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The Effectiveness of Vestibular Rehabilitation on Balance Related Impairments among Multiple Sclerosis Patients: A Systematic Review

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Abstract

Background: Balance related dysfunction remains a debilitating clinical manifestation among people with Multiple Sclerosis (pwMS) causing significant morbidity and reduced quality of life. Imbalance is found to stem primarily from neurophysiological causes. Current management strategies have shown to have small but clinically insignificant results with little consideration towards vestibular sources of postural instability. Vestibular rehabilitation (VR) provides a promising treatment strategy to mediate balance dysfunction among people with pwMS.

Design: Systematic Review, guided by PRISMA guidelines and presenting a best evidence synthesis.

Data sources: 10 electronic databases were searched from inception until September 2019.

Eligibility criteria for study selection: Article of original research, population of patients with multiple sclerosis aged over 18, interventions detailing VR protocols, measurement of outcomes pre-VR/post-VR.

Results: Seven articles satisfied the eligibility criteria. 6/7 studies were rated as high quality and regarded as level one evidence. 5 studies consisted of standardised VR protocols while 2 studies consisted of customised VR. All studies identified improvements of mixed significance in balance, fatigue and dizziness outcomes post VR. Heterogeneity among VR prescription patterns limited optimal prescription guidelines.

Conclusions: The available evidence shows promise that VR is a safe and effective strategy to provide short term benefits in balance related dysfunction in pwMS. Recommendations of mixed strength are made based on the quality of current literature. Current evidence for optimal prescription and long-term effects of VR is limited. Further high-level studies evaluating the effects of VR in patients with multiple sclerosis with vestibular and/or balance dysfunction are required.

Keywords: Multiple sclerosis • Multiple sclerosis patients • Vestibular rehabilitation • VR protocols • PRISMA guidelines • Balance dysfunction • Stroke survivors • Neurodegenerative disorder • Neurological impairment • Central vestibular disorders

Introduction

Multiple sclerosis is an auto-immune mediated neurodegenerative disorder characterised by the development of lesions along the central nervous system resulting in neurological impairment [1].

Balance related impairments present a common clinical manifestation in pwMS. Activities of daily living requires the ability to process, prioritize and integrate an array of sensory information from peripheral sources and in response, generate appropriate motor commands for goal directed tasks [2].

Deficits in peripheral sources of balance are consistently reported in pwMS [3] and can be present in the absence of clinical disability [4]. Balance related impairments have been found to contribute to functional limitations, decreased work productivity, feelings of social isolation and lost independence and an overall reduced quality of life [5-7]. Further, impaired balance control has been documented to be the most disruptive symptom in those reporting ambulatory complications [8] and are directly associated with increased falls among pwMS [9].

Non-pharmacological approaches are considered the primary strategies to improve balance related dysfunctions among pwMS. To date, most rehabilitation strategies to improve balance have yielded inconsistent results. Paltamaa et al. [10], systematically reviewed a multitude of interventions aimed at improving balance. While positive effects were identified across all interventions, the clinical implications of results were limited due to the poor methodological design of included studies. Similarly, while Gunn et al. [11], outlined the effectiveness of balance specific programs on postural control among pwMS, they failed to demonstrate any clinically relevant changes on balance related outcomes. Interestingly, despite the importance of sensory integration for balance, most rehabilitation strategies have focused primarily on strengthening the weighting of visual and proprioceptive components with little to no inclusion of the vestibular consideration.

Vestibular pathology, of either peripheral or central origin can occur in 36-56% of pwMS [10,11]. Vestibular deficits have been shown to result in impaired ocular motor reflexes producing symptoms of dizziness, imbalance and impaired mobility particularly when performing simultaneous head and eye movements [12].

Balance control is imperative among people with MS due to its impact on routine functional tasks and for safe and efficient participation in personal and societal activities. As multiple sclerosis has the capacity to affect peripheral and central sources of the balance system, treatment strategies must be comprehensive in addressing both components of balance [13].

Vestibular rehabilitation (VR) is an exercise-based treatment designed to promote central nervous system (CNS) neuroplastic adaptations by improving the ability to process vestibular, proprioceptive and visual inputs to form new internal feed forward models [14]. Historically, VR was primarily developed for the treatment of peripheral vestibular disorders. However, in recent years, there has been emerging evidence for its use in improving balance related dysfunction among those with mild traumatic brain injury [15] and gait performance in stroke survivors [16]. Despite the evidence of VR use in the management of centrally derived balance disorders, to date, no review has investigated the effects of VR among pwMS.

The purpose of this research is to review contemporary literature regarding the effectiveness of vestibular rehabilitation on balance related function among MS people. This review aims to examine the application of VR protocols within the MS population and determine the interventions

effectiveness with the hope of guiding clinical practice recommendations and providing recommendations for future research.

Methods

Search strategy

An extensive literature search using a devised eligibility criterion was performed up to September 2019 through the following databases; Ebsco (Academic Search Complete, CINAHL, Medline, PsychArticles, PsychInfo, SportDiscus, Biomedical Reference Collection), Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science. As VR is considered an emergent treatment paradigm among pwMS, no limitations were applied to study methodology or year of publication. Limits of English language and human studies were applied. Suitable keywords and controlled vocabulary terms were generated from discussion between the investigating authors and modified in terms of the glossary of each database and combined using Boolean operators. The reference lists from retrieved articles were screened for any additional relevant articles.

Study identification

Selection criteria for articles included in this review comprised: (i) article of original research, (ii) population consisting of clinically diagnosed multiple sclerosis patients over 18 years of age (iii) interventions detailing VR, (iv) measurement of outcomes pre-VR and post-VR to evaluate treatment effect. A secondary outcome of interest was the description of treatment prescription patterns. From the preliminary literature search, the references of eligible articles were exported from the searched databases to EndNote software and duplicates removed. The titles of abstracts of potential articles were screened by one author and the remaining full texts independently reviewed by the authors for relevancy based on the defined inclusion criteria.

Data extraction

The investigating authors collaboratively screened and extracted the data relating to study design (type of study and level of evidence based on methodological quality), population demographics (age, sex, MS classification, recruitment source), intervention protocols and outcome measures (addressing balance, fatigue and dizziness) using the data extraction form recommended by the PRISMA-P guidelines. Data collection was completed by marking a Yes, No or Partial/unclear alongside relevant comments made at the time of undertaking the process. Where information was available about the VR intervention delivered, it was extracted using the Frequency, Intensity, Type and Time (FITT) taxonomy.

Risk of bias

Risk of potential biases was evaluated using the Cochrane risk of bias tool. The following domains were assessed for risk of bias; random sequence generation, allocation concealment, blinding of participants and research personnel, blinding of outcome assessments, accountability of incomplete outcome data, selective outcome reporting, other bias identified. Identified bias in the following domains were described as reported within studies. A judgement about the adequacy of each recorded entry was then made and a rating of low risk, high risk or unclear assigned was reported within the analysis of findings and provides an indication of the rigor of selected articles.

Quality appraisal

Quality assessment was conducted using the critical appraisal skills programme (CASP) and physiotherapy evidence database (PEDro) tools to provide a comprehensive evaluation of included articles rigor in terms of methodological design and internal validity. Pedro scores of 6 or greater were deemed level I evidence of 'high quality' and scores of 5 or less were level II evidence of 'low quality' [17]. Treatment fidelity was evaluated using the standardised Template for Intervention Description and Replication (TIDieR) checklist to determine the validity and reliability of treatment interventions and where possible, isolate interventions active ingredients for the establishment evidence-based practice guidelines [18]. Levels of evidence were assigned to each study following the appraisal process.

Data Synthesis

A descriptive narrative approach to analysis was undertaken, summarising the literature pertaining to patient demographics and VR by outcomes of interest relating to balance, dizziness and fatigue.

Following the narrative review, a best evidence synthesis was carried out according to the international guidelines of evidence-based medicine. Studies excluded from the best evidence synthesis were those deemed likely to be at high risk of bias due to selection, information or confounding factors threatening both the internal and external validity of studies. Comparable results from studies judged to be scientifically admissible were pooled in a meta-analysis. Standard mean differences (SMD) were calculated with 95% confidence intervals. Based on the clinical merits and pooled results of the data was abstracted into an evidence table relating to statements on VR outcomes of interest. Grading of the strength of recommendations was assigned for each statement to provide guidance for clinical practice based on a strength of the appraised evidence base.

Results

Figure 1 provides detailed information regarding study identification and selection in accordance with PRISMA guidelines. A total of 323 studies were identified through relevant databases. Following the removal of duplicates, the titles and abstracts of 64 articles were screened for eligibility. The full texts of 11 articles were examined for eligibility. An additional search of the article's references yielded an additional 1 paper for examination. 4 studies did not meet the prerequisite inclusion criteria. Primary reasons for exclusion included publication in a non-English language and lack of VR specific interventions. Consensus on study eligibility was agreed by both primary researchers. As such, a total of 7 studies satisfied the inclusion criteria all of which were RCT's.

Study demographics

The study design, study population, intervention, outcome measures, results and level of evidence of included studies are presented in Table 1. Where possible, variables were expressed as mean +/- standard deviation. However, due to the non-normal distribution of outcome variables, characteristics listed by Ozgen et al. are expressed with medians (IQR). A total of 323 subjects were recruited across all included studies and included male and female genders. Over two thirds (n=230) of the sample population were female which is reflective of the increased susceptibility of females to autoimmune conditions. The age of participants ranged from 20-63 years. All studies described the sample population by using the expanded disability status scale (EDSS) scores or the disease's clinical course. Four out of seven studies included a mixed group of MS disease classifications, including patients with relapse remitting, secondary progressive and primary progressive. One study included only relapse remitting clinical courses. Two of the seven studies included patients with EDSS scores of less than 6/10 indicative of a high level of function and mobility among the study population.

Quality assessment

The overall methodological quality of the included studies was varied with total scores ranging from 5 to 8 points. All but one study was deemed to be of high quality in accordance with the PEDro scale [17]. Sources of bias were documented throughout but where possible, authors attempted to implement strategies to reduce the impact of bias on the study's internal validity. Five of the seven studies satisfied criteria relating to adequate representation of the target population. While all studies employed appropriate randomisation methods, only four out of the seven studies applied allocation concealment. Six studies failed to achieve adequate blinding of participants predisposing an increased likelihood of bias and exaggerated treatment effects. However, in six of the seven studies, assessor blinding was achieved and has been demonstrated to reduce potential inaccuracies associated with treatment effect overestimations such as the Hawthorne effect [19]. Five studies comprehensively documented details relating to follow up which strengthened their internal validity and allowed accurate conclusions of treatment effects to be drawn. Four studies reported dropouts and only one study incorporated intention to treat (ITT) analysis. While omission of ITT analysis can predispose to selection bias, its exclusion can be associated to recent criticism reporting that ITT analysis can result in an increased risk of type II errors and overestimated treatment effects through the inclusion of non-adherent participants [20].

Efficacy of interventions

All studies reported improvement in outcome measures of interest among the VR intervention groups. No adverse responses to the interventions were

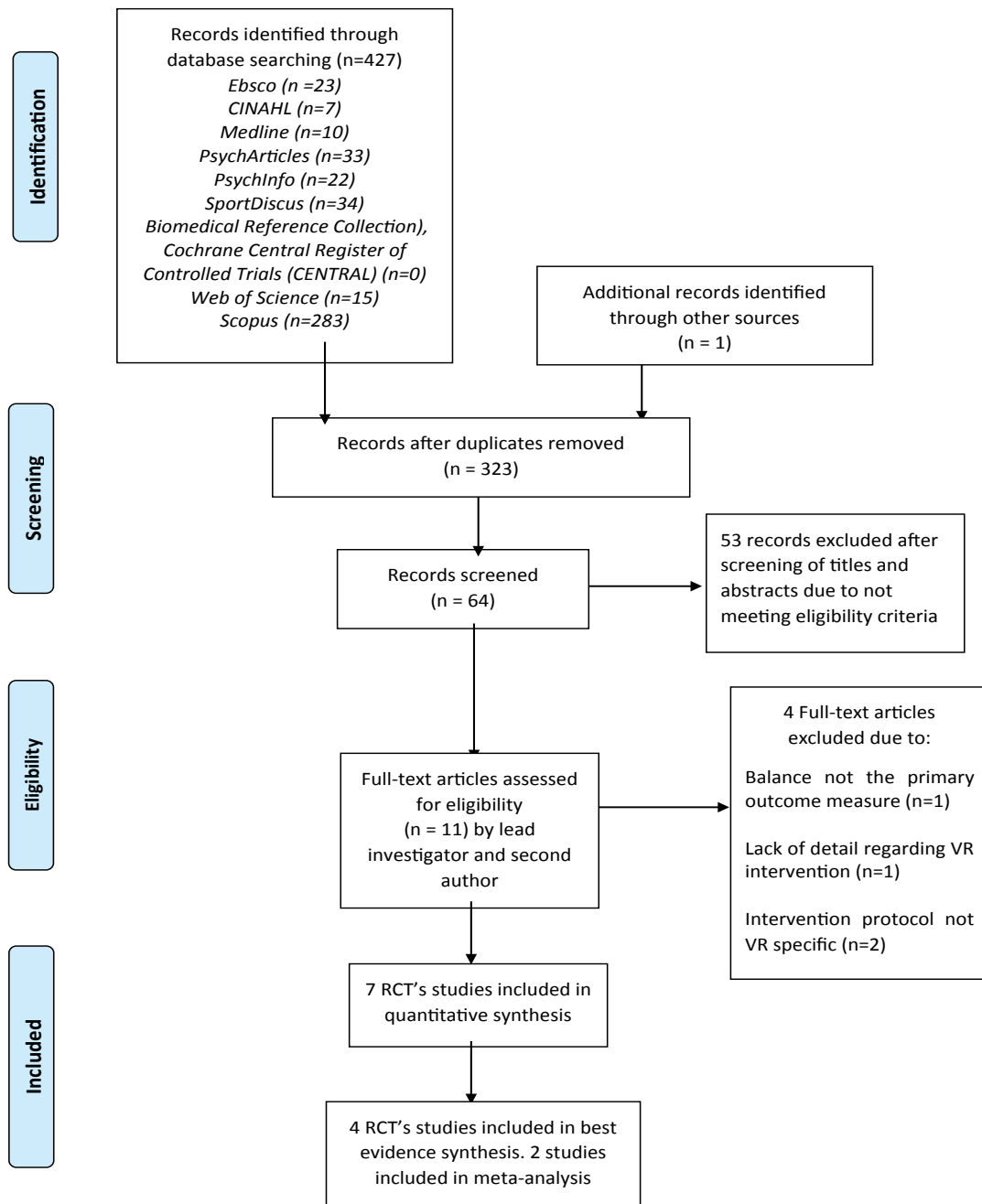


Figure 1. PRISMA Flow Diagram for identification of studies included in this systematic review.

documented in any of the studies except for Tramontano et al. where one participant was released for related side effects.

Balance

All included studies employed outcome measures investigating the effect of VR on balance related measures both pre and post intervention. All studies measured objective dynamic balance tests with Ozgen et al. also incorporating self-reported balance measures. Three studies incorporated computerised dynamic posturography (CDP-SOT) to determine the effects of VR on balance impairment. Hebert et al. (level I evidence) reported a significant mean change of 18.5 (± 12.3) points following the VR treatment (p<0.001 95% CI: 10.7-26.3). This change was found to be significantly greater than the aerobic exercise group (p=0.001 Cohen D=1.37 95% CI: 4.9-21.6) and control group (p=0.001 Cohen D=1.28 95% CI: 3.7-20.05) of large effect. Similarly, Hebert et al. (level I evidence) reported a significant improvement in CDP-SOT scores between the VR and control group (p<0.0001 95%CI: 4.73-11.9) [21]. In both studies, the improvements in CDP-SOT scores exceeded the prespecified MCID of 13.5 points indicating clinically significant effects. Number needed to treat (NNT) was employed by Hebert et al. reporting that a value of 1.9 was needed to achieve a CDP-SOT improvement score beyond the MCID. Ozgen et al. employed static posturography and found no significant differences between groups in falling index measures (p=0.024).

Four studies employed the Berg Balance Scale as measures of balance pre and post VR intervention. Ozgen et al. reported a significant mean change of 9.5 points with Afrasiabifar et al. demonstrating a change of 8.9 points, both satisfying the MCID of 7 points [22]. Three of the four included studies reported significant differences between groups (p ≤ 0.004). Two of the four studies reported their results in terms of interaction effects limiting the ability to accurately determine true treatment effects. Both Tramontano et al. and Brichetto et al. demonstrated significant interaction effects (time*group) in favour of VR (p<0.001).

Shady et al. utilised Biodex Balance Master indices as their measure of balance and found significant improvements in antero-posterior, medio-lateral, dynamic, and limit of stability indices in the VR group only (p<0.05) [23]. Ozgen et al. also reported a mean Romberg eyes closed improvement of 19.45 seconds (p=0.003), an improvement of 21.6 seconds for tandem eyes open (p<0.001), an improvement of 20.6 seconds for foam Romberg eyes closed (p<0.001), mean improvement of 5.26 seconds for the timed up and go (p<0.001) and a mean change of 5 points for the Dynamic Gait Index achieving the MCID of 4.19-5.54 (p<0.001). Further, significant differences between groups were reported for Romberg eyes open, Romberg eyes closed, tandem eyes open eyes closed, foam Romberg eyes closed, Timed Up and Go (TuG) and Dynamic Gait Index (DGI) (p<0.001).

Table 1. Detailed account of RCT studies (n=7) including sample size, level of evidence, quality score, intervention, risk of bias and results of primary outcome for balance, fatigue and dizziness.

Authors	Design & quality	Sample	Intervention	Primary Outcomes	Results of primary outcomes	Risk of Bias
Hebert et al. 2011 [19]	RCT Pedro = 8/10 Level I	Mixed population of MS subtypes N=38	VR Aerobic exercise Control: Usual care	CDP-SOT	Balance: Mean change 18.5 points* (95% CI: 10.7 to 26.3) Between group difference of large effect (D= 1.37 95% CI: 4.9- 21.8; D=1.28 95% CI:3.7 - 20.05)	Low
Hebert et al. 2018 [20]	RCT Pedro = 7/10 Level I	Mixed population of MS subtypes N=88	VR Control: Usual care	CDP-SOT	Balance: Mean change 18.5 points* (95% CI: 10.7 to 26.3) Between group difference of large effect (D= 1.37 95% CI: 4.9- 21.8; D=1.28 95% CI:3.7 - 20.05) Between group difference (p,0.001 95% CI: 4.4.73 to 11.9)	Low
Brichetto et al. 2014 [21]	RCT Pedro = 6/10 Level I	Mixed population of MS subtypes N=32	Tailored VR Standardised VR	BBS	Balance: Mean change 18.5 points* Interaction effect: Time <0.001 Time*Group p<0.001	Low
Shady et al. 2018 [22]	RCT Pedro = 6/10 Level I	Mixed sample of RR MS patients N=30	Medication + VR Control: Standard neurorehabilitation	OSI APSI MLSI	Balance: LoS pre:24.3 post:31.9 p=0.0025 DSI pre: 1.74 post:2.28 p=0.0003 MLSI pre: .71 post:1.97 p=0.0022 APSI pre:1.58 post: 1.80 p=0.0399	Low
Afrasiabifar et al. 2017 [23]	RCT Pedro = 6/10 Level II	Mixed population of MS subtypes N=72	VR Frenkel Control: Usual care	BBS	Balance: Mean change 8.8 points Interaction effect: Time <0.001 Time*Group p>0.05	High
Tramontano et al. 2018 [24]	RCT Pedro = 6/10 Level II	Mixed sample of MS EDSS classification scores	VR Control: standard neurorehabilitation	BBS TBG	Balance: 16.8% ↑ BBS. Between group difference p=0.0004 Interaction effect: Time*Group p=0.01 17.5↑ TBG Between group difference p=0.0005 Interaction effect: Time*Group p=0.03	High
Ozgen et al. 2016 [25]	RCT Pedro = 5/10 Level II	Mixed population of MS subtypes N=40	Customised VR Control: Usual care	SOT (tetrax fall index) BBS VAS DHI, ABC FGA TUG Romberg	Balance: Mean change pre and post VR intervention for BBS, VAS, DGI, FGA, ABC, TUG, p<0.001 Between group differences for BBS, VAS, DGI, FGA, Romberg, ABC, TUG, p<0.001 Mean change for SOT fall index p<0.084 Between group differences SOT fall index p<0.024	High
Authors	Design & quality	Sample	Intervention	Primary Outcomes	Results of primary outcomes	Risk of Bias
Hebert et al. 2011	RCT Pedro = 8/10 Level I	Mixed population of MS subtypes N=38	VR Aerobic exercise Control: Usual care	MFIS	Fatigue: Mean change 21.5 points*(95% CI: -31.1- to 11.9) Between group difference of large effect (D= 1.06 95% CI: 1.06- 28.0; D=1.33 95% CI:4.5 - 30.9)	Low
Brichetto et al. 2014	RCT Pedro = 6/10 Level I	Mixed population of MS subtypes N=32	Tailored VR Standardised VR	MFIS	Fatigue: Mean change 8.8 points Interaction effect: Time < 0.001 Time*Group p>0.05	Low
Tramontano et al. 2018	RCT Pedro = 6/10 Level II	Mixed sample of MS EDSS classification scores	VR Control: Standard neurorehabilitation	FSS	Fatigue: 8.5% ↑ FFS for VR group p=0.007	High
Authors	Design & quality	Sample	Intervention	Primary Outcomes	Results of primary outcomes	Risk of Bias
Hebert et al. 2011	RCT Pedro = 8/10 Level I	Mixed population of MS subtypes N=38	VR Aerobic exercise Control: Usual care	CDP-SOT MFIS DHI	Dizziness: Mean change 18.7 points (95% CI: -31.9- to -5.5) Between group difference of large effect (D= 1.03 95% CI: 2.3- 30.6; D=1.12 95% CI:3.9 - 32.2)	Low
Hebert et al. 2018 [20]	RCT Pedro = 7/10 Level I	Mixed population of MS subtypes N=88	VR Control: Usual care	CDP-SOT	Dizziness: Between group difference (p < 0.0001 (95% CI -19.3 Low to -8.62)	Low
Ozgen et al. 2016	RCT Pedro = 5/10 Level II	Mixed population of MS subtypes N=40	Customised VR Control: Usual care	SOT DHI ABC Romberg	Dizziness: Mean change DHI 23 points. Between group difference p<0.001	High

Note: CDP-SOT: Posturography DHI: Dizziness handicap inventory MFIS: 21 item modified fatigue scale BBS: berg balance scale TUG: Timed up and go 5TSTS: Five times sit to stand DGI: Dynamic gait index FGA: Functional gait assessment OSI: Overall Stability Index APSI: Antero-Posterior Stability Index MLSI: Medio-lateral stability index TBG: tinetti balance and gait FSS: Fatigue severity scale 2MWT: 2-minute walk test T25FW: Timed 25-foot walk test

*Achieved MCID

Ozgen et al. found significant improvements for the VR group and between group differences ($p < 0.001$) in self-reported measures on the severity of imbalance and activities specific balance and confidence scale.

Two studies (19,20) were included within the meta-analysis for best evidence synthesis. Vestibular rehabilitation was found to more effective in improving balance (SMD = 2.12; 95% CI = 0.49, 3.75; $p = 0.01$; $I^2 = 89\%$) when compared to waiting list controls.

Dizziness

Three studies investigated the effects of VR on dizziness pre and post intervention using self-reported measures of dizziness including the Dizziness Handicap Inventory and VAS scale [24,25]. Ozgen et al. reported a non-significant improvement ($p = 0.10$) of 18.7 points (± 20.7 95% CI: -31.9 to -5.5) in dizziness related symptoms following the VR intervention. This change was found to be non-significant in comparison to aerobic exercise ($p = 0.018$ Cohen D=1.03 95%CI: 2.3 to 30.6) and waiting list controls ($p = 0.009$ Cohen D=1.12 (95% CI: 3.9 to 32.2) of large effect. Ozgen et al. reported a mean improvement of 23 points in DHI scores ($p < 0.001$) and severity of dizziness as measured by VAS ($p = 0.003$) post the customised VR intervention. Significant between group differences ($p < 0.001$) was also found between the VR intervention group and waiting list control. Hebert et al. reported significant between group differences in DHI scores between the BEEMS protocol and waiting list control ($p < 0.001$ 95% CI: 19.3 to 8.62) with the VR group demonstrating a mean improvement of 19.2 points compared to an improvement of 1.4 points among the control group. Similarly, Hebert et al, found significant between group differences between the VR group and waiting list control (-13.9 $p < 0.0001$ 95% CI -19.3 to -8.62). It must be noted however that no study failed to achieve the MCID score of 22.5 points [26].

Two studies (19,20) were included within the meta-analysis for best evidence synthesis. Vestibular rehabilitation was found to more effective in improving dizziness as measured by the DHI (SMD = -17.43; 95% CI = -29.99, -4.87; $p = 0.007$; $I^2 = 66\%$) when compared to waiting list controls.

Fatigue

Three studies included measures evaluating the effect of VR on MS related fatigue pre and post intervention. Outcome measures included the Modified Fatigue Impact Scale (MFIS) and fatigue severity scale [24,25,27]. Hebert et al. reported a significant improvement of 21.5 (± 15) points ($p < 0.001$ 95% CI: 31.9 to 11.9) in MFIS scores in comparison to 6.7 (± 15) points for the Aerobic exercise group ($p = 0.085$ 95% CI: 14.5 to 1.1) and 3.8 (± 11.4) points for the control group ($p = 0.255$ 95% CI: -10.6 to 3.1). Non-significant between group differences were reported for the VR group in comparison to aerobic exercise ($p = 0.024$ Cohen D=1.06 95% CI: 1.6 to 28.0) with significant between group differences between VR and control group of large effect ($p < 0.005$ Cohen D=1.33 95% CI: 4.5 to 30.9). Brischetto et al. reported non-significant improvements in MFIS scores for both the VR and control group of 8.8 and 14.2 points respectively. A significant interaction effect was reported for time ($p < 0.001$) with non-significant interaction effects documented for time*group ($p > 0.05$). Hebert et al. reported significant between group differences in MFIS scores between the VR and waiting list control ($p < 0.001$ 95% CI: -16.7 to -7.79). Tramontano et al. reported a significant improvement of 10.6 (± 5) points in the fatigue severity scale for the cawthorne-cooksey exercise group. This result was reported to be significantly greater than that of conventional therapy group ($p < 0.007$). Only Hebert et al. exceeded the prespecified MCID improvement of 15 points for the MFIS indicating clinically significant effects.

Treatment fidelity-Prescription and progression patterns

All studies provided information on the structuring and implementation of VR treatment protocols. Table 2 illustrates the VR prescription details for all included studies under the headings of frequency, intensity, time and type (FITT). Where reported, information on exercise progression is also included. Only two studies provided comprehensive information relating to exercise prescription in terms of FITT taxonomy. A lack of consistency in VR prescription is clear across all studies. A wide variation in treatment protocols

Table 2. RCT studies (n=7) intervention protocols including intervention duration, training frequencies. Intensity, type and progressions.

Authors	Year	Intervention	Duration (weeks)	Frequency (sessions per week)	Intensity	Time (minutes)	Progression
Hebert et al.	2011	Standardised BEEMS protocol (VOR stimulation, OME, balance exercises)	6	2x supervised 1x DHEP	1-2 min per exercise	Supervised: 55 DHEP: NR	Modifying posture/ base of support, support surface, availability of sensory information
Brichetto et al.	2014	Tailored vestibular rehabilitation exercises (VOR stimulation, OME, habituation exercises, balance exercises)	4	3x supervised	NR	Supervised: 60	Modifying posture/ base of support, support surface, availability of sensory information
Ozgen et al.	2016	Customised Vestibular Rehabilitation exercises (VOR stimulation, OME, habituation exercises, balance exercises)	8	1x supervised 2x DHEP	NR	Supervised: 30-45 DHEP: 15-20	Modifying posture/ base of support, support surface, availability of sensory information
Afrasiabifar et al.	2017	Cawthorne-Cooksey exercise protocol (VOR stimulation, OME, habituation exercises, balance exercises)	12	3x supervised	Weekly increases in speed of performing exercises and altering posture/ base of support	60 mins (2x 30 min session with 15 min rest period)	Modifying posture/ base of support, support surface, availability of sensory information
Hebert et al.	2018	Standardised BEEMS protocol (VOR stimulation, OME, balance exercises)	14	0-6 weeks: 2x supervised 7x HEP 0- 8weeks: 1x supervised 1x DHEP	1-2 min per exercise	Supervised: 55 DHEP: NR	Modifying posture, base of support, support surface, availability of sensory information
Shady et al.	2018	Medication, customised VR (VOR stimulation, OME, and Particle repositioning manoeuvre)	6	3x supervised	NR	30-45 mins	↑ speed and duration of exercise, postural adaptation/base of support
Tramontano et al.	2018	Gaze stability postural control exercises (stand/march blindfolded on compliant surface with turning)	4	2x daily	4-10 minutes	40 min session of standard neurorehabilitation 20 min VR specific protocol	↑ time performing exercises

Note: DHEP: Daily Home Exercise Program OME: Ocular motor adaptation exercises NR: Not reported.

Table 3. Best evidence Synthesis the use of VR for balance, fatigue and dizziness symptoms in people with MS.

Best evidence synthesis statement	Evidence Quality	Grade of Recommendation
Does vestibular rehabilitation improve balance related dysfunction among pwMS?	Level one evidence to support the statement that vestibular rehabilitation improves balance related dysfunction in pwMS.	Moderate to strong
Does vestibular rehabilitation improve reports of dizziness among pwMS?	Level one evidence supports the statement that vestibular rehabilitation improves reports of dizziness among pwMS	Moderate
Does vestibular rehabilitation improve reports of fatigue among pwMS?	Level one evidence supports the statement that vestibular rehabilitation improves reports of fatigue among pwMS	Low to Moderate

was reported demonstrated a wide variance ranging from 4 to 14 weeks with duration of 6 weeks most commonly reported. A wide variation in supervised training sessions was also illustrated ranging between once a week to twice daily 5 times a week. Three studies documented daily home exercise programs (HEP) with only one study specifying the HEP prescription frequency and duration. Four studies reported on exercise intensity. A large heterogeneity exists among exercise intensity with Hebert et al. performing each exercise for a period of one to two minutes, Tramontano et al. performing exercises for a period of 4-10 minutes and Afrasiabifar et al. performing 10 slow repetitions of each exercise followed by 10 faster repetitions [28]. Information on whether clinicians received formal training in VR was specified in only two studies. Three studies provided information on the level of expertise of the clinician administering the supervised VR programme. Two studies reported clinicians to have 12 years' experience in either neuro-rehabilitation or treating pwMS. Only Ozgen et al. specified clinicians to have 3 years specialising in vestibular and balance rehabilitation.

The type of VR intervention used also varied across studies. Three studies considered VR as a single intervention. Four studies reported VR as a part of a multimodal intervention including VR and fatigue management education, VR and conventional neuro-rehabilitation incorporating stretching, postural alignment, active-assisted mobilizations, neuromuscular facilitation and balance training and VR incorporating particle repositioning manoeuvres combined with pharmacotherapy. Hebert et al. however provided the same fatigue management strategy to both the VR and control groups to isolate the efficacy of VR on their selected outcome measures. Four studies employed standardised VR protocols with three studies employing customised VR protocols based on deficits in peripheral balance afferent systems or individual needs based on the ICF framework or otherwise.

Heterogeneity surrounding studies VR intervention design restricts the ability to synthesise the available data within the systematic review. Further, the omission of detailed VR prescription limits the author's ability to identify the key factors representative of successful VR programmes for pwMS. Vestibulo-ocular adaptation exercises, involving the use of head and/or eye movements to induce retinal slip and facilitating the gain of the vestibular response were documented in all included studies. Ocular motor adaptation exercises incorporating alternative strategies to act as substitutes for lost vestibular function were described in six studies. Habituation exercises aimed at reducing the magnitude of response to repetitive somatosensory stimulation by gradual increasing exposure to provoking stimuli was employed in three studies. Balance exercises, designed to strengthen individual's ability to process, integrate, weight and evaluate sensory information and generate appropriate motor responses were employed in 6 studies.

Treatment progressions were described in all included studies. Exercise progression was described by either increasing the time performing the exercise, modifying the base of support; the type of support surface; the posture in which the exercise was performed; the type of sensory information available and the direction of head movements. Ozgen et al. additionally employed exercise progression through modifying the direction of whole-body movements or target distance when performing the vestibulo-ocular exercise [25].

Best evidence synthesis

Following the narrative review, the included a best evidence synthesis was proposed based on the evaluation of the internal validity and clinical merits of each included study. Studies identified in the review but not included in best evidence synthesis were those deemed to be of low quality and likely to be at

high risk of bias. Data from studies judged to be scientifically admissible were then abstracted into an evidence table addressing each outcome of interest [Table 3]. Where a study related to more than one outcome, it was included more than once.

Discussion

Vestibular rehabilitation is a symptom-based approach that allows the balance system to undergo central reorganisation and compensation resulting in functional recovery [29]. To date, few published studies have investigated the effects of VR in centrally derived vestibular and balance related disorders. This is the first review to examine the effects of VR on balance related outcomes in pwMS. This review highlights that VR is an effective management strategy providing short-term improvements in balance related outcomes among pwMS.

The best evidence synthesis consisted of four studies of mixed age, gender and disease classifications outlining the clinical applicability of VR protocols to all MS populations and subtypes. There is limited evidence to suggest the effectiveness of VR on pwMS who possess an EDSS score greater than 4.5 and immobile.

Currently, the level of evidence supporting the use of VR to improve balance related outcomes in pwMS is mixed. Level one evidence of moderate to strong recommendation supports the use of VR to improve balance outcomes in pwMS. Recent reviews support this, highlighting the effectiveness of VR in improving centrally derived balance disorders such as mild traumatic brain injury [30]. Further, balance related improvements were demonstrated in comparison to both endurance exercise or waiting list controls, indicating that treatment effects were attributable solely to VR. VR was found to be superior to other forms of conventional balance related interventions. This aligns with previous research showing VR to be as good as conventional balance interventions and superior to non-vestibular interventions in improving postural and mobility responses among geriatric and chronic dizziness populations [31,32].

Level one evidence of moderate recommendation exists for the use of VR to improve dizziness in pwMS. This result is in contrast to a review by Danicic et al [33] who found VR to be ineffective in improving dizziness in pwMS as measured by the DHI. However, recent evidence highlights that the DHI has been shown to correlate poorly with the severity of balance related vestibular dysfunctions with 95% of variation in scores owing to individual behavioural determinants [34]. Although failing to achieve the MCID, improvements in DHI scores were greater than motor sensory interventions highlighting VR to be superior at improving dizziness than non-vestibular interventions with more high-quality studies offering more definitive conclusions.

Level one evidence of low to moderate recommendation exists for the use of VR to improve MS related fatigue. Improvements in MS related fatigue offers insight into the benefit of VR to augment the capacity of cerebellar and brainstem functional systems. It addresses the central sensory integration centres and improves the ability to modulate pyramidal and extra pyramidal functional systems therefore reducing the cognitive load associated with postural control [35]. Improvements in fatigue have been associated with moderated neurological exacerbation rates and increased daily activity [35] leading to improved quality of life. This provides further indication to investigate the effects of VR on MS related physical activity.

Prescription and progression patterns

The ability to identify optimal guidelines for VR exercise prescription in terms of FITT taxonomy is critical for clinical application. Guidelines are

essential for the design and implementation of effective interventions. Improvements in balance outcomes were noted among all studies post intervention, however the large heterogeneity and lack of detailed descriptions restricts the ability of this systematic review to identify the key prescriptive factors that resulted in successful VR programmes for people with MS [37]. Despite this heterogeneity, a general trend was noted that a minimum of 4-6 weeks is required to provide significant improvements in balance. This is consistent with the American Physical Therapy Association guidelines that recommend 4-8 weeks for peripheral vestibular disorders with central originating vestibular or balance related disorders requiring longer periods of VR to observe clinically meaningful changes [14,38]. This is most likely attributed to the reduced ability of affected central pathways to induce compensatory mechanisms for recovery [39].

Gold standard VR provision has been documented to constitute the prescription of customised treatment programmes based on functional limitations identified through assessment [40]. However, significant improvements in balance were recorded for all included studies despite the diversity in exercise prescription, be it individualised or generic. This contrasts previous findings as Horak et al. [41] highlighted individualised VR programs to be more effective than generic exercise programs. Generalised VR is non-specific to either patient or diagnosis, focusing rather on improving the most common elements influencing balance and postural control. Generalised VR has been shown to be an effective form of treatment among traumatic brain injury survivors [42]. It is important to note the heterogeneity of session durations demonstrates the ability of customised VR programs to elicit clinically relevant improvements in balance within half the duration of standardised VR programs. This highlights the need for further research comparing the efficacy of customised *versus* standardised programs in improving balance among the MS population.

Limitations and Recommendations for Future Research

A major limitation within the included studies is the researcher's inability to distinguish if balance difficulties among selected participants were derived from peripheral or central origins. As previously mentioned, pwMS are found to suffer from both peripheral and central derived vestibular lesions affecting the sensory integratory centres [11]. However, peripheral vestibular lesions have been shown to resolve spontaneously within a period of 14 days [37]. While improvements in balance could be attributed to the natural resolution of symptoms, deficits in vestibular signalling or utricular dysfunction can remain warranting the need for a course of VR [43]. Future research should include vestibular assessments in their experimental design to determine the role that peripheral and central vestibular pathology plays on MS related imbalance to more accurately determine the clinical effect of VR.

Quality assessment of the included studies identified several methodological flaws with the potential of the trustworthiness, interpretation and generalisability of the results being affected. The lack of research, small sample sizes and varied methodological quality of included studies stresses the need for more high-quality research examining the effects of VR on MS related dysfunction. This would provide more definitive evidence for evaluating the clinical practicality of VR on balance related outcomes among the pwMS.

While this systematic review reports the improvement in balance capabilities in people with MS as measured by commonly used clinical balance measures, this review is limited in its ability to distinguish whether such improvements translate into functional parameters such as reduced falls risk. Future research should focus on the effect of VR on falls rates in pwMS.

While immediate short-term improvements in balance were noted, the long-term effects of VR on MS related balance capabilities remain uncertain.

Evidence has demonstrated balance specific interventions lead to increased social participation and self-management. This is achieved through increased confidence and control of their bodily functions which transfers into ADL ability. VR was demonstrated to improve balance outcomes in people with MS; however its direct impact on an individual's HRQoL is uncertain.

Conclusions and Clinical Implications

Current NICE guidelines on the management of MS recommend the use of VR for balance dysfunction and fatigue based on the study by Hebert et

al. This review extends the support for such recommendations. This review illustrates and recommends VR to be a safe and effective strategy for short-term improvements in balance in pwMS irrespective of whether or not the dysfunction is of peripheral or central origin. Based on available findings, it is recommended that a minimum of 6 weeks is required to provide significant improvements in balance. This is reflective of the American Physical Therapy Association guidelines for vestibular hypofunction outlining that VR programs should be prescribed for a minimum of 6 weeks for chronic vestibular disorders [43]. From the available evidence, recommendations can be made for implanting standardised interventions to provide balance related improvements with these improvements achieved faster with customised interventions. There is limited evidence to suggest that these short-term improvements are sustained over a long period or translate to reduced falls risk. Further high-quality studies focusing on VR prescription protocols are required to establish best practice guidelines for VR on central vestibular disorders.

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