory integration in these patients. Balance training for patients with MS has been reported to improve upright postural control, although the impact on fatigue has not been tested.

Therefore, we postulated that vestibular rehabilitation would be an effective approach to the improvement of both fatigue and upright postural control in patients with MS. The purpose of this investigation was to examine the effects of such a rehabilitation program on fatigue and upright postural control in people with MS. Specifically, we hypothesized that individuals who participate in the vestibular rehabilitation intervention would have significantly reduced self-reported fatigue and significantly improved upright postural control compared with participants in a general exercise program (endurance and stretching program) and participants in a wait-listed control group (usual medical care).

The Bottom Line

What do we already know about this topic?

People with multiple sclerosis (MS) have a multitude of symptoms. Fatigue is the most common complaint, followed by impaired mobility. Balance training is an effective treatment for patients with MS who have impaired upright postural control (ie, balance); however, the evidence for the effectiveness of interventions for MS-related fatigue is limited and inconsistent. Previously, no studies have investigated the effectiveness of a vestibular rehabilitation program on both MS-related fatigue and balance.

What new information does this study offer?

This study provides early evidence of the feasibility and effectiveness of a vestibular rehabilitation program on fatigue, balance, and disability due to dizziness or disequilibrium for people with MS.

If you’re a patient or caregiver, what might these findings mean for you?

If you have MS and have fatigue and balance problems, participation in a program of vestibular rehabilitation may improve fatigue and balance and reduce disability related to dizziness or disequilibrium, with no known side effects. Larger follow-up studies are needed, however, to support these results.
Method

Design Overview

The study was a 3-arm, 14-week, single-blinded, stratified blocked randomized controlled trial. The study consisted of 3 phases (Fig. 1). All participants underwent 3 outcome measurement sessions during a 4-week, nonintervention baseline phase. They then were randomly assigned to 1 of 3 study arms. There were 2 exercise arms (experimental and exercise control) and a wait-listed control arm. Participants in both exercise groups were treated twice weekly for 6 weeks (intervention phase). All participants then began a 4-week follow-up phase. Participants in the wait-listed control group received treatment consistent with the protocols of this study within the clinical setting upon completion of their participation in the study (if they chose to receive the treatment).

Setting and Participants

Most participants were recruited through clinics at the Rocky Mountain MS Center (RMMSC) at the University of Colorado, Anschutz Medical Campus, Aurora, Colorado. In addition, the RMMSC and the Colo-
rado Chapter of the National Multiple Sclerosis Society disseminated information about the study. Over a 33-month period, 123 volunteers were screened for study eligibility (Fig. 2). Inclusion criteria were: 18 to 65 years of age; clinically definite MS; able to walk 100 m with or without a single-sided device; a score of ≥45 out of 84 on the Modified Fatigue Impact Scale questionnaire; and a composite score of <72 on the computerized Sensory Organization Test (SOT), demonstrating limited standing balance. Exclusion criteria were: unable to walk; use of pharmacological agents to control fatigue or that caused fatigue; change in MS-specific disease modification medication within 3 months prior to the study; documented MS-related relapse within 6 months prior to the study; other conditions that may cause fatigue (including depressive and

Figure 2.
Prospective participant and study participant flow diagram.
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sleep disorders); impaired upright postural control or limited participation in an exercise program; and participation in a vestibular or endurance exercise program within 8 weeks prior to the study.

An SOT composite score of 7.0 as a clinically meaningful difference resulted in a sample size estimate of 30 to achieve 0.80 power at a significance level of .05. The 7.0-point effect size was derived from a previous investigation reporting a 6.7-point effect size indicated a tendency toward statistical significance. Oversampling was performed to account for possible dropouts, resulting in 38 as the final study size.

A physical therapist with 5 years of experience evaluating patients with neurological disorders, including MS, performed all outcome measurements in an outpatient clinical setting and was blinded from group assignments. An investigator with 12 years of experience as a physical therapist treating patients with MS implemented all exercise protocols in a human performance laboratory and was blinded from all outcome measurements. All participants gave written informed consent.

Randomization and Interventions

Following the baseline phase, 2 strata were formed based on the most recent magnetic resonance imaging report: participants with and without brain-stem or cerebellar neurological involvement. Block sizes of 3 were randomly selected for each strata. A clinician not involved in the study concealed the block sequences and provided the random group assignments. Participants then were randomly allocated to 1 of 3 arms: an experimental group, an exercise control group, or a wait-listed control group. All supervised intervention sessions in both the experimental group and the exercise control group were performed in the same human performance laboratory, with each participant having the same amount of supervision and interaction with the investigator.

Individuals in the experimental group participated in a standardized vestibular rehabilitation program consisting of upright postural control and eye movement exercises (Appendix 1) based on clinical experience and published literature. Each item was performed for 1 to 2 minutes, for a total of 55 minutes. Specific items were selected for a daily independent home exercise program (HEP), which was assigned throughout the intervention and follow-up phases (Appendix 1).

The exercise control group participated in endurance and stretching exercises. To account for a possible abnormally low heart rate response to exercise (blunted heart rate response) frequently observed in patients with MS, participants in the exercise control group first performed a submaximal modified YMCA cycle ergometry graded exercise test (GET) (Appendix 2). Peak heart rate (HRpeak), which was the highest value of heart rate at the time of symptom-limiting GET termination, served as the value for endurance exercise intensity prescription.

The endurance exercise consisted of stationary bicycling: 5-minute warm-up, two 15-minute sessions; and 2- to 5-minute cool-down. The training intensity during the 15-minute sessions was 65% to 75% of HRpeak; 11 to 14 (moderate intensity of exertion) on the Borg Rating of Perceived Exertion (RPE) Scale, ranging from 6 (“no exertion at all”) to 20 (“maximal exertion”); and constant pedal rate of 50 rpm. The level of intensity and duration of cycling were based on the typical capacity of individuals with MS and recommendations in the literature. The stretching exercises included stretches of the following muscles: gastrocnemius-soleus, quadriceps, hamstrings, gluteus maximus, and iliopsoas and rectus femoris. Stretches were held for 30 seconds. A daily independent HEP was assigned throughout the intervention and follow-up phases. The HEP included the stretching exercises and stationary bicycling or an alternative activity (eg, walking) at levels consistent with the supervised training sessions.

Both exercise groups received the same 5-minute fatigue management education. Included were discussions of: daily rest intervals, self-monitoring of exertion levels, work station ergonomics, and heat intolerance education. A daily log was issued to each individual in the exercise groups to record adherence to the HEP and fatigue management components.

Outcomes and Follow-up

Primary outcome measures. Self-reported fatigue was measured using the 21-item Modified Fatigue Impact Scale (MFIS). The MFIS is reported to be a reliable and valid measure for patients with MS. Responses are scored from 0 to 4, with total scores ranging from 0 to 84 and with higher scores indicating a larger impact of fatigue.

Static upright postural control was measured using a posturography test (ie, Sensory Organization Test [SOT]), which has been used in prior studies to illustrate balance disorders in people with MS. The Smart Balance Master System® was used for this test. This test assesses upright postural control during 6 different conditions of sensory feedback. Postural sway is recorded and converted

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* NeuroCom International Inc, 9570 SE Lawnfield Rd, Clackamas, OR 97015.
to a percentage of equilibrium (composite score).

Walking capacity was measured using the Six-Minute Walk Test (6MWT), which has been used measure functional exercise capacity in this population.\(^{48}\) Standard instructions and testing guidelines were implemented.\(^{49}\) Distance (in feet)\(^{1}\) was recorded.

**Secondary outcome measures.** Self-reported disability due to dizziness or disequilibrium was measured using the 25-item Dizziness Handicap Inventory (DHI). Each item has 3 responses: “yes,” “sometimes,” and “no.” Total scores range from 0 to 100, with higher scores indicating greater disability due to dizziness or disequilibrium. The DHI has high reliability and discriminates “fallers” from “nonfallers” in the MS population.\(^{50}\)

Self-reported depression was measured using the 21-item Beck Depression Inventory–II (BDI-II).\(^{51}\) Each item has 4 responses, with the total score ranging from 0 (“no depression”) to 63 (“greatest depression”). The MFIS, DHI, and BDI-II were administered 8 times throughout the study, and the SOT and 6MWT were administered 4 times (Fig. 1).

Data from the baseline phase were averaged to provide a point estimate for the 4 weeks prior to the intervention phase. Outcome measure analyses occurred at the end of the intervention phase (baseline to 10-week follow-up) and at the end of the follow-up phase (10-week follow-up to 14-week follow-up).

**Data Analysis**

All outcome measures were analyzed as continuous data. One-way analysis of variance was used for multigroup comparisons of preintervention and postintervention data and of postintervention to end of follow-up data for each outcome variable and for multigroup comparisons of time duration in the study. Prior to performing post hoc, pair-wise comparisons, a robust test of equality of means (ie, the Welch statistic) was performed to verify the valid application of a Bonferroni correction method. Outcome measures that underwent multigroup Bonferroni correction met the statistical significance of equality of means ($P < .05$).

For within-group comparisons of preintervention and postintervention data and of postintervention to end of follow-up data, the paired $t$ test was used. For experimental group and exercise control group comparisons of adherence to the HEP and fatigue management, the independent $t$ test was used. The Fisher exact test was used for baseline analysis of nominal data.\(^{52}\) Correlational analyses were performed to test the relationship between mean changes in MFIS total score, SOT composite score, and DHI total score for the combined study sample from baseline to the end of the intervention phase and from baseline to the end of the follow-up phase. The Pearson product moment correlation coefficient test was used for the analysis of associations. All tests were 2-tailed, using .05 as the level of statistical significance. Standard deviations and 95% confidence intervals (CIs) also were calculated. The numeric difference in change of outcome measure between groups is presented as effect size. Standardized difference of the mean (SDM) was calculated based on Cohen $d$ standard effect size index: small (SDM: $\leq 0.2$), medium (SDM: $> 0.2$ but $\leq 0.7$), and large (SDM: $> 0.8$ to 2.0).\(^{53-55}\) Event rates for each group and the subsequent number needed to treat are presented for the primary outcome measures of fatigue (MFIS total score) and upright postural control (SOT composite score). A change in the MFIS total score of $\geq 15.0^{10}$ and a change in the SOT composite score of $\geq 7.0^{44}$ were used as the meaningful changes and cutoff scores for event rate calculations.

Intention-to-treat analysis was implemented to address any loss to follow-up. The average of the group change for each outcome measure at each analysis period served as the value applied to data missing from loss to follow-up. Unless otherwise stated, statistical analyses were performed using SPSS for Windows, version 17.0.\(^2\)

**Role of the Funding Source**

This study was partially supported by the National Multiple Sclerosis Society (NMSS) (Pilot Project no. PP1501), which approved the design of the study, but did not control the conduct of the research team, including recruitment, patient participation, data analyses, and manuscript preparation.

**Results**

Characteristics of the sample, including demographic data and baseline data for the outcome measures, are presented in Table 1. No differences were found among the 3 groups.

**Primary and Secondary Outcomes (Baseline to 10 Weeks)**

We first examined differences in the primary and secondary outcomes following the 6-week intervention phase (baseline to 10 weeks). These data are depicted in Table 2.

**Fatigue.** As hypothesized, the experimental group demonstrated significant improvement in MFIS total score (Tab. 2). Groups were significantly different on MFIS total score ($P = .004$), with the experimen-
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Table 1. Baseline Demographics and Characteristics<sup>a</sup>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Experimental Group (n=12)</th>
<th>Exercise Control Group (n=13)</th>
<th>Wait-Listed Control Group (n=13)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>46.8 (10.5)</td>
<td>42.6 (10.4)</td>
<td>50.2 (9.2)</td>
<td>.175&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Sex, female/male</td>
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<td>11/2</td>
<td>11/2</td>
<td>.767&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>MS diagnosis duration (y)</td>
<td>6.5 (5.6)</td>
<td>5.1 (3.2)</td>
<td>9.1 (7.3)</td>
<td>.206&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
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<td>MS diagnosis subtype</td>
<td>Relapsing-remitting</td>
<td>11</td>
<td>11</td>
<td>1.00&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Secondary progressive</td>
<td>2</td>
<td>2</td>
<td>1.00&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>MS-related lesion location</td>
<td>Non-brain stem/cerebellar</td>
<td>4</td>
<td>4</td>
<td>1.00&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Brain stem/cerebellar</td>
<td>8</td>
<td>9</td>
<td>9.00&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>MFIS total score</td>
<td>51.0 (6.8)</td>
<td>51.0 (8.6)</td>
<td>55.9 (11.6)</td>
<td>.312&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>6MWT (ft)</td>
<td>1,335.6 (320.3)</td>
<td>1,066.1 (335.9)</td>
<td>1,049.2 (328.9)</td>
<td>.066&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>SOT composite score (%)</td>
<td>60.2 (14.0)</td>
<td>50.3 (16.3)</td>
<td>59.5 (12.1)</td>
<td>.164&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>BDI-II total score</td>
<td>16.5 (9.1)</td>
<td>17.3 (8.6)</td>
<td>18.5 (6.4)</td>
<td>.817&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>DHI total score</td>
<td>48.0 (10.7)</td>
<td>47.0 (12.1)</td>
<td>56.4 (14.6)</td>
<td>.132&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values expressed as means (SD), except for sex, MS diagnosis subtype, and MS-related lesion location, which are expressed as nominal counts.

<sup>b</sup> P values assessed by one-way analysis of variance.

<sup>c</sup> P values assessed by Fisher exact test.

Upright postural control. As hypothesized, the experimental group improved significantly in the SOT composite score (Tab. 2). There was a significant difference among the groups (P<.001). The experimental group showed significant improvement compared with the exercise control group (P=.001) and the wait-listed control group (P=.003). No difference was found between the exercise control group and the wait-listed control group (P=1.00). Large SOT composite score SDMs were found for the experimental group compared with the exercise control group (d=1.37) and the wait-listed control group (d=1.28), and the difference in SOT composite score SDMs between the exercise control group and the wait-listed control group was minimal (d=0.21). Based on 92% of the experimental group and 38% of both the exercise control group and the wait-listed control group improving on the SOT by ≥7.0, the number needed to treat was 1.9.

Self-reported disability due to dizziness or disequilibrium. The experimental group improved significantly in DHI total score, whereas the other groups failed to improve (Tab. 2). Groups were significantly different (P=.005) at the end of the intervention phase; the experimental group’s improvement was significant compared with that of the exercise control group (P=.018) and the wait-listed control group (P=.009). No difference was found between the exercise control and wait-listed control groups (P=1.00). Large DHI total score SDMs were found for the experimental group compared with both the exercise control group (d=1.03) and the wait-listed control group (d=1.12), and the difference in DHI total score SDMs between the exercise control group and the wait-listed

Table 2.
Fatigue, Upright Postural Control, Disability Due to Dizziness or Disequilibrium, Walking Capacity, and Depression: Baseline to End of Intervention Phase (10 Weeks)\(^a\)

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Experimental Group (n = 12)(^b)</th>
<th>Exercise Control Group (n = 13)(^b)</th>
<th>Wait-Listed Control Group (n = 13)(^b)</th>
<th>Experimental Group Compared With Exercise Control Group</th>
<th>Experimental Group Compared With Wait-Listed Control Group</th>
<th>Exercise Control Group Compared With Wait-Listed Control Group</th>
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<tr>
<td>MFIS</td>
<td></td>
<td></td>
<td></td>
<td>Effect Size(^c) (d)</td>
<td>Effect Size(^c) (d)</td>
<td>Effect Size(^c) (d)</td>
</tr>
<tr>
<td>Baseline</td>
<td>51.0 (6.8)</td>
<td>51.0 (8.6)</td>
<td>55.9 (11.6)</td>
<td>-0.001 0.085</td>
<td>.024</td>
<td>.005</td>
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<td>End of intervention phase</td>
<td>29.5 (15.8)</td>
<td>44.3 (16.4)</td>
<td>52.1 (17.1)</td>
<td>14.8 1.06</td>
<td>17.7 1.33</td>
<td>2.9 0.24</td>
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<td>Change in MFIS</td>
<td>-21.5 (15.0)</td>
<td>-6.7 (12.9)</td>
<td>-3.8 (11.4)</td>
<td>1.6 to 28.0</td>
<td>4.5 to 30.9</td>
<td>-10.0 to 15.9</td>
</tr>
<tr>
<td>95% CI</td>
<td>-31.1 to -11.9</td>
<td>-14.5 to 1.1</td>
<td>-10.6 to 3.1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(P)</td>
<td>&lt;.001</td>
<td>.085</td>
<td>.255</td>
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<tr>
<td>SOT</td>
<td></td>
<td></td>
<td></td>
<td>Effect Size(^c) (d)</td>
<td>Effect Size(^c) (d)</td>
<td>Effect Size(^c) (d)</td>
</tr>
<tr>
<td>Baseline</td>
<td>60.2 (14.0)</td>
<td>50.3 (16.3)</td>
<td>59.5 (12.1)</td>
<td>10.7 to 26.3 0.91</td>
<td>3.2 to 9.5</td>
<td>4.9 to 21.8</td>
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<td>End of intervention phase</td>
<td>78.7 (6.0)</td>
<td>55.5 (14.9)</td>
<td>65.9 (14.5)</td>
<td>13.3 1.37</td>
<td>12.1 1.28</td>
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<td>Change in SOT</td>
<td>18.5 (12.3)</td>
<td>5.2 (6.2)</td>
<td>6.4 (5.2)</td>
<td>1.4 to 8.9</td>
<td>3.7 to 20.5</td>
<td>-7.0 to 9.5</td>
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<td>95% CI</td>
<td>10.7 to 26.3</td>
<td>1.4 to 8.9</td>
<td>3.2 to 9.5</td>
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<tr>
<td>(P)</td>
<td>&lt;.001</td>
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<td>.001</td>
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<td>DHI</td>
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<td>Effect Size(^c) (d)</td>
<td>Effect Size(^c) (d)</td>
<td>Effect Size(^c) (d)</td>
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<tr>
<td>Baseline</td>
<td>48.0 (10.7)</td>
<td>47.0 (12.1)</td>
<td>56.4 (14.6)</td>
<td>-31.9 to -5.5 0.011</td>
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<td>End of intervention phase</td>
<td>29.3 (18.6)</td>
<td>44.8 (11.6)</td>
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<td>1.6 0.17</td>
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<td>Change in DHI</td>
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<td>-0.6 (9.6)</td>
<td>2.3 to 30.6</td>
<td>3.9 to 32.2</td>
<td>-12.3 to 15.5</td>
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<td>95% CI</td>
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<td>-8.0 to 3.5</td>
<td>-6.4 to 5.2</td>
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<tr>
<td>(P)</td>
<td>.010</td>
<td>.415</td>
<td>.821</td>
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<td>6MWT</td>
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<td></td>
<td>Effect Size(^c) (d)</td>
<td>Effect Size(^c) (d)</td>
<td>Effect Size(^c) (d)</td>
</tr>
<tr>
<td>Baseline</td>
<td>1,335.6 (320.3)</td>
<td>1,066.1 (335.9)</td>
<td>1,049.2 (328.9)</td>
<td>-15.3 0.12</td>
<td>-9.1 0.24</td>
<td>-23.6 0.18</td>
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<td>End of intervention phase</td>
<td>1,420.7 (283.6)</td>
<td>1,112.1 (391.3)</td>
<td>1,071.6 (375.0)</td>
<td>39.1 0.24</td>
<td>62.7 0.49</td>
<td>23.6 0.18</td>
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<td>Change in 6MWT</td>
<td>85.1 (159.5)</td>
<td>46.0 (168.7)</td>
<td>22.4 (88.1)</td>
<td>-16.3 to 186.4 -56.0 to 148.0 30.9 to 75.6 -104.8 to 182.9</td>
<td>-81.1 to 206.5</td>
<td>-117.3 to 164.5</td>
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<tr>
<td>95% CI</td>
<td>-15.3 to 0.12</td>
<td>-9.1 0.24</td>
<td>-23.6 0.18</td>
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<tr>
<td>(P)</td>
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(Continued)
Table 2. Continued

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<tr>
<th>Outcome Measure</th>
<th>Experimental Group (n=12)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Exercise Control Group (n=13)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Wait-Listed Control Group (n=13)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Experimental Group Compared With Exercise Control Group</th>
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<th>Exercise Control Group Compared With Wait-Listed Control Group</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Effect Size&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Effect Size Index (d)</td>
<td>Effect Size&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>BDI-II Baseline</td>
<td>16.5 (9.1)</td>
<td>17.3 (8.6)</td>
<td>18.5 (6.4)</td>
<td>9.5 (7.4)</td>
<td>4.4</td>
<td>5.0</td>
</tr>
<tr>
<td>End of intervention phase</td>
<td>7.0 (7.3)</td>
<td>12.2 (6.5)</td>
<td>14.0 (9.0)</td>
<td>.90</td>
<td>.70</td>
<td>5.0</td>
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<tr>
<td>Change in BDI-II</td>
<td>−9.5 (7.4)</td>
<td>−5.1 (4.9)</td>
<td>−4.5 (9.2)</td>
<td>.00</td>
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<tr>
<td>95% CI</td>
<td>−14.2 to −4.8</td>
<td>−8.0 to −2.1</td>
<td>−10.1 to 1.1</td>
<td>−3.0 to 11.9</td>
<td>−2.5 to 12.4</td>
<td>−6.8 to 7.8</td>
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*Baseline, end of intervention phase, and change in outcome measure values expressed as mean (SD), 95% CI = 95% confidence interval. Effect size = numeric difference in change of outcome measure among groups. Effect size index (d) = Cohen’s d standard effect size index. MFIS = Modified Fatigue Impact Scale total score; SOT = Sensory Organization Test, composite score (percentage); DHI = Dizziness Handicap Inventory total score; 6MWT = Six-Minute Walk Test score (feet); BDI-II = Beck Depression Inventory-II total score.

<sup>b</sup> Within-group comparison of change in outcome measure (paired t-test).

<sup>c</sup> Between-group comparison of change in outcome measure (post hoc pair-wise comparisons following one-way analysis of variance).
### Table 3.
Fatigue, Upright Postural Control, Disability Due to Dizziness or Disequilibrium, Walking Capacity, and Depression: End of Intervention Phase (10 Weeks) to End of Follow-up Phase (14 Weeks)

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Experimental Group (n=12)</th>
<th>Exercise Control Group (n=13)</th>
<th>Wait-Listed Control Group (n=13)</th>
<th>Experimental Group Compared With Exercise Control Group</th>
<th>Experimental Group Compared With Wait-Listed Control Group</th>
<th>Exercise Control Group Compared With Wait-Listed Control Group</th>
</tr>
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<tr>
<td></td>
<td>Effect Size&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Effect Size Index (d)</td>
<td>Effect Size&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Effect Size Index (d)</td>
<td>Effect Size&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>MFIS</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
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<td>29.5 (15.8)</td>
<td>44.3 (16.4)</td>
<td>52.1 (17.1)</td>
<td>-0.4</td>
<td>-0.03</td>
<td>-0.3</td>
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<td>Change in MFIS</td>
<td>0.8 (1.5)</td>
<td>0.4 (9.0)</td>
<td>0.5 (7.1)</td>
<td>-11.3 to 10.5</td>
<td>-11.3 to 10.5</td>
<td>-10.6 to 10.7</td>
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<tr>
<td>95% CI</td>
<td>-8.9 to 10.4</td>
<td>-5.0 to 5.8</td>
<td>-3.8 to 4.8</td>
<td>-11.3 to 10.5</td>
<td>-11.3 to 10.5</td>
<td>-10.6 to 10.7</td>
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<tr>
<td>P</td>
<td>.867</td>
<td>.880</td>
<td>.819</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>SOT</td>
<td></td>
<td></td>
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<tr>
<td>End of intervention phase</td>
<td>78.7 (6.0)</td>
<td>55.5 (14.9)</td>
<td>65.9 (14.5)</td>
<td>-2.7</td>
<td>-0.46</td>
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<td>Change in SOT</td>
<td>-0.4 (3.9)</td>
<td>2.3 (7.4)</td>
<td>1.0 (3.5)</td>
<td>-8.5 to 3.2</td>
<td>-7.2 to 4.5</td>
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<tr>
<td>95% CI</td>
<td>-2.8 to 2.1</td>
<td>-2.1 to 6.8</td>
<td>-2.3 to 4.3</td>
<td>-8.5 to 3.2</td>
<td>-7.2 to 4.5</td>
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<tr>
<td>P</td>
<td>.770</td>
<td>.280</td>
<td>.524</td>
<td>.787</td>
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<td>1.00</td>
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<td>DHI</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>End of intervention phase</td>
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<td>55.8 (20.9)</td>
<td>-4.8</td>
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<td>Change in DHI</td>
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<td>1.7 (3.9)</td>
<td>-16.0 to 6.5</td>
<td>-13.1 to 9.5</td>
<td>-8.1 to 14.0</td>
</tr>
<tr>
<td>95% CI</td>
<td>-7.7 to 14.7</td>
<td>-6.1 to 3.6</td>
<td>-0.7 to 4.1</td>
<td>-16.0 to 6.5</td>
<td>-13.1 to 9.5</td>
<td>-8.1 to 14.0</td>
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<tr>
<td>P</td>
<td>.507</td>
<td>.590</td>
<td>.144</td>
<td>.895</td>
<td>1.00</td>
<td>1.00</td>
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<td>6MWT</td>
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<tr>
<td>End of intervention phase</td>
<td>1,420.7 (283.6)</td>
<td>1,112.1 (391.3)</td>
<td>1,071.6 (375.0)</td>
<td>33.6</td>
<td>0.14</td>
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<td>Change in 6MWT</td>
<td>-24.6 (11.2)</td>
<td>-58.2 (308.5)</td>
<td>38.9 (143.6)</td>
<td>-47.8 to 125.7</td>
<td>-176.7 to 244.0</td>
<td>-273.8 to 146.8</td>
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<td>95% CI</td>
<td>-95.6 to 46.7</td>
<td>-244.7 to 128.2</td>
<td>-47.8 to 125.7</td>
<td>-176.7 to 244.0</td>
<td>-273.8 to 146.8</td>
<td>-303.2 to 108.9</td>
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<tr>
<td>P</td>
<td>.463</td>
<td>.509</td>
<td>.348</td>
<td>1.00</td>
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<td>.731</td>
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(Continued)
Table 3. Continued

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<tr>
<th>Outcome Measure</th>
<th>Experimental Group (n=12)</th>
<th>Exercise Control Group (n=13)</th>
<th>Wait-Listed Control Group (n=13)</th>
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<th>Effect Size Index ( \text{d} )</th>
<th>Effect Size ( \text{d} )</th>
<th>Effect Size Index ( \text{d} )</th>
<th>Effect Size ( \text{d} )</th>
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<tr>
<td>BDI-II</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>End of intervention phase</td>
<td>7.0 (7.3)</td>
<td>12.2 (6.5)</td>
<td>14.0 (9.0)</td>
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<tr>
<td>End of follow-up phase</td>
<td>11.6 (12.3)</td>
<td>12.9 (8.0)</td>
<td>16.6 (9.6)</td>
<td></td>
<td></td>
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<tr>
<td>Change in BDI-II</td>
<td>4.6 (10.0)</td>
<td>0.7 (3.4)</td>
<td>2.6 (3.2)</td>
<td>-3.9</td>
<td>-0.52</td>
<td>-2.0</td>
<td>-0.27</td>
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<td>0.58</td>
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<td>95% CI</td>
<td>-1.8 to 11.0</td>
<td>-1.4 to 2.8</td>
<td>0.7 to 4.5</td>
<td>-10.2 to 2.4</td>
<td>-8.3 to 4.3</td>
<td>-4.2 to 8.1</td>
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<tr>
<td>( P )</td>
<td>.141</td>
<td>.477</td>
<td>.011</td>
<td>.385</td>
<td>1.00</td>
<td>1.00</td>
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</table>

*End of intervention phase, end of follow-up phase, and change in outcome measure values expressed as mean (SD), 95% CI = 95% confidence interval. Effect size = numeric difference in change of outcome measure between groups. Effect size index \( \text{d} \) = Cohen's standard effect size index. MFIS = Modified Fatigue Impact Scale total score; SOT = Sensory Organization Test, composite score (percentage); DHI = Dizziness Handicap Inventory total score; 6MWT = Six-Minute Walk Test score (feet); BDI-II = Beck Depression Inventory-II total score.

Within-group comparison of change in outcome measure (paired \( t \) test).

Between-group comparison of change in outcome measure (post hoc pair-wise comparisons following one-way analysis of variance).

Adverse Events

One participant in the exercise control group incurred a minor ankle sprain.

Group equality following randomization allocation. We also examined the length of time in the study for each group and adherence to the HEP and fatigue management by the experimental and exercise control groups. Each of the exercise groups had 4 participants who did not return their daily logs. Of the remaining participants, those in the experimental group had greater adherence to their HEP compared with those in the exercise control group (average of 60.5 days vs. 42.7 days; \( 95\% \text{ CI} = 8.9 \text{ to } 25.6, \ P = 0.39 \)). The HEP group's duration in the study (17 weeks) was different from that of the wait-list control group (15.5 weeks; \( 95\% \text{ CI} = 0.2 \text{ to } 4.2, \ P = 0.05 \)).
Effects of Vestibular Rehabilitation on Multiple Sclerosis–Related Fatigue and Upright Postural Control

sprain during a session. This incident did not require medical care and did not limit continued participation. After being randomly allocated to the wait-listed control group, one individual dropped out of the study due to unhappiness with group assignment.

Discussion

Findings from this study demonstrate the feasibility of a vestibular rehabilitation program and its effectiveness on fatigue (MFIS total score), upright postural control (SOT composite score), and disability due to dizziness or disequilibrium (DHI total score). The improvements found were significantly greater for participants in the experimental group (who underwent a vestibular rehabilitation program) than for participants in either the exercise control group (who underwent an endurance and stretching program) or the wait-listed control group.

The main variable of interest was fatigue, with the results showing that the experimental group was the only group to improve. The improvement of −21.5 points (P<.001) in MFIS total score was significant and exceeded previous reports from multifaceted rehabilitation studies: 12-week program (−13.0 points, P=.02), 4-week program (−15.5 points, P=.001), and 8-week program (−4.0 points, P=.64). In contrast, the changes in MFIS total scores for both the exercise control group and the wait-listed control group were minimal and statistically similar. The large effect sizes found for the experimental group met the clinically relevant difference of 15.0 points. The limited improvement in fatigue found for the exercise control group is comparable to previous findings of several studies that investigated the possible effect of aerobic training on fatigue.

The second variable of interest was upright postural control. Changes in SOT composite scores for the exercise control group and the wait-listed control group were minimal and statistically similar. These changes are consistent with known learning effect found in a population of healthy individuals; an improvement of 8.0 indicates a true treatment effect. In the current study, 2 baseline measurements were conducted to account for learning effect. The experimental group demonstrated a significant improvement in SOT composite score of 18.5 (P<.001), which is greater than the score of 14.8 (P=.001) reported by Badke et al, who investigated the implementation of a vestibular and balance-related rehabilitation program involving a “mixed and central vestibular dysfunction” group. More importantly, the experimental group’s improvement was significantly greater compared with that of the exercise control and waiting-list control groups.

The third major finding of this study was that the experimental group was the only group to improve significantly in disability due to dizziness or disequilibrium, with large effect sizes. The improvement in DHI total score of −18.7 points (P=.010) is greater than the improvement of −14.3 points (P=.02) reported by Badke et al.

This study was not designed to test the underlying reasons for the improvements in fatigue, upright postural control, and disability due to dizziness or disequilibrium. However, the conceptual framework that led to our investigation may provide insight into the theoretical reasoning. The balance training portion of the vestibular rehabilitation program can be seen as an attempt to condition the central nervous system to provide efficient upright postural control while performing tasks in standing and walking.

Moderate to strong associations were found among the changes in fatigue, upright postural control, and disability due to dizziness or disequilibrium. Because both postural control and dizziness reflect central processing, these correlations lend further support to the proposition that impairments of central sensory processing contribute to fatigue in people with MS. Furthermore, these findings suggest that changes in one of these variables could potentially have a coupled reaction in one or both of the other variables.

Demyelination and axonal degeneration found in patients with MS often result in impaired motor control, with evidence of partial spontaneous neural repair, including axonal and dendritic collateral sprouting. This neural plasticity has been shown to be enhanced in patients with MS following task-specific rehabilitation training. With this knowledge, it can be theorized that vestibular rehabilitation provides the necessary task-specific stimuli for neural reorganization, fostering central sensory integration and resulting in improved upright postural control.

Ocular motor training, in the form of eye movement exercises, plays a key role in neuromuscular reorganization. Abnormal eye movements are strongly associated with advanced disability in patients with MS. Because visual feedback plays a key role in coordinated limb movement, it is possible the eye movement exercises included in the vestibular rehabilitation program contributed to the improved postural control found in the experimental group.

Peripheral physiological changes also may be involved, including...
improved muscle endurance due to repetitive balance training. Improved muscular function may assist in lessening the negative effects of motor fatigue on anticipatory postural adjustments.\textsuperscript{71}

Because of impaired central sensory processing mechanisms, people with MS may require increased conscious or mental attention while performing daily upright tasks. This increase in attention could be an important reason for elevated perception of fatigue in these individuals. This concept is supported by Filippi et al.,\textsuperscript{72} who found that patients with MS who reported greater levels of fatigue had elevated brain activity in the areas devoted to attentional tasks and lower activity in the motor planning and execution regions.

Taken together, findings from this investigation support the theory that fatigue in patients with MS is linked to impairments of central sensory integration. Specifically, an intervention program, based on principles of rehabilitation for individuals with vestibular dysfunction and impaired sensorimotor integration, improved upright postural control and fatigue.

We also measured depression and walking capacity, both of which changed marginally. Depression in patients with MS has been found to be associated with fatigue,\textsuperscript{73} with a recent investigation showing a weaker relationship.\textsuperscript{74} We found that both exercise groups improved in self-reported depression; however, the change was not significantly different between the groups. The lack of significant change in depression following exercise performance is comparable to previous reports.\textsuperscript{75} Additionally, it should be noted that severe depression was an exclusion criterion, potentially attenuating our findings.

At baseline, the experimental group appeared to have had a greater walking capacity, based on the 6MWT scores, compared with the exercise control and wait-listed control groups; however, these differences were not significant and were comparable to the range reported previously in people with MS (670 – 1,978 ft).\textsuperscript{76–78} The 85.1-foot improvement on the 6MWT by the experimental group is greater than that reported by Rampaello and colleagues\textsuperscript{14} (32.8 ft, \( P = .17 \)) following an 8-week “neurological rehabilitation” program; however, this improvement also was found to be insignificant (\( P = .092 \)).

Considering this information and the significant findings for fatigue, upright postural control, and disability due to dizziness or disequilibrium in our study, the 6MWT may not be appropriate for detecting dynamic upright postural control changes in this population and more specifically for this exercise-based investigation.

Changes between the 10-week and 14-week periods (Tab. 3) suggest that the outcome measure scores remained stable for 4 weeks following the intervention phase; however, a larger-scale study with a longer follow-up is needed to improve the validity of concluding long-term benefit retention.

Lastly, it should be noted that the 2 training groups were different with respect to duration of time in the study and adherence to HEP and fatigue management. However, the differences were not statistically significant, nor were they sufficiently large to be confounding from a clinical perspective.

Limitations should be acknowledged. The sample size was too small to permit comparisons between patients with and without brain-stem and cerebellar lesions. Additionally, smaller samples have large variance; although in our study the clinical differences were sufficient that the variances were not a problem for the major outcomes.

We chose to include the same fatigue management education in the exercise groups in order to avoid unequal attention to discussions of the typical approach to management of MS-related fatigue. The fact that the exercise control group’s change in all outcome measures was statistically similar compared with the wait-listed control group and that reported adherence to fatigue management was similar between the experimental and exercise control groups illustrates that the education approach in this study was not effective; providing further support for the isolated effects of vestibular rehabilitation found in the experimental group.

Based on the findings from this investigation, several issues should be examined in future studies. Specifically, these findings should be replicated in a larger sample with comparisons between individuals who have brain-stem and cerebellar lesions and those without these lesions. Furthermore, analyses should examine other factors that predict which other patients are most likely to respond to such an intervention. Finally, more-specific measures of vestibular and eye movement functions, such as video-oculography,\textsuperscript{79} should be included in order to investigate underlying mechanisms.

**Conclusion**

Findings from this study provide strong evidence supporting the effectiveness of vestibular rehabilitation for the treatment of people with MS who have deficits of fatigue and upright postural control. The large treatment effects occurred after a relatively short intervention period, and changes after 4 weeks of supervised intervention were small, suggesting that vestibular rehabilitation...
Effects of Vestibular Rehabilitation on Multiple Sclerosis–Related Fatigue and Upright Postural Control

is a viable treatment option for patients with MS who experience fatigue and impaired upright postural control.

Dr Hebert, Dr Corboy, and Dr Schenkman provided concept/idea/research design, project management, and fund procurement. All authors provided writing. Dr Hebert and Dr Manago provided data collection and data analysis. Dr Corboy provided participants. Dr Schenkman provided facilities/equipment. Dr Corboy and Dr Schenkman provided institutional liaisons. Dr Manago provided clerical support. Dr Corboy and Dr Manago provided consultation (including review of manuscript before submission). The authors thank the Rocky Mountain MS Center, Anschutz Medical Campus, Aurora, Colorado, and the Colorado Chapter of the National Multiple Sclerosis Society for assistance in recruitment for this study. A Colorado Multiple Institutional Review Board approved this study. This study was partially supported by the National Multiple Sclerosis Society, Pilot Project no. PP1501.

Trial registration: ClinicalTrials.gov Identifier: NCT01216137.


References


Appendix 1.
Vestibular Rehabilitation Protocol: Tasks Performed in Sequential Order 1 to 26

Upright Postural Control

A. Static Body Position: Standing

Eyes Open
1. BOS: firm surface—heels and toes together*
2. BOS: firm surface—partial heel to toes*
3. BOS: firm surface—full heel to toes (tandem)*
Perform 1–3 with:
— Ball catching and tossing (from and to investigator)
— Head movement: rotate side to side*
— Head movement: head up (neck extension) and down (neck flexion)*

Eyes Closed
4. BOS: firm surface—shoulder width apart*
5. BOS: firm surface—heels and toes together*
6. BOS: firm surface—partial heel to toes*
7. BOS: firm surface—full heel to toes (tandem)*

Eyes Open
8. BOS: foam cushion—heels and toes together*
9. BOS: foam cushion—partial heel to toes*
10. BOS: foam cushion—full heel to toes (tandem)*
Perform 8–10 with:
— Ball catching and tossing (from and to investigator)
— Head movement: rotate side to side*
— Head movement: head up (neck extension) and down (neck flexion)*

Eyes Closed
11. BOS: foam cushion—shoulder width apart*
12. BOS: foam cushion—heels and toes together*
13. BOS: foam cushion—partial heel to toes*
14. BOS: foam cushion—full heel to toes (tandem)*

Eyes Open
15. BOS: tiltboard
Perform 15 with:
— Side-to-side
  Frontal plane of motion, rock tiltboard in plane of motion and stabilize tiltboard in neutral plane of motion position
— Head rotated side to side
  Right rotation when tiltboard rocked to right, left rotation when tiltboard rocked to left
— Forward and backward
  Sagittal plane of motion, rock tiltboard in plane of motion and stabilize tiltboard in neutral plane of motion position
— Head movement: head up (neck extension) and down (neck flexion)
  Neck extension when tiltboard rocked backward, head flexion when rocked forward

B. Static Body Position: Half-Kneeling

Eyes Open
16. BOS: half-kneeling
Perform 16 with:
— Bilateral arm flexion (both arms lifted above head at same time)*
— Alternate arm flexion/extension (one arm lifted above head, other arm moved backward), with trunk rotation*

(Continued)
Appendix 1.
Continued

C. Static Body Position: Standing

Eyes Open
17. BOS: trampoline—shoulder width apart
   Perform 17 with:
   — Head movement: rotate side to side
   — Head movement: head up (neck extension) and down (neck flexion)
   — Marching in place combined with turning body 360° right and left
18. BOS: trampoline—heels and toes together
19. BOS: trampoline—partial heel to toes
20. BOS: trampoline—full heel to toes (tandem)
   Perform 18–20 with:
   — Head movement: rotate side to side
   — Head movement: head up (neck extension) and down (neck flexion)

Eyes Closed
21. BOS: trampoline—shoulder width apart
22. BOS: trampoline—heels and toes together
   Perform 22 with:
   — Short squats: 5 repetitions
23. BOS: trampoline—partial heel to toes
24. BOS: trampoline—full heel to toes (tandem)

D. Dynamic Body Motion: Walking
25. Walking
   — Heel-toe walking forward and back with and without head movements*
   — Walking tossing ball side to side and up and down while visually tracking ball
   — On-command walking with 180° change in direction, stop-start, and transition into and out of standing on
     one leg

Eye Movement Training
26. Eye movements
   — Saccades
     Perform with: quick eye movement between 2 stationary objects in horizontal, vertical, and 2-direction
     diagonals*
   — Smooth pursuit
     Perform with: visually tracking a moving object in horizontal, vertical, and 2-direction diagonals*
   — Vestibular ocular reflex
     Perform with: visually fixating on immovable object while turning head side to side and up and down*

*BOS = base of support. Asterisk indicates item included in home exercise program.
Appendix 2.
Submaximal Graded Exercise Test (GET) Protocol

Equipment/Instruments:
— Bicycle ergometer
— Borg Rating of Perceived Exertion (RPE) Scale (6–20)
— Heart rate monitor
— Stethoscope and blood pressure cuff

Pretest measurements:
— Heart rate
— Borg RPE Scale rating
— Blood pressure

Stages:
Initial stage
— 2- to 3-minute warm-up
— Pedal rate of 50 rpm
— Workload of approximately 25 W (1 lb [0.5 kg])
— Heart rate continuously monitored
— Blood pressure at end of stage

Incremental stages (2 minutes each)
— Pedal rate maintained at 50 rpm
— Incremental workload increases of approximately 12.5 W (0.5 lb [0.25 kg]) per stage
— Heart rate continuously monitored
— Blood pressure recorded at the end of each stage
— Borg RPE Scale rating at the end of the last minute of each stage

Test termination:
— Patient reports unable to continue due to exertion or fatigue symptoms, serving as the symptom-limiting endpoint for the submaximal GET
— Record: Borg RPE Scale rating and peak heart rate