CRITICALLY APPRAISED TOPIC

FOCUSED CLINICAL QUESTION

For a 60-year-old female patient with progressive multiple sclerosis (MS), are dynamic balance exercises in comparison to progressive strengthening exercises, able to decrease falls risk as measured by the BERG balance score?

AUTHOR

Prepared by	Whitney Huryta	**Date**	November 23, 2016
Email address	whitney_wilson@med.unc.edu		

CLINICAL SCENARIO

In the clinic, during my past rotation (at UNC CRC), I worked with several patients who had transitioned from relapsing remitting MS to progressive MS. One specific patient was having problems with falling, specifically during dynamic balance tasks such as walking on uneven ground. She was approximately 60 years old and had recently retired from her job as a researcher at the university.

This question is important to my clinical practice given that I have a passion to work with this patient population and am currently enrolled in the MS Step Up Program. Additionally, based on the current literature, 50% of patients will need help with their walking within 15 years of onset of the disease[1]. 80% of patients with MS have relapsing remitting MS, while 20% have secondary progressive[1]. Additionally, it is common for relapsing remitting MS to transition to secondary progressive MS within approximately 10-15 years[2]. Therefore, it is likely to work with this patient population as I continue in my practice as a clinician. Also, I chose the BERG balance test because it has been highly recommended for use with patients with MS[3] and it is an outcome measure that I have implemented in the clinic.

SUMMARY OF SEARCH

From the three databases that were searched, ten studies met the inclusion and exclusion criteria. This includes four systematic reviews and six randomized control trials. Evidence from three articles that were characterized as the best evidence show that:

- Different physical therapy approaches have shown to improve balance in patients with MS, including specific balance exercises, progressive resistance and aerobic training, sensory integrated balance training and neuropathic approaches
- While strength training in isolation can lead to lead to improvements in muscle strength, fatigue, quality of life, and functional capacity, it is unclear whether or not balance is improved in patients with MS
- Interventions should be salient, task-specific (ie. to balance), challenging and progressed over time to maximize improvements in balance

CLINICAL BOTTOM LINE

Current best evidence suggests that specific balance exercises, which incorporate various sensory challenges, may lead to greater improvements in balance than strength training in isolation for patients who have MS. However, evidence also suggests that there are benefits to utilizing multiple intervention approaches in improving overall quality of life and addressing other symptoms that could be limiting to a patient with MS. Therefore, physical therapists with a primary aim to improve balance for a patient with MS should prescribe specific balance exercises that are challenging and progressed over time, as well as consider the utilization of other techniques, such as progressive resistance and aerobic training, as well as other neuropathic approaches.

This critically appraised topic has been individually prepared as part of a course requirement and has been peer-reviewed by one other independent course instructor

SEARCH STRATEGY

Terms used to guide the search strategy			
Patient/Client Group	**I**ntervention (or Assessment)	**C**omparison	**O**utcome(s)
“Multiple Sclerosis” MS	Balance “balance exercise” “balance training” Rehabilitation “physical therapy” PT physiotherapy	“resistance exercise” “resistance training” “strength training” “strength exercise” strength resistance	BERG “BERG balance test” BBS “falls risk” falls

Final search strategy:

PubMed Search Strategy

1. “Multiple Sclerosis” OR MS
2. Balance OR “balance exercise” OR “balance training”
3. “physical therapy” OR “PT” OR rehabilitation OR physiotherapy
4. “resistance exercise” OR “resistance training” OR “strength training” OR “strength exercise”
5. BERG OR “BERG balance test” OR BBS
6. “falls risk” OR falls
7. #1 AND (“balance exercise” OR “balance training”)
8. #1 AND #4
9. #1 AND #2 AND #4

Databases and Sites Searched	Number of results	Limits applied, revised number of results (if applicable)
• PubMed • Cochrane • CINAHL	• 37 • 1 • 18	• Searched also for line 7 (above) to obtain articles more relevant specifically to balance (36 results) • 1 under “other”, there are 26 others under “trials” • None

INCLUSION and EXCLUSION CRITERIA

Inclusion Criteria
• Studies published in English • Studies focusing on population of patients with Multiple Sclerosis • Studies implementing an exercise program either with balance or resistance exercises • Studies including adults • Studies include a measure of balance or indicator of falls risk
Exclusion Criteria
• Levels of evidence 3-5 in the hierarchy: i.e., case studies, case series, qualitative studies, narrative review articles, expert opinion papers, dissertations

RESULTS OF SEARCH

Summary of articles retrieved that met inclusion and exclusion criteria

Author (Year)	Study quality score	Level of Evidence	Study design
Cattaneo et al. 2006[4]	PEDro 7/10	2b	RCT (pilot) study with 1 control and 2 experimental groups, measures taken pre- and post- intervention, also comparing across groups
Paltamaa et al. 2012[5]	AMSTAR 8/11	1a	Systematic Review and Meta-analysis of RCTs
Hogan and Coote 2009[6]	AMSTAR 5/11	2a	Systematic Review of RCTs and cohort studies
Kjølhede et al. 2012[7]	AMSTAR 4/11	2a	Systematic Review of RCTS and non-randomized control trials
Brændvik et al. 2015[8]	PEDro 6/10	2b	Single blinded randomized parallel group trial
Frevel and Mäurer 2015[9]	PEDro 6/10	2b	Randomized, controlled study: 2 groups (hippo therapy and e-training) with measures taken pre- and post-intervention, also comparing across groups
Cruickshank et al. 2015[10]	AMSTAR 7/11	2a	Systematic Review and meta-analysis of randomized and non-randomized controlled trials
Debolt and McCubbin 2004[11]	PEDro 6/10	2b	RCT with pre-test/post-test experimental design, comparing between control and experimental group
Gandolfi et al. 2015[12]	PEDro 7/10	1b	Single-blind, randomized, controlled trial with 1 experimental group and 1 control, measures taken before, after and at 1 month follow up to intervention
Brichetto et al. 2014[13]	PEDro 6/10	2b	RCT with 1 experimental group and 1 control group, measures taken pre- and post- intervention and comparisons made between the groups

BEST EVIDENCE

The following 3 studies were identified as the 'best' evidence and selected for critical appraisal. Reasons for selecting these studies were:

- **Gandolfi et al. 2015**[12] was chosen due to its higher relative score on the PEDro (7/10) and level of evidence (1b, higher quality RCT). Additionally, it specifically evaluates the impact of tailored balance training on typical rehabilitation (typical rehabilitation including strengthening), with use of the BBS as an outcome measure. While it does not specifically report the use of dynamic balance exercises, the study does focus on the use of balance exercises completed on varying surfaces and with perturbations, that are progressed as the patient improves. However, in comparison to other available literature, it is the closest to a direct comparison of strengthening and balance exercise on balance in patients with MS.
- **Cruickshank et al 2015**[10] was chosen as it is a systematic review and meta-analysis (level 2a evidence) of the overall impact of strength training on people with MS. It specifically, only, included articles that utilized strength training in isolation with patients with MS, in order to more fully understand how that intervention influences different symptoms (including balance). This article is more recent and includes several of the other RCTs within consideration of best evidence. Furthermore, this article scored higher on the AMSTAR than the other available reviews for evaluating impact of strength training on patients with MS.
- **Paltamaa et al. 2012**[5] was chosen because it highlights several different physical therapy interventions (specific balance exercises, aerobic and resistance exercise, whole-body vibration, group therapy and neuro-therapeutic approaches) and the impact they have on balance in patients with MS (including on the BBS). It scored higher on the AMSTAR (8/11) and is level 1a evidence with a meta-analysis of each groups' impact on balance. This article can provide information on PT interventions (specific balance exercises and resistance training) and their impact on balance in patients with MS.

SUMMARY OF BEST EVIDENCE

(1) Description and appraisal of Effects of physiotherapy interventions on balance in multiple sclerosis: A systematic review and meta-analysis of randomized controlled trials by (Paltamaa et al., 2012).

Aim/Objective of the Study/Systematic Review:
"To determine the effects of physiotherapy interventions on balance in people with multiple sclerosis (MS)."
Study Design
Systematic Review with Meta-analysis of RCTs Search Strategy: **Time period**: Beginning of each database until December 2008; also, an update search for OVID Medline and CINAHL was conducted from January 2009 until March 2011 **Databases:** OVID Medline, Cumulative Index to Nursing & Allied Health Literature (CINAHL) and Embase **Researchers:** 2 information specialists along with research authors **Key words:** Type of disease (ie. multiple sclerosis, MS, demyelinating autoimmune diseases) AND type of physical therapy intervention (ie. exercise therapy, balance, ambulation) AND type of study (ie. randomized control trial) Selection Criteria: Studies included were RCTs involving patients with MS, physical therapy interventions, and an objective measure of balance that were published in English, Finnish, Swedish, or German. Methods: **Review Process:** 2 reviewers screened all titles and abstracts to identify eligible and relevant studies. With disagreement, a 3rd reviewer was consulted. **Rating:** Articles were rated by van Tudler scale by 2 blinded and independent reviewers. Disagreements were settled with either consensus or 3rd reviewer consult. **Data Extraction:** 7/11 studies (230 participants) were accepted for meta-analyses and divided into intervention subgroups (specific balance exercises, resistance and aerobic training, whole-body vibration, group therapy and neurotherapeutic approaches). Outcome measures (excluding QOL questionnaires) were linked to ICF model factors. Statistical Analysis: Calculated pooled effect estimates for combinations of single effects of RCTs and standardized mean differences. Authors used inverse variance weighted random effects method. Controls were divided so not counted more than once. Overall effect tested with *z*-test (alpha <0.05).
Setting
1 inpatient study, and 10 outpatient studies (3 of which also included home-based therapy).
Participants
11 studies were included, which were published from 1998-2011. These studies included a total of 340 patients with MS within the intervention groups. Their mean age was 46, 68% of them were women and all participants were ambulatory with a minimal-moderate level of disability. These studies included RRMS only, progressive MS only and a combination of both types.
Intervention Investigated
Control
Control groups received either conventional therapy not aimed at improving balance, no physical therapy, supportive phone calls, or social/educational classes. Several studies were cross-over design or comparing 2

different physical therapy treatments.

Experimental

Durations of interventions ranged from 3 weeks to 20 weeks, with a mean of 9 weeks.

Sample sizes varied from 12-50, most being small (with 5 out of the 10 studies having ≤ 26 total participants).

Interventions of included studies involved:

- Specific balance exercises (ie. motor and sensory strategies)
- Resistance and aerobic training (ie. Cycling progressive resistance exercise, home-based approach for strengthening and balance, quadriceps strengthening, ACSM-based resistance program)
- Whole-body vibration (vibration with and without exercise)
- Group therapy (Awareness through movement classes)
- Neurotherapeutic approaches (ie. Neuromuscular rehabilitation with and without pressure splints, facilitation techniques, PNF, Frenkel Coordination Exercise)

Outcome Measures (Primary and Secondary)

11 outcome measures were used throughout the research articles. Specific measures included: Berg Balance Scale (BBS), Dynamic Gait Index (DGI), Dizziness Handicap Index (DHI). Activities-specific Balance Confidence (ABC Scale), Timed-up and Go (TUG), Functional Reach test (FR), Falls Efficacy Scale (FES), Timed Transfer, Time maintained on pivot board, Equiscale, Computerized balance assessment on balance (mCTSIB, COP sway, LOS), Timed 1 leg stance, Timed anterior balance and Timed equilibrium coordination tests.

Better function= higher scores on BBS, FR, ABC, mDHI, longer time for single leg balance, lower time for TUG and lower score for FES

Several **measures were most common** among the studies:

- TUG
- BBS (total of 14 items, max score: 56)
- Timed one-leg stance
- FR
- DGI (total of 8 items, max score:24)

Authors used standardized effect sizes to combine overall effects across multiple measures, as well as for each measure individually.

Main Findings

The authors utilized a pooled effect size for combinations of single effects of RCTs and standard mean differences to determine the impact of that treatment on balance outcomes. The results of their meta-analyses are presented below:

<u>Motor or sensory training versus control (no treatment):</u>

- There was a small and significant effect of inpatient training of specific motor and sensory strategies (separately) on balance using BBS, DGI, ABC and DHI when compared to controls (Effect size (ES): 0.34; 95% CI: 0.01,0.67), with the strongest effects observed for BBS
- There was no difference in treatment effects on balance measures between motor strategies compared to sensory (ES: 0.13, 95% CI: -0.35,0.62; p=0.59)

<u>Resistance and Aerobic Training versus control (no treatment):</u>

- Resistance and aerobic training versus no treatment had significant effect on FR test (ES: 0.56; 95%CI: 0.02,1.11) but not a significant overall effect (ES: 0.22, 95% CI: -0.09,0.53; p=0.17)
- Progressive resistance cycling versus home-based exercise had a significant impact on overall balance (ES:0.55; 95% CI: 0.14,0.97)
- ACSM exercise program versus ACSM exercise program and e-stim did not have significant differences on balance (ES:0.38, 95% CI: -0.39,1.16; p=0.33)

<u>Whole-body vibration Therapy:</u>

- Not included in meta-analysis, however both studies concluded that no significant differences in TUG between groups with vibration therapy versus no therapy or exercise alone.

<u>Group Therapy:</u>

- Awareness through Movement Classes versus educational sessions did not have a significant overall effect on balance (ES: 0.32, 95%CI: -0.37,1.01; p=0.11)

<u>Neuropathic Approaches:</u>

- Individualized problem solving approach (outpatient and home-based) versus no treatment yielded a positive overall effect on timed-one leg stance (ES: 0.63; 95% CI: 0.36,0.91)

- Neuromuscular rehabilitation with Johnstone pressure splints versus neuromuscular rehabilitation alone had a significant positive impact on timed-one leg stance (ES:2.23, 95% CI: 1.52,2.95)
- A facilitation (impairment) based approach versus task-oriented (disability-focused) approach did not have significant impact on the BBS (ES:0.09, 95% CI: -0.79,0.96, p=0.85)
- Hospital outpatient PT with facilitation approach versus home exercises with functional approach did not have significant impact on on-leg stance (ES: -0.14, 95% CI:-0.45,0.17; p=0.39)

Original Authors' Conclusions

There is some evidence for the use of balance exercises for patients with MS that are specific to their needs, including specific balance exercises, progressive resistance and aerobic training and neuropathic approaches. Also, there were generally no differences among comparisons between interventions, so no conclusions can be drawn as to what intervention is best for balance training in patients with MS (just that intervention is better than no intervention).

Critical Appraisal

Validity

AMSTAR 8/11: The key limitations were that grey literature was not searched, full list of excluded studies was not provided, and the likelihood of publication bias was not assessed.

In considering the AMSTAR score, the study has fairly good internal validity in answering the original question as to how physical therapy interventions affect balance in patients with MS. The authors conducted a search with a repeatable strategy, assessing quality of each of the included studies and carefully taking the quality into consideration when forming their conclusions. Another strength was in their methods of conducting their meta-analyses being appropriate in the use of a random-effects model. However, in not addressing publication bias, the authors are not able to draw conclusions about small publications with negative results that may have not been published and could impact to the conclusions that have been drawn from the systematic review. Furthermore, in not searching the grey literature, the study has not fully explored and considered all of the research that is available and this could also introduce bias in their findings. Lastly, there was not a list of the excluded studies available for the reader to access, which does not hold the authors to as much accountability and therefore impacts internal validity as well.

Furthermore, though the studies included in this review were all RCTs, they each had a high to moderate source of bias ranging from 2/11 to 6/11 on the van Tulder rating scale. Sources of bias within these studies include lack of blinding of the patient and provider, no concealment of the group allocation, no intention-to-treat analysis, and in some cases, no blinding of the outcome assessor (which is particularly concerning). Though the systematic review rated higher on the AMSTAR scale, the data that was used from the individual studies could be more impacted by bias, thus influencing the internal validity of the study (garbage in, garbage out principle).

Additionally, the authors had an error in the presentation of their findings (duplicate results plot) for the effects of progressive resistance cycling in comparison to home-based exercise on balance in patients with MS.

Interpretation of Results

When considering these modes of intervention and their clinical significance on the patients, most of the effect sizes were small to moderate. There was a moderate effect size (0.63) of the effects of an individualized problem-solving approach in both outpatient and home-based therapy versus no treatment on one-leg stance time. Also, there was a large effect size (2.23) of the use of neuromuscular rehabilitation with Johnstone Pressure Splints in comparison to neuromuscular rehabilitation alone (also on one-leg stance time). However, all other effect sizes were small, and therefore the clinical significance of each of the interventions may also be small. Many of the included RCTs also had small sample sizes, low methodological quality, low power and heterogeneity in outcomes, which could also impact the data, variation and effect sizes. Additionally, some of the insignificant results of the meta-analyses had very small effect sizes, and may not have been sufficiently powered to detect a meaningful change. More robust research is warranted in this area, with accurate power to detect clinically meaningful results.

Taking into consideration the effect sizes, reporting inaccuracies and the low to moderate quality of the included RCTs, some conclusions can still be drawn from this systematic review and meta-analysis that are relevant to clinical practice. There were some significant differences in balance measures, favouring the utilization of physical therapy interventions targeting balance in comparison to no interventions. Additionally, there were no negative effects of this training on participants. Therefore, therapists should consider the use of specific balance training, progressive aerobic and resistance training, and neuropathic approaches when working with patients who have MS. Also, as there were no significant or clinically meaningful differences between types of physical therapy interventions, it can be concluded that physical therapy interventions chosen should aim to improve balance in a salient and task-specific approach with patients who have MS.

(2) Description and appraisal of A Systematic Review and Meta-Analysis of Strength Training in Individuals with Multiple Sclerosis or Parkinson Disease by (Cruickshank et al., 2015)

Aim/Objective of the Study/Systematic Review:
To determine the impact of strength training on patients with MS or Parkinson Disease (PD).
Study Design
Systematic Review and meta-analysis of randomized and non-randomized controlled trials Search Strategy: **Time period**: Beginning of each database until July 2014 **Databases:** Physiotherapy Evidence Database, PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and CINAHL **Key words:** Population (Parkinson disease, multiple sclerosis, Alzheimer disease, amyotrophic lateral sclerosis, Huntington disease, and spinocerebellar ataxia) AND intervention (strength training, progressive strength training, resistance training, weight training, and strengthening programs) AND comparison AND outcome (strength, disease severity, gait, balance, fatigue, functional capacity, mood, and quality of life) Selection Criteria: Studies included were RCTs and non-RCTs that examined the impact of strength training (muscle exercise against external resistance) programs on patients with MS or PD. Methods: **Review Process:** Two authors acted as independent reviewers for data extraction and quality assessment. **Rating:** Articles were rated by PEDro scale by two blinded and independent reviewers. Disagreements were settled with either consensus or third reviewer consult. **Data Extraction:** Data extraction was performed using a "specialized extraction form." 15 total articles reported on a strength outcome. Statistical Analysis: • The studies were divided (into two groups) by type of disease for analyses • The only outcome examined within the meta-analysis was strength • Strength data from three articles from Dalgas et al. were from the same trial, thus were pooled together to form a single effect size • Pre- and post- strength mean values for intervention and control groups were used to form standardized effect sizes for comparison • Effect sizes were corrected by using a method by Hedges and Olkin (1985) to account for the magnitude sample sizes • Egger Regression test was used to determine publication bias ($p \leq 0.10$)
Setting
For the purposes of answering the proposed PICO question, only information from trials involving MS (seven total) will be reported for the remainder of the article description. Reported settings for the trials involving patients with MS include: rehabilitation centre, community gym, health facility, and home-based care. Three of the trials did not report a location.
Participants
Seven studies involving patients with MS were included (five RCTs and two non-RCTs), which were published from 2009-2014. These studies included a total of 151 patients with MS within the intervention groups. Their mean age was approximately 51 and EDSS scores ranged from 1.0 to 6.5 (mild-moderate disability). These studies included RRMS only and a combination of RRMS and progressive MS. Three studies did not report which

type of MS the participants had. Gender distribution was not reported and duration of illness was classified as early to middle stages of disease. Participant retention for MS trials ranged from 73.3% to 100%. Participant adherence was reported in four of the trials, all being >90% for participants within the experimental groups.

Intervention Investigated

Control

Sample sizes varied from 7 to 37 participants in the control group.

Interventions included:

- "standard care"
- Endurance exercise
- Normal living habits

No other information about the control groups was listed.

Experimental

Durations of interventions ranged from three weeks to six months (20 weeks), of two to five sessions of supervised training weekly.

Sample sizes varied from 7 to 39 participants in the experimental group

Interventions included:

- Lower body strength training on machines including single joint and multi joint exercises (knee-extension (bilateral, concentric, eccentric), leg press, knee flexion, hip flexion, hip extension, calf raises, reverse leg press, leg curl)
- Upper body, lower body and core strength training (chest press, seated row, shoulder abduction, sit to stand, lunges, hip abduction, step ups, tandem stance)
- Weighted vest
- Home-based resistance training (chair raises, forward lunges, step-ups, heel and toe raise, leg curls)

Intensity ranged from: 2-4 sets of 8-15 repetitions of each exercise

Outcome Measures (Primary and Secondary)

The study focused on many outcomes, however only specific details of balance measures will be reviewed as that is the focus of the PICO question.

Strength outcome measures:

- MVIC (maximum voluntary isometric contractions)
- Maximum voluntary dynamic contraction
- 1 repetition maximum strength protocols with pneumatic resistance machines
- Dynamometers
- Leg Extensor Power Rig

*Strength outcomes were the only ones evaluated in meta-analysis: pre- and post- strength mean values were used to form standardized effect sizes for comparison

Functional mobility outcome measures:

- 2-minute walk test
- 10-meter walk test
- Timed 25-foot walk
- Timed Up and Go (TUG)

Balance outcome measures:

- Functional Reach Test: the patient reaches as far forward as possible without taking a step and the location of the 3rd metacarpal is recorded; in community dwelling elderly, a score of less than 7 inches indicated limitations in mobility[14]
- Four Square Step Test: the patient is instructed to step through a sequence of 4 squares (created with 4 canes in the shape of a cross) in a clockwise and then counter clockwise direction as fast as possible without touching the canes; in older adults a time of greater than 15 seconds indicated a risk of falling[15]
- Accusway^{PLUS} Force platform: can be used to measure center of pressure, average velocity and sway area

Functional capacity measures:

- 1/4 [chair stand test$_{post}$/chair stand test$_{pre}$]+[stair climb test$_{post}$/stair climb test$_{pre}$]+[10meter walk test$_{post}$ /10 meter walk test$_{pre}$]+[6 minute walk test$_{post}$ /6 minute walk test$_{pre}$]x100)

Quality of life outcome measures:

- Short Form-36
- World Health Organization Quality of Life-BREF

Fatigue outcome measures:

- Modified Fatigue Scale
- Fatigue Severity Scale
- Multidimensional Fatigue Inventory

Mood outcome measures:

- Major Depression Inventory
- Beck Depression Inventory

Main Findings

Functional Mobility: Two RCTs and one non-RCT found no reported differences in functional mobility (2 minute-walk test, 10 meter walk test, timed 25 foot walk test, an TUG) after strength training.

Balance: One RCT study reported an improvement in balance (Functional Reach Test), while two non-RCTs did not find significant improvements in balance (Functional Reach Test, Four Square Step Test, and Accusway^{PLUS} force platform) after strength training.

Functional capacity: One RCT reported an improvement in functional capacity (computation listed in outcomes above) after strength training.

Quality of life: Two RCTs reported an improvement in QOL (Short Form-36, World Health Organisation Quality of Life-BREF) and one non-RCT did not find an improvement in QOL (Short Form-36) after strength training.

Electromyography Activity: Two RCTs found improvements in activity of specific and trained muscle groups after strength training.

Skeletal muscle volume and architecture: One RCT found a significant increase in cross sectional area of type 2 and 2a muscle fibres after strength training.

Fatigue: Two RCTs and One non-RCT reported improvements in fatigue (10-24% improvement in fatigue) after strength training.

Mood: One RCT found a significant improvement in mood (Major Depression Inventory, -2.4 points) and one non-RCT found no difference in mood (Beck Depression Inventory) after strength training.

Muscle endurance: One RCT found improvement and one RCT did not find improvements in muscle endurance after strength training.

Strength: Meta-analysis revealed that strength training leads to a significant improvement in strength (d=0.31; CI: 0.15, 0.48) in patients with MS.

Original Authors' Conclusions

Strength training can lead to improvements in muscle strength, fatigue, quality of life, muscle power, electromyography activity, and functional capacity for patients with MS. The impact of strength training on balance, functional mobility and mood in patients with MS is unclear.

Critical Appraisal

Validity

AMSTAR 7/11: The key limitations were that there was no supplemental search performed, grey literature was not searched, full list of excluded studies was not provided, and conflict of interest was not included.

In considering the AMSTAR score, there was moderate internal validity in the author's ability to answer their question as to how strength training influences patients with MS. The study had several strengths, including that the authors established criteria before reviewing the evidence, had duplicate selection and extraction of data, provided detailed tables of the characteristics of the included studies, and appropriately addressed the quality of the studies that were included. It was particularly good that the authors chose evidence that evaluated the impact of strength training in isolation, as to avoid confounding their data with additional interventions. However, in not performing a supplemental search or including grey literature, the authors did not fully consider all available data and may have missed evidence that should have been included in the analysis. Furthermore, without listing excluded studies for the readers to review, there is no accountability and this influences internal validity as well.

Additionally, the authors left out several details that could have affected their conclusions. Firstly, a more thorough explanation of the control interventions would have been helpful, for example "standard care" can be interpreted differently amongst therapists and research studies. Furthermore, the authors did not include statistical values in their findings that could have been helpful when assessing conflicting results amongst the included studies.

Furthermore, though the studies included in this review were mostly RCTs with several non-RCTs, they each had a high to moderate source of bias ranging from 4/10 to 8/10 on the PEDro rating scale. Sources of bias within these studies include lack of blinding of the patient and provider, no concealment of the group allocation, and no blinding of the outcome assessor (which is particularly concerning). Also, as randomization aims to minimize bias in group composition and distribution (accounting for any characteristic that the individual may have that could influence the outcome), those studies that were not randomized are at a higher risk of bias. Furthermore, the studies did not sufficiently report on progression and supervision of the strength training, which could impact patient outcomes. Though the systematic review rated moderately on the AMSTAR scale, the data that was included and used in the assessment (from the individual studies) is confounded by bias, thus influencing the internal validity of the study.

Interpretation of Results

The authors found that strength training, in isolation from other interventions, mainly leads to improvements in strength. However, this meta-analysis yielded a small effect size (0.31), meaning there is only a minor effect of the intervention on strength. Also, the confidence interval of this effect ranges from a small effect to a moderate one (0.15, 0.48), meaning that there is variability within the data, which impacts the precision of the point estimate. This also brings into question the clinical significance of the use of strength training on improving strength in patients with MS.

While there was little data and too much heterogeneity within the included studies to perform additional meta-analyses on other outcomes, strength training may have other benefits for patients with MS including a positive impact on functional capacity, power, quality of life, and fatigue. It is also important to note that there is inconsistency within the evidence in regards to the impact of strength training on balance. Therefore, strength training should be considered as a part of the intervention plan for patients with MS, however should not be performed in isolation from other interventions or treatment options. Furthermore, if improving balance is a main objective, other interventions may prove to be more beneficial and the therapist needs to prioritize the session accordingly.

Additionally, many of the studies that were included have small sample sizes (more than half of the studies had less than 20 participants in the experimental groups), which can lead to high variation and low statistical power to detect differences between the groups. Therefore, more research is needed with greater sample sizes, and more robust experimental designs in order to determine if strength training could impact other areas of function for patients with MS.

(3) Description and appraisal of Sensory integration balance training in patients with multiple sclerosis: A randomized, controlled trial (Gandolfi et al., 2015)

Aim/Objective of the Study/Systematic Review:

To determine the impact of sensory integration balance training in comparison to conventional balance rehabilitation for patients who have MS (specifically evaluating balance, confidence, QOL, fatigue, falls, and sensory integration).

Study Design

Single-blind, randomized, controlled trial with 1 experimental group (sensory integration balance training) and 1 control group

Blinding: There was a single examiner, blinded to group assignment.

Outcome Measures: Measures were taken before, after and at 1-month follow-up to intervention.

- Primary: Berg Balance Scale (BBS)
- Secondary: Activities-specific Balance Confidence Scale (ABC), Sensory Organization Balance Test (SOT), Multiple Sclerosis Quality of Life-54 (MSQL-54), Fatigue Severity Scale (FSS), number of falls

Randomization: Computer generated random number tables were used to assign patients to treatment groups by a blinded physician, with 2 strata of EDSS scores ($\leq$3.5 or >3.5).

Statistics:

- A priori power: 20 patients per group provides 90% power to detect a 3-point difference in BBS; authors expected high dropout rates so they recruited 2x participants (total n=80)
- Intention-to-treat analysis used
- Last-observation carried forward method for missing data
- Descriptive statistics: mean, median, standard deviation, confidence intervals

- ANOVA used for pre- and post-treatment scores for all outcome measures with Bonferroni adjustments ($p<0.025$)
- ANCOVA used to adjust for pre-treatment scores, age, EDSS, and disease duration

Setting

Treatments were carried out at the Neurological Rehabilitation Unit (AOUI Verona).

Participants

Time period: March 2010 to December 2011

Convenience Sampling: Consecutive outpatients with RRMS referred to local MS Centre of Clinical Neurology Unit

Eligibility criteria included: ≤ 65 years old, EDSS of 1.5-6.0, MMSE ≥ 24, balance impairments, no recent relapses, no vertigo, no recent therapy for balance, no other confounding conditions

Demographics: No significant differences between groups at time 0 in respect to demographics or baseline outcome measures.

- Control group: Mean age-49.56 years; Male to Female ratio- 10/31; Median EDSS: 3.66; Mean disease duration: 15.24 years
- Experimental group: Mean age-47.21 years; Male to Female ratio- 11/28; Median EDSS: 3.00; Mean disease duration: 12.25 years

Sample Size: 80 total patients (experimental group: 39 (7 withdrew, so 32 completed study); control group: 41 (5 withdrew, so 36 completed study)). Patients who withdrew were due to medical reasons or difficulty arranging transportation.

Intervention Investigated

Control

Treatment procedures: 1 physical therapist per treatment group carried out the sessions. Sessions were individualized with progression of complexity as appropriate, 50-minutes long, and occurred 3 days/week, for a total of 5 weeks.

Patients in control group completed:

- Passive and active lower extremity joint mobilizations: internal/external hip mobilization, active/passive straight leg raise, flexion/extension knee and ankle mobilization
- Stretching: prone active and passive hip extensions, hamstring stretch against the wall or assisted, seated calf stretch with towel, runner's gastrocnemius stretch
- Strengthening exercises with resistance bands or cycling

Experimental

Sensory integration balance training with graded exercises with 3 levels of difficulty, under 3 different sensory conditions (normal vision, blindfolded, visual-conflict dome).

The three levels were:

1. Firm surface, external COM destabilization
2. Firm surface, self-destabilization of COM
3. Compliant surfaces, self- and external COM destabilization

During each session: 3 level-1-exercises, 3 level-2-exercises, and 4 level-3-exercises were repeated 2-5x for 5 minutes.

Outcome Measures (Primary and Secondary)

A single examiner, blinded to group assignment carried out outcomes at the Neurological Rehabilitation Unit

Primary:

- Berg Balance Scale (BBS): 14 items total (static and dynamic balance tasks), score range 0-56, with higher scores indicating better performance of balance

Secondary:

- Activities-specific Balance Confidence Scale (ABC): self-report measure of confidence in balance while performing ADLs, 0-100 points per activity, with greater points indicating greater confidence
- Sensory Organization Balance Test (SOT): tests influence of sensory interactions on balance, balance maintained on compliant and non-compliant surfaces, 3 visual conditions (normal, blindfolded, dome),

measuring postural reactions during 5, 30-second trials. Scores range from 0-150, with a higher score indicating better performance

- Multiple Sclerosis Quality of Life-54 (MSQL-54):54 item self-report measure with 12 subscales of QOL (generic and MS-specific). The score ranges from 0-100, with higher scores indicating better performance
- Fatigue Severity Scale (FSS):9-item self-report measure of fatigue with range from 1-7, higher scores indicating worse performance
- Number of falls: Unexpected event with landing on lower surface, unplanned

Main Findings

Time Zero: No significant differences in clinical or demographic data

Berg Balance Scale:

- There was a significant interaction effect (of time X group) at T1 ($p<0.001$; 95%CI:2.83, 7.15) and T2 ($p<0.001$; 95%CI: 2.50, 6.69), with greater improvements in the sensory-integrated balance group (Mean between group difference at T1: 4.99, T2: 4.60)
- Furthermore, there were significant main effects of time and group ($p<0.001$, $p=0.001$)

Secondary outcomes:

- Significant time X group interaction for **FSS** ($p=0.002$; 95%CI for T1: -1.46, -0.03; 95%CI for T2: -1.95, -0.53), **number of falls** ($p=0.002$, 95%CI for T1: -0.452, -0.08; 95% CI for T2: -0.385, 0.003) and **SOT** (EO firm surface, T1: $p=0.04$, 95%CI: -9.90, 16.66; EC firm surface, T1: $p=0.001$, 95%CI:5.36, 31.86; Dome firm surface, T1: $p=0.002$, 95% CI: -4.75, 22.87; EO compliant surface, T1: $p<0.001$; 95%CI: 3.35, 30.56; EC compliant surface, T1" $p<0.001$, 95% CI: 0.35, 24.85; Dome compliant surface, T1: $p<0.001$, 95% CI:3.44, 29.61)
- On average, there were greater improvements in sensory-integrated balance group
- No significant time X group interaction for **ABC** ($p=0.31$, 95% CI at T1: 0.72, 17.22 and at T2: 0.72, 16.14), **MSQOL-54** ($p=0.48$, 95% CI at T1: 1.44, 10.40 and at T2: -1.12, 9.92)

Original Authors' Conclusions

Integrated sensory balance training may yield more improvements (fewer falls, decreased fatigue, and better central integration processing) in balance than conventional rehabilitation, which can be maintained for at least 1-month post-treatment.

Critical Appraisal

Validity

Pedro Score (7/10): The key limitations were that the subjects and therapists were not blinded and there was not adequate follow-up.

The study's internal validity was impacted by the lack of blinding of the subjects and therapists, as this could have introduced bias into their results. Furthermore, as there was only follow-up for 1 month after the intervention was carried out, long-term implications of the author's findings cannot be drawn.

Also, the authors reported that detecting a significant difference of 3 points on the BBS was clinically meaningful. While there is no set minimally clinically important difference (MCID) for the BBS, the minimal detectable change (MDC) ranges from 3.3 to 6.3 points for adults[16], is reported as 5 points for patients with Parkinson Disease[17], and is reported as 8 points for institutionalized older adults[18]. Therefore, 3 points may be too low of a threshold to choose for a clinically meaningful difference, with a range from 6 to 8 points-difference being more realistic.

Another consideration for this study would be the appropriateness of the control group. The authors report that stretching, joint mobilization and strengthening compose a conventional balance rehabilitation program. While these components may be part of a conventional program, there were no interventions aimed at improving balance specifically within the control treatment protocol. This impacts internal validity, in how well the authors are able to answer their question (if there is a difference in outcomes for the use of sensory integrated balance training and conventional balance training in patients with MS).

Additionally, the average BBS for the groups at baseline was relatively higher (~47/56), which could impact how much room for change these patients had. On the other hand, it may be considered a benefit of the study that a difference could be detected in patients who have less disability and balance impairment, as MS has been shown to impact balance at an early stage in the disease process[19].

Though there were limitations to this study, overall the study had good internal validity and is applicable to practice. Several strengths of this paper include, a large sample of participants (strong power to detect a difference between the groups), and a relatively low drop-out rate (15%). Also, the authors utilized multiple balance measures that are commonly used with patients who have MS[3], and an experimental intervention protocol that would be easy to incorporate into practice. Furthermore, the study exhibited good methodological quality overall with blinding of the examiner, randomization of participants, specific eligibility criteria, concealed allocation, and effective reporting of outcomes and findings within their paper.

Interpretation of Results

The results of this study indicate that sensory-integrated balance training may improve outcomes in balance for patients who have relapsing remitting MS, including in regards to the BBS, SOT, and FSS. This difference, though significant, may not be clinically meaningful for all outcome measures presented (ie. 3 points on BBS) and has only been demonstrated to last for 1-month post completion of the intervention. Additionally, there are wide confidence intervals for the mean of the between-group difference both after the intervention is completed and at the 1-month follow-up for the BBS. This indicates that there is moderate to high variability and less precision for the mean estimate.

While this study has the aforementioned limitations and lower precision, the results of their RCT can be applied to practice. Many patients with MS experience balance deficits, even early on in the disease process[19], and this study shows that specific balance exercises can significantly improve outcomes, greater than the use of strengthening, stretching and joint mobilization interventions. This study also emphasizes the importance of progression in challenge of the balance interventions in maximizing the improvement seen. Furthermore, the interventions and outcome measures used within this study are feasible for clinical use and did not yield any adverse reactions.

EVIDENCE SYNTHESIS AND IMPLICATIONS

Findings and implications on clinical intervention

The evidence presented above provides insight in considering the original question, whether balance exercises or strength training would be a better intervention in improving balance, as measured by the BBS in a female patient with progressive MS. Several interventions have proven successful in improving balance in patients with MS including sensory integrated balance training[12], progressive aerobic and resistance training and neuropathic approaches[5]. In regards to showing improvement on the BBS specifically, sensory integrated balance training, has demonstrated the ability to yield improvements in the BBS[12]. That being said, meta-analysis of some of these interventions elude that one intervention (specific balance training, resistance and aerobic exercise training or neuropathic approaches) has not been proven better than another in enhancing balance for patients with MS[5].

However, most of the studies evaluating the impact of strength or resistance training on balance include other interventions along with strength training, which confound the results of the study[20,21]. In a systematic review, the impact of strength training in isolation was evaluated[10]. The authors resolved that strength training alone is inconclusive in its impact on balance[10]. Consequently, it could be concluded that strength training should not be used in isolation for the primary goal of improving balance.

Therefore, as a clinician, salient and task-specific interventions should be utilized to create an individualized plan for each patient. For a patient with MS, whose primary goal involves improving balance, a combination of multiple interventions can be successful, including sensory-integrated balance training, specific balance tasks, as well as, progressive aerobic and resistance training and other neuropathic approaches. Though use of multiple techniques can be successful, evidence suggests that emphasis should be placed on task-specific interventions with prioritization of balance training.

Quality of research included and implications for future research

As evidenced by the articles above, there were no studies specifically focused on the impact of dynamic balance interventions in direct comparison to progressive strengthening exercises in patients with MS, with measures of balance as the outcome. Therefore, the evidence that is being utilized to answer this clinical question is being applied outside of the original context of the studies, which must be done with caution. In this way, quality research specifically designed to compare interventions (in isolation) and their impact on balance outcomes is needed, in the future, to guide clinical decisions on how to best improve balance outcomes for patients with MS.

Additionally, this research was influenced by bias, which also impacts clinical decision making. Overall, this evidence includes a variation of level 1 and 2 evidence, with a range of quality. The RCTs evaluating the impact of tailored balance exercises[13] and sensory integrated balance training[4,12] on patients with MS were limited by blinding of subjects[12,13], blinding of therapists[4,12,13], and follow-up[12,13]. Blinding subjects and therapists in performing physical intervention-based research is a challenge, and may not be entirely possible. However, adequate follow-up should be a goal of every research study, as sufficient follow up is required to determining the long-term impact and implications of the interventions. The RCTs that evaluated the impact of resistance training on mobility, including indicators of balance and falls risk within their outcomes[8,11], were also influenced by bias. The main focus of these studies was not to examine balance and these studies also presented with limitations in blinding of subjects and assessors[8,11], blinding of therapists[11] and concealed allocation[8]. A lack of blinding of assessors is particularly concerning and future research should ensure adequate blinding of assessors to decrease bias. Additionally, several of the studies are limited in sample size, and have wide confidence intervals, thus impacting the precision of the parameter estimates in the study[12,13]. Research moving forward needs to be adequately powered to detect a difference in the outcome that is being measured, which can also be difficult in studies focused on a specific patient population without much funding. As in the study by Gandolfi et al., control groups often are deemed as a conventional treatment group for improving a specific trait (such as balance), but they do not include any interventions specific to that trait. Therefore, it is also important to ensure that the control treatments are adequate as a comparison group in future research.

The systematic reviews that were utilized were also subject to bias, including a lack of supplemental or grey literature search, without a list of excluded studies, and did not include conflict of interest[5,10]. In the future, systematic reviews should include these elements to ensure all available data is fully considered and there is full accountability to the authors for selection of included studies. Additionally, at least one of the systematic reviews included results from non-randomized studies. This data was, at times, conflicting with results of other (randomized) control trials. As randomization aims to reduce bias, it may be beneficial to only include RCTs in the reviews moving forward or at least address the conflicting results more thoroughly.

Overall, the research considered in this CAT demonstrates that there is a high need for further research in this area (comparison of individual interventions on balance in patients with MS) with robust randomized control trials that are adequately powered to detect a meaningful clinical difference in standardized balance measures. It would be ideal if studies could minimize heterogeneity in their data, for instance by utilizing the same set of outcome measures to improve comparability and by improving methodological quality to decrease bias within the studies (ie. blinding of assessors, adequate follow up, sufficient control groups).

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