
M SBEST

MULTIPLE SCLEROSIS BEST EVIDENCE-BASED STRATEGIES
AND TREATMENT/THERAPIES FOR REHABILITATION

Spasticity: Non-pharmacological Rehabilitation Interventions

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Key Points

- Group exercise training targeting flexibility, strength, and balance may improve spasticity in persons with MS.
- Locomotor training using body weight supported treadmill training may reduce lower extremity spasticity in persons with secondary progressive MS.
- It is unclear if unloaded leg cycling alone improves clinical measures of spasticity in persons with MS; however, it may have a positive impact on subjective measures of spasticity.
- Unloaded leg cycling may improve spasticity in combination with pharmacological management.
- Participation in recreational sports activities such as sports climbing or yoga may not reduce spasticity in persons with MS.
- Hydrotherapy may improve subjective measures of spasticity more than land-based exercise in persons with MS.
- Cryotherapy may not reduce clinical measures of spasticity in persons with MS; however, cryotherapy may have a positive impact on subjective measures of spasticity.
- Repetitive transcranial and trans-spinal magnetic stimulation may reduce spasticity in persons with MS.
- Intermittent theta-burst stimulation may be an effective intervention to reduce spasticity in persons with relapsing-remitting MS.
- Transcranial direct current stimulation may not improve spasticity in persons with relapsing-remitting MS.

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- Transcutaneous electrical nerve stimulation may not reduce spasticity in persons with MS.
- Subcutaneous nerve stimulation (SCNS) may reduce spasticity in persons with MS. SCNS does not seem to be harmful and may temporarily reduce clonus at the ankle.
- Spinal cord stimulation may be a beneficial modality for treating spasticity in persons with MS.
- Hip flexion assist orthoses may not be an effective intervention to reduce lower limb spasticity in persons with MS. There is no evidence related to the utility of other types of orthoses for reducing spasticity in persons with MS.
- Radial shock wave therapy may be effective for reducing spasticity in persons with MS.
- Reflexology may reduce spasticity in persons with MS.
- Acupuncture may reduce spasticity in ambulatory persons with MS.
- It is unclear if massage therapy improves spasticity in the lower extremities of persons with MS.
- Intermittent theta-burst stimulation, in combination with exercise therapy, may reduce spasticity in persons with relapsing-remitting MS.
- Combining massage therapy with exercise therapy may not reduce spasticity in persons with MS more than either therapy alone.
- The use of supported standing may not improve spasticity more than a home exercise program in persons with secondary progressive MS.
- Whole body vibration, in combination with exercise, may not reduce clinical measures of spasticity in persons with MS; however, it may have a positive impact on subjective measures of spasticity.

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- Functional electrical stimulation-supported lower extremity cycling may reduce spasticity immediately following treatment in persons with chronic progressive MS.
- Multidisciplinary inpatient rehabilitation may not improve subjective measures of spasticity in clinically stable persons with MS.
- Both orthopedic surgical and neurosurgical interventions may be effective for reducing severe spasticity in persons with MS.
- Transcutaneous electrical nerve stimulation may reduce lower extremity spasticity in persons with MS to a greater degree than oral baclofen.
- Oral baclofen in combination with a stretching program may reduce spasticity more than placebo in persons with MS, but may not be more effective than baclofen alone.
- A combination of oral dantrolene sodium and physical therapy interventions following surgical management of contractures may improve spasticity in persons with severe MS.
- Botulinum toxin, when followed by early physiotherapy, may provide greater reduction in spasticity than botulinum toxin alone in persons with secondary progressive MS.
- Segmental muscle vibration, or a combination of segmental muscle vibration with botulinum toxin, may provide greater reduction in spasticity in persons with secondary progressive MS compared to botulinum toxin alone.

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Abbreviations

AI	Ambulation Index
AS	Ashworth Scale
AT	Ambient Temperature
CAM	Complementary and Alternative Medicine
CS	Clonus Score
EDSS	Expanded Disability Status Scale
EMG	Electromyography
ET	Exercise Therapy
FES	Functional Electrical Stimulation
GSS	Global Spasticity Scale
HFAO	Hip Flexion Assist Orthosis
iTBS	Intermittent Theta-Burst Stimulation
MAS	Modified Ashworth Scale
MDT	Microsurgical Dorsal Root Entry Zone (DREZ)-otomy
MS	Multiple Sclerosis
MSSS-88	Multiple Sclerosis Spasticity Scale
PCT	Prospective Controlled Trial
PEdRo	Physiotherapy Evidence Database
PEMG	Polyelectromyography
PPMS	Primary Progressive Multiple Sclerosis
PRMS	Progressive Relapsing Multiple Sclerosis
PSFS	Penn Spasm Frequency Scale
PSS	Penn Spasm Scale
PwMS	Persons with Multiple Sclerosis
RCT	Randomized Controlled Trial
RRMS	Relapsing-Remitting Multiple Sclerosis
RSWT	Radial Shock Wave Therapy
rTMS	Repetitive Transcranial Magnetic Stimulation
SCNS	Subcutaneous Nerve Stimulation
SCS	Spinal Cord Stimulation
SPMS	Secondary Progressive Multiple Sclerosis
SPR	Selective Posterior Rhizotomy
TBS	Theta-Burst Stimulation
tDCS	Transcranial Direct Current Stimulation
TENS	Transcutaneous Electrical Nerve Stimulation
VAS	Visual Analog Scale

Spasticity:

Non-pharmacological Rehabilitation Interventions

1.0 Introduction

Individuals with multiple sclerosis (MS) experience a variety of impairments depending on the location and extent of the lesions and neural damage from the disease. Spasticity is frequently reported as one of the most disruptive symptoms, and in some, may lead to impaired mobility affecting transfers and ambulation, and can impact activities of daily living and social participation. Spasticity has also been reported to significantly decrease quality of life and may even be considered a health issue (Arroyo, Massana, & Vila, 2013; Flachenecker, Henze, & Zettl, 2014; Svensson, Borg, & Nilsson, 2014). Spasticity often leads to a decrease in range of motion, pain or discomfort, and poor positioning, with secondary effects on health and hygiene.

Spasticity is traditionally challenging to define. The Lance definition of spasticity (1980) is a well-accepted one: "...a motor disorder characterized by a velocity dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflexes, as one component of the upper motoneuron syndrome" (Lance, 1980). However, the word "spasticity" clinically often refers to the *spasticity syndrome*, which is far more complicated. The spasticity syndrome includes hyperactive tendon reflexes, clonus, and spasms (Katz, Rovai, Brait, & Rymer, 1992; O'Dwyer, Ada, & Neilson, 1996). The National Institutes of Health Task Force definition (Sanger et al., 2003) attempts to further define spasticity as a type of hypertonia in which one or both of the following signs are present: 1) resistance increases with externally imposed movement and with increasing speed of stretch, and varies with the direction of joint movement, and/or 2) there is a threshold speed or joint angle above which the resistance to externally imposed movement rises rapidly. Thus, it is critical that when communicating about or reading literature related to spasticity, one is clear about how it is being defined.

A variety of approaches exist to help manage spasticity in persons with MS (PwMS). These include pharmacological as well as non-pharmacological approaches. Pharmacological treatments include medications that act within the nervous system (e.g., baclofen), at the neuromuscular junction (e.g., botulinum toxin), or directly on skeletal muscle (e.g., dantrolene). Non-pharmacological rehabilitation approaches, such as physical or occupational therapy, may utilize any combination of prolonged stretching and range of motion exercises, casting/splinting, and electrical stimulation to help minimize the detrimental effects of spasticity. Exercise may include weight bearing (e.g., locomotor training) or non-weight bearing (e.g., cycling) activities. Alternative approaches can include acupuncture and massage. Often, treatment for spasticity will be some combination of pharmacological and non-pharmacological approaches and requires a team-based approach for effective management. Surgical approaches may be utilized for sub-optimal response to these pharmacological and non-pharmacological approaches.

This module provides an overview of the available evidence for non-pharmacological interventions for spasticity rehabilitation in PwMS.

2.0 Non-pharmacological Interventions

2.1 Exercise

Various types of exercise can yield benefits for reduction of spasticity. Exercise modalities include interventions targeting flexibility, range of motion, strengthening and balance exercises, progressive resistance training, leg cycling, and body weight supported treadmill training. A few studies have investigated the effects of different types of exercise-programming on spasticity in PwMS.

2.1.1 Group Exercise Training

Group exercise training can be one mechanism to accomplish exercise interventions, whereby individuals participate in a training program together with other individuals.

Table 1. Studies Examining Group Exercise Training for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
<p>Tarakci et al. 2013</p> <p><i>Group exercise training for balance, functional status, spasticity, fatigue and quality of life in multiple sclerosis: a randomized controlled trial</i></p> <p>Turkey RCT PEDro=8 N_{Initial}=110, N_{Final}=99</p>	<p>Population: <i>Exercise group (n=51):</i> Mean age=41.49yr; Gender: females=34, males=17; Disease course: RRMS=32, PPMS=10, SPMS=9; Mean EDSS=4.38; Mean disease duration=9.0yr. <i>Control group (n=48):</i> Mean age=39.65yr; Gender: females=30, males=18; Disease course: RRMS=33, PPMS=8, SPMS=7; Mean EDSS=4.21; Mean disease duration=8.42yr.</p> <p>Intervention: Participants were randomized to a group exercise or control group (no intervention). The exercise group performed a variety of exercises targeting flexibility, range of motion, lower extremity strength, core stabilization, balance and coordination, and functional activities. Exercise sessions were 60min long and were performed 3x/wk for 12wks. Outcomes were assessed at baseline and after treatment.</p> <p>Outcomes/Outcome Measures: Modified Ashworth Scale (MAS).</p>	<ol style="list-style-type: none"> 1. The exercise group had significant improvement in all MAS measures post intervention (p<0.01). 2. The exercise group had significantly greater improvements in spasticity compared to the control group on all MAS measures: right hip flexors MAS (p<0.001), left hip flexor MAS (p=0.015), right hamstring MAS (p<0.001), left hamstring MAS (p<0.001), right Achilles MAS (p=0.014), left Achilles MAS (p<0.001).

Discussion

Tarakci et al. (2013) evaluated 99 MS participants who were ambulatory with or without an assistive device (Expanded Disability Status Scale (EDSS) 2.0-6.5) and randomized them to either a group exercise training program or a control group (no intervention) and evaluated lower extremity spasticity as a secondary outcome measure, using the Modified Ashworth Scale (MAS). The exercise intervention, 60 minutes three times per week for 12 weeks, was performed in a group setting led by a physical therapist with a variety of exercises targeting flexibility, strengthening, balance, coordination, and functional

activities. The intervention group showed statistically significant ($p<0.01$) improvements in all MAS measures compared to the control group.

Conclusion

There is level 1b evidence (from one randomized controlled trial; Tarakci et al. 2013) that a group exercise training program targeting lower extremity flexibility, strength, and balance may improve spasticity compared to no intervention in persons with MS.

Group exercise training targeting flexibility, strength, and balance may improve spasticity in persons with MS.

2.1.2 Locomotor Training

Locomotor training involves specific walking training either over-ground or using a treadmill system, with or without body weight support, to help address components of an individual's walking ability, including underlying impairments (e.g., spasticity), balance, endurance, as well as adapting to real-life contexts.

Table 2. Studies Examining Locomotor Training Exercise for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Giesser et al. 2007 <i>Locomotor training using body weight support on a treadmill improves mobility in persons with multiple sclerosis: a pilot study</i> USA Pre-Post N _{Initial} =4, N _{Final} =4	Population: Mean age=47yr; Gender: males=1, females=3; Disease course: SPMS; Mean EDSS=7.25; Mean disease duration=20yr. Intervention: Participants underwent locomotor training using body weight support on a treadmill. Subjects received 1hr sessions 2x/wk for a total of 39-42 sessions. Outcomes/Outcome Measures: Modified Ashworth Scale (MAS).	<ol style="list-style-type: none"> Three participants showed decreased lower limb muscle tone post intervention as evidenced by MAS score improvements. Results of statistical analyses were not reported.

Discussion

Giesser et al. (2007) evaluated the impact of locomotor training using body weight support on a treadmill on the functional mobility of four participants with secondary progressive MS (SPMS), and measured spasticity as a secondary outcome. This study involved participants with an average EDSS score of 7.25 and primarily spinal cord presentations of their MS. All four participants completed an average of 40

sessions (2 times per week for 20 weeks), consisting of 60 minutes of weight bearing with 20 minutes of stepping activity. Following intervention, three of the four participants demonstrated a reduction in their spasticity as measured by MAS scores.

Conclusion

There is level 4 evidence (from one pre-post study; Giesser et al. 2007) that locomotor training using body weight supported treadmill training may improve spasticity in persons with secondary progressive MS.

Locomotor training using body weight supported treadmill training may reduce lower extremity spasticity in persons with secondary progressive MS.

2.1.3 Unloaded Cycling

Cycling, as a therapeutic intervention, is believed to modulate spasticity via the influence of pre-synaptic mechanisms leading to a decrease in excitation of excitatory neurotransmitter release resulting in diminished activation (Frigon, Collins, & Zehr, 2004; Grey et al., 2008).

Table 3. Studies Examining Unloaded Cycling Exercise for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Sosnoff et al. 2010 <i>Effect of acute unloaded arm versus leg cycling exercise on the soleus H-reflex in adults with multiple sclerosis</i> USA PCT N _{Initial} =10, N _{Final} =10	Population: Mean age=33.2yr; Gender: males=3, females=7; Disease course: RRMS; Mean EDSS=1.85; Mean disease duration=8.7yr. Intervention: Patients received 20min of either unloaded arm exercise, unloaded leg cycling exercise, or the control condition (quiet sitting). Outcomes were assessed pre-condition, and 10 and 30min post condition. Outcomes/Outcome Measures: H-reflex; Modified Ashworth Scale (MAS).	<ol style="list-style-type: none"> For the mean scores of the H-reflex, results showed a significant condition*time interaction effect ($p<0.001$). There was a small, significant effect after unloaded arm cycling, and a moderate, significant effect after unloaded leg cycling, on the H_{max}/M_{max} ratio. The control condition was not significantly associated with a change in the H_{max}/M_{max} ratio, and the effect was minimal. For the mean scores of MAS, a statistically significant condition* time interaction was found ($p<0.001$). Post-hoc analyses indicated a moderate-large, significant effect after unloaded arm cycling, and a large, significant effect after unloaded leg cycling. The effect of the control condition on MAS scores was non-significant and small.
Sosnoff et al. 2009	Population: Exercise condition ($n=12$): Mean age=45.6yr; Gender: unspecified; Mean EDSS=3.5; Mean disease duration=8.6yr.	<ol style="list-style-type: none"> A statistically significant interaction effect was found for condition*time for the H_{max}/M_{max} ratio, indicating that there

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
<p><i>Effect of a 4-week period of unloaded leg cycling exercise on spasticity in multiple sclerosis</i></p> <p>USA PCT N_{Initial}=22, N_{Final}=22</p>	<p><i>Control condition (n=10):</i> Mean age=46.0yr; Gender: unspecified; Mean EDSS=3.0; Mean disease duration=9.9yr. For total study sample: Disease course: RRMS=19, PPMS=2, SPMS=1. Intervention: A quasi-experimental method was used to assign participants to either the exercise condition (unloaded leg cycling, 30 min/session, 3x/wk for 4wks) or to the control condition which controlled for passage of time and instrumentation effects. Outcomes were assessed at baseline and 1d, 1wk, and 4wks after intervention. Outcomes/Outcome Measures: H-reflex; Modified Ashworth Scale (MAS); Multiple Sclerosis Spasticity Scale (MSSS-88).</p>	<p>were differences in the means. Post-hoc analyses revealed that the effect of the control condition was significantly associated with lower H_{max}/V_{max} ratio values immediately after the control intervention. The effect of the exercise condition was significantly associated with lower H_{max}/V_{max} ratio values 4wks post intervention.</p> <ol style="list-style-type: none"> There were no significant main effects or interaction effects for MAS scores. A statistically significant interaction effect was found for condition*time for overall MSSS-88 scores. Post-hoc analyses showed that the exercise condition group was significantly associated with a reduction in MSSS-88 scores immediately after the intervention as well as at 1 and 4wks post intervention. The magnitude of change for MSSS-88 scores were small.
<p>Motl et al. 2007</p> <p><i>Effect of acute unloaded leg cycling on spasticity in individuals with multiple sclerosis using anti-spastic medications</i></p> <p>USA PCT N_{Initial}=6, N_{Final}=6</p>	<p>Population: EDSS=0.5-4.5. No further information provided. Intervention: Participants undertook an exercise condition (20min of unloaded leg cycle ergometry) or a control condition that involved sitting for 20min which controlled for passage of time and instrumentation effects. Outcomes were assessed at baseline and 10, 30, and 60min after intervention. Outcomes/Outcome Measures: H-reflex; Modified Ashworth Scale (MAS).</p>	<ol style="list-style-type: none"> H-reflex assessments measured by the H_{max}/M_{max} ratio for the interaction effect of condition*time was significant (p<0.0001). There was a significant decrease in the ratio at 10 (d = -0.52), 30 (d= -0.56) and 60min (d= -0.52) post experimental condition. No statistically significant changes were found after the control condition. Mean MAS scores showed a statistically significant condition*time interaction effect. Mean MAS scores decreased significantly at 10min (d = -1.14) and 30min (d = -0.55) after unloaded leg cycling, and significantly increased following the control condition at 60min.

Discussion

Three studies examined the effects of unloaded leg cycling on MS-related spasticity. Motl et al. (2007) recruited six participants with MS (EDSS 0.5-4.5) with mild to moderate spasticity taking oral baclofen and evaluated spasticity via H-reflex measurements and MAS scores. Participants underwent an exercise condition (20 minutes of unloaded leg cycle ergometry) or a control condition (20 minutes of sitting quietly). Both the H-reflex and MAS scores were significantly reduced 10 and 30 minutes after exercise and the H-reflex remained reduced 60 minutes after exercise. The results of this study suggest that unloaded leg cycling may be an effective adjuvant to pharmacological spasticity management in PwMS. A similar study by Sosnoff et al. (2009) assigned 22 participants with MS (relapsing-remitting (RRMS), primary progressive (PPMS), or SPMS) to either an exercise condition (unloaded leg cycling 30 minutes

per session, 3 times per week for 4 weeks) or a control condition and evaluated spasticity using the H-reflex, MAS, and Multiple Sclerosis Spasticity Scale (MSSS-88). The study found neither an improvement or worsening in long term clinical or neurophysiological measures of spasticity apart from the effect of the exercise condition being significantly associated with lower Hmax/Vmax ratio values four weeks following intervention. However, a significant improvement in the participants' perception of spasticity (MSSS-88) was noted.

Another study by Sosnoff et al. (2010) compared the effects of acute unloaded arm cycling versus acute unloaded leg cycling on lower extremity spasticity in PwMS. Ten participants with RRMS and slight to moderate spasticity of the lower extremities participated in three separate sessions evaluating acute unloaded arm cycling or acute unloaded leg cycling as compared to a control condition of quiet sitting. Spasticity was evaluated as the primary outcome measure and measured clinically using the MAS and electrophysiologically via electromyography and H-reflex measurements. After acute unloaded arm cycling, a small, statistically significant reduction in Hmax/Mmax amplitude – indicative of decreased spasticity – was measured in addition to a moderate to large, statistically significant reduction in MAS scores. After acute unloaded leg cycling, a moderate, statistically significant reduction in Hmax/Mmax amplitude was measured along with large, statistically significant decreases in MAS scores. While the current study found statistically significant changes in both cycling conditions, it is important to note that there were greater reductions of the soleus H-reflex and MAS scores in unloaded leg cycling as compared to arm cycling. Furthermore, the study also demonstrated a statistically significant increase in spasticity over time as seen in the control session. Overall, this study demonstrated clinical and neurophysiological reductions in spasticity with unloaded cycling, with a greater effect when the muscles tested were activated by the cycling activity.

Conclusion

There is conflicting evidence (from two prospective controlled trials; Sosnoff et al. 2010; Sosnoff et al. 2009) regarding whether or not unloaded leg cycling reduces spasticity compared to quiet sitting in persons with MS.

There is level 2 evidence (from one prospective controlled trial; Sosnoff et al. 2010) that unloaded leg cycling may reduce spasticity more as compared to unloaded arm cycling in persons with relapsing-remitting MS.

There is level 2 evidence (from one prospective controlled trial; Motl et al. 2007) that unloaded leg cycling may be an effective adjuvant to pharmacological spasticity management compared to quiet sitting in persons with MS.

It is unclear if unloaded leg cycling alone improves clinical measures of spasticity in persons with MS; however, it may have a positive impact on subjective measures of spasticity.

Unloaded leg cycling may improve spasticity in combination with pharmacological management.

2.1.4 Mixed Fitness Recreational Activities

Participation in mixed fitness recreational activities such as yoga and sports climbing may provide potential opportunities for fun and alternative exercise options while improving symptoms of MS. However, there is a lack of evidence regarding the incorporation of recreational physical activities and the impact of the activity on MS symptoms.

Table 4. Studies Examining Mixed Fitness Recreational Activities for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Velikonja et al. 2010 <i>Influence of sports climbing and yoga on spasticity, cognitive function, mood and fatigue in patients with multiple sclerosis</i> Slovenia RCT PEDro=3 N _{Initial} =20, N _{Final} =20	Population: <i>Sports Climbing group (n=10):</i> Median age=42yr; Gender: unspecified; Disease course: RRMS, PPMS, SPMS; Median EDSS=4; Mean disease duration: unspecified. <i>Yoga group (n=10):</i> Median age=41yr; Gender: unspecified; Disease course: RRMS, PPMS, SPMS; Median EDSS=4.2; Mean disease duration: unspecified. Intervention: Participants were randomly assigned to sports climbing exercise or yoga exercise 1x/wk for 10wks. Outcomes were assessed at baseline and post treatment. Outcomes/Outcome Measures: Modified Ashworth Scale (MAS).	1. There was no significant difference in MAS scores from baseline to post treatment for either sports climbing (p=0.574) or yoga (p=0.673) groups.

Discussion

A study by Velikonja et al. (2010) examined the influence of mixed fitness recreational activity participation on various symptoms of MS. Twenty subjects with RRMS, PPMS, or SPMS (EDSS<6.0) were randomized to either sports climbing or yoga, once a week for a period of 10 weeks. Spasticity was a primary outcome measure and was evaluated using the MAS. The sports climbing group participated in wall climbing activities that provided functional opportunities for whole body strengthening, balance, and coordination, depending on the ability level of the participant. The yoga group participated in yoga exercises requiring postural control, body awareness, and isometric muscle contraction and relaxation. The study found no reduction in MAS scores after either intervention; however, neither intervention increased spasticity in the affected muscle groups. There was a statistically significant improvement in EDSS pyramidal scores in the sports climbing group (p=0.046), which indirectly measures muscle strength and flexibility in conjunction with muscle spasticity.

Conclusion

There is level 2 evidence (from one randomized controlled trial; Velikonja et al. 2010) that mixed fitness recreational activities such as sports climbing or yoga may not reduce spasticity in persons with MS.

Participation in recreational sports activities such as sports climbing or yoga may not reduce spasticity in persons with MS.

2.1.5 Hydrotherapy

Hydrotherapy is a modality which utilizes the therapeutic benefits of water to promote healing and restore function. Aquatic therapy programs may offer benefits including gravity reduced exercise and increased freedom of movement in individuals with cerebral palsy (Dimitrijevic et al., 2012) and post stroke (Zhang et al., 2016).

Table 5. Studies Examining Hydrotherapy Exercises for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Castro-Sanchez et al. 2012 <i>Hydrotherapy for the treatment of pain in people with multiple sclerosis: a randomized controlled trial</i> Spain RCT PEDro=6 N _{Initial} =73, N _{Final} =71	<p>Population: <i>Ai-Chi group (n=36):</i> Mean age=46.0yr; Gender: males=10, females=26; Disease course: PPMS=6, SPMS=9, unknown=21; Mean EDSS=6.3; Mean disease duration=10.7yr. <i>Relaxation group (n=37):</i> Mean age=50.0yr; Gender: males=13, females=24; Disease course: PPMS=9, SPMS=12, unknown=16; Mean EDSS=5.9; Mean disease duration=11.9yr.</p> <p>Intervention: Participants received either relaxation exercises or Ai-Chi exercises 2d/wk for 20wks. Ai-Chi was performed for 60min followed by a 10min relaxation period, both in a swimming pool. The relaxation group performed relaxation exercises on an exercise mat. Outcomes were assessed at baseline and at 4wks, 10wks, 20wks, 24wks, and 30wks.</p> <p>Outcomes/Outcome Measures: Visual Analog Scale (VAS) (spasms).</p>	1. Significant between-group differences were found post treatment at 20 and 24wks for spasm VAS (p<0.048 and p<0.042, respectively) in favour of the Ai-Chi group.

Discussion

One study has examined the effect of an aquatic exercise program compared to land-based exercises for reducing spasticity in PwMS. Castro-Sanchez et al. (2012) investigated the efficacy of a hydrotherapy Ai-Chi program for PwMS and evaluated spasms (as a component of the spasticity syndrome) as a secondary outcome. It would be important to note that Ai-Chi is an aquatic therapy grounded in Tai chi chuan and qigong principles thus emphasizing the importance of the breath as well as progressive resistance training.

In this study, 73 PwMS were randomized to a control group consisting of land-based breathing and relaxation exercises, or to an experimental group which received Ai-Chi exercises in a swimming pool. Each group participated in hour long biweekly sessions over 20 weeks with a focus on deep breathing and relaxation for both the control and experimental groups. The study found a significant difference in spasm visual analog scale (VAS) scores at the termination of the study (week 20), with the hydrotherapy group demonstrating a significant decrease in spasms which was maintained at week 24 (four week follow up), but not at week 30 (10 week follow up), which is suggestive of a temporarily maintained effect following the conclusion of the aquatic therapy program. Furthermore, the authors hypothesized that the beneficial effects of an aquatic therapy program are due in part to the gravity reducing environment allowing for greater voluntary movements and overall exercise capability as compared to land-based therapies. While there is insufficiently powered evidence to definitively conclude that aquatic exercise is an effective intervention for MS-related spasticity, the initial evidence is favourable.

Conclusion

There is level 1b evidence (from one randomized controlled trial; Castro-Sanchez et al. 2012) that an aquatic Ai-Chi exercise program may reduce spasticity compared to land-based breathing and relaxation exercises in persons with MS.

Hydrotherapy may improve subjective measures of spasticity more than land-based exercise in persons with MS.

2.2 Cryotherapy

It is well known that many PwMS have altered signs and symptoms due to temperature fluctuations, with function tending to deteriorate with increases in ambient or core temperature (Uhtoff's phenomenon) and tending to improve with cooling. Typically, changes associated with exposure to cooling include reduced fatigue as well as possible positive impacts on spasticity, strength, sensation, and mobility (Mead, 1966). The presumed mechanism of action may relate, in part, to improvements in neural transmission within demyelinated circuits with changes in core body temperature that enhance axonal transmission properties and minimize instances of conduction block (Frohman et al., 2013). Limited literature exists regarding the effect of cold on functional mobility, specifically the impact of cold on MS-related spasticity.

Table 6. Studies Examining Cryotherapy for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Nilsagard et al. 2006	Population: Mean age=52yr; Gender: males=13, females=30; Disease course: RRMS=22, PPMS=8, SPMS=13; Median EDSS=4.0; Mean disease duration: unspecified.	1. Mean change in MAS score from baseline was not significantly different after cooling compared to the control condition (-0.50 vs. 0.00, p=0.296).

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
<p><i>Evaluation of a single session with cooling garment for persons with multiple sclerosis – a randomized trial</i></p> <p>Sweden RCT Crossover PEDro=8 N_{Initial}=48, N_{Final}=43</p>	<p>Intervention: Participants were randomized to receive a cooling (-20°C) or control (22°C) garment for 45min, and the alternate treatment after a ≥7d washout period. Outcomes were assessed before and after each treatment.</p> <p>Outcomes/Outcome Measures: Modified Ashworth Scale (MAS); subjective experience of spasticity.</p>	<p>2. Statistically significant effects were reported for the subjective experience of spasticity in favour of cooling compared to the control condition (p<0.001).</p>
<p>Chiara et al. 1998</p> <p><i>Cold effect on oxygen uptake, perceived exertion, and spasticity in patients with multiple sclerosis</i></p> <p>USA RCT Crossover PEDro=3 N_{Initial}=14, N_{Final}=14</p>	<p>Population: Mean age=43.6yr; Gender: males=2, females=12; Disease course: unspecified; Mean EDSS=3.0; Mean disease duration=6.3yr.</p> <p>Intervention: All participants began the treatment with 15min of rest in an ambient temperature room (AT). Individuals then underwent either rest at AT or rest in a cold temperature water bath (24°C) for 20min. Participants returned on another day to complete the other condition. Spasticity was assessed at baseline, immediately following the session, and 30min post session.</p> <p>Outcomes/Outcome Measures: Modified Ashworth Scale (MAS).</p>	<p>1. Spasticity was significantly increased immediately following cold temperature compared to AT as per the MAS (p<0.05).</p>
<p>Kinnman et al. 1997</p> <p><i>Temporary improvement of motor function in patients with multiple sclerosis after treatment with a cooling suit</i></p> <p>Sweden Pre-Post N_{Initial}=28, N_{Final}=28</p>	<p>Population: <i>Ambulatory MS patients (n=14):</i> Median age=45yr; Gender: males=6, females=8; Disease course: unspecified; Mean EDSS=4 (2-6.5); Disease duration range=4-30yr. <i>Wheelchair-dependent MS patients (n=6):</i> Median age=48yr; Gender: males=3, females=3; Disease course: unspecified; EDSS range=7-7.5; Disease duration range=8-21yr. <i>Healthy controls (n=8):</i> Median age=46yr; Gender: males=3, females=5.</p> <p>Intervention: All participants were informed about the cooling garment. The participants used the cooling garment for 40-45min on four occasions during a 2wk period. Participants were assessed before and after (immediately and 1.5hr later) cooling.</p> <p>Outcomes/Outcome Measures: Ashworth Scale; Subjective assessment of patients' evaluation of overall effect of cooling.</p>	<p>1. 5 out of 6 ambulatory MS patients with spasticity were significantly improved after cooling.</p> <p>2. All 6 wheelchair-dependent MS patients were improved in spasticity after cooling.</p> <p>3. There was total agreement between functional improvement and the patient's subjective judgement in the ambulatory MS group, however the wheelchair-dependent group showed a tendency to underestimate improvement.</p>

Discussion

Three studies have examined the effects of prolonged cryotherapy on MS-related spasticity. Two studies (Kinnman et al., 1997; Nilsagard et al., 2006) evaluated the use of a specialized cooling garment on motor

function in PwMS. Nilsagard et al. (2006) recruited 43 temperature-sensitive PwMS (RRMS, PPMS, and SPMS, EDSS 3.0-6.0) in a randomized crossover study and compared the effect of a cooling garment with a placebo garment on physical functioning. This study examined various functional mobility outcomes before and after wearing a cooling vest (-20°C) or placebo vest (22°C) for 45 minutes, including spasticity (assessed using the MAS). While the study found no statistically significant differences in changes on the MAS between groups, there were statistically significant subjective improvements in patients' perception of their spasticity. In contrast, Kinnman et al. (1997) studied the repeated use of a cooling suit on motor function – with spasticity evaluated as a secondary measure – in 14 participants who were ambulatory (EDSS 2.0-6.5) and six participants who were wheelchair dependent (EDSS 7.0-7.5) in addition to eight healthy controls. Spasticity was present in six of the 14 participants who were ambulatory; five of the six had improved spasticity after using the cooling suit. Furthermore, all six participants who were wheelchair dependent demonstrated improved spasticity following use of the cooling suit.

Interestingly, Chiara et al. (1998) examined the effect of a cold bath on MS-related spasticity in 14 ambulatory MS participants (EDSS<5.0). All participants underwent 20 minutes of rest in a “cold” bath (24°C/75°F) in a hydrotherapy tank and 20 minutes of rest in ambient room temperature (24°C/+0.6/76°F). While the temperature difference between the control and experimental conditions was negligible, the study noted increased spasticity under the experimental condition. As a result, the study found that cooling by immersion does not reduce mild to moderate spasticity in PwMS and may result in increased spasticity. This finding would support the notion that certain instances of cooling may act as a noxious stimulus and lead to a hypertonicity wind-up phenomenon in addition to negatively impacting visco-elastic properties of connective tissues. In clinical practices located in regions with extreme winter weather, it would not be uncommon to hear complaints of worsening spasticity with cold exposure in some persons living with MS.

Conclusion

There is level 1b evidence (from two randomized controlled trials; Nilsagard et al. 2006; Chiara et al. 1998) that cryotherapy may not reduce spasticity compared to ambient temperature in persons with MS.

Cryotherapy may not reduce clinical measures of spasticity in persons with MS; however, cryotherapy may have a positive impact on subjective measures of spasticity.

2.3 Electrical Stimulation

Electrical stimulation is a well-known therapeutic modality that is widely used in several forms and has been shown to have positive effects on spasticity in spinal cord injury and acquired brain injury populations (Fernández-Tenorio, Serrano-Munoz, Avendano-Coy, & Gomez-Soriano, 2016; Khan, Amatya, Bensmail, & Yelnik, 2017; Sadowsky et al., 2013). Multiple studies have examined a variety of stimulation modalities and their effects on MS-related spasticity. Electrical stimulation can be delivered at any point along the neural axis; stimulation interventions of the brain include repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and theta-burst stimulation (TBS), whereas stimulation delivered peripherally includes transcutaneous electrical nerve stimulation (TENS),

neuromuscular electrical stimulation, functional electrical stimulation (FES), spinal cord stimulation (SCS), and subcutaneous nerve stimulation (SCNS). Several of these have been evaluated for the management of spasticity in PwMS. Though a full discussion of the safety and tolerability of these various modalities is beyond the scope of this module, caution should be exercised in using modalities that stimulate the central neuraxis (especially brain) in those persons with a history of seizure. For modalities stimulating elements of the peripheral neuraxis (especially peripheral nerve and muscle), caution should be exercised in using these modalities on persons with comorbid neuropathy, polyneuropathies, or relevant focal neuropathies/active motor radiculopathies. In the same vein, caution must be exercised in using peripherally stimulating modalities in persons suffering from a comorbid primary muscle condition. Pre-treatment evaluations via electroencephalogram or electrodiagnosis (nerve conduction studies and electromyography) may be prudent.

2.3.1 Repetitive Transcranial Magnetic Stimulation

rTMS is a form of noninvasive brain stimulation that has been used therapeutically since 1985. rTMS involves the use of a magnet to stimulate targeted areas of the brain to elicit a specific response, such as modulating cortical excitability (Hallett, 2000). One theory suggests that stimulation of the motor cortex with rTMS will increase inhibitory input through the corticospinal tract to ultimately reduce muscle spasticity (Mori, Koch, Foti, Bernardi, & Centonze, 2009; Valle et al., 2007).

Table 7. Studies Examining Repetitive Transcranial/Trans-spinal Magnetic Stimulation for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Centonze et al. 2007 <i>Repetitive transcranial magnetic stimulation of the motor cortex ameliorates spasticity in multiple sclerosis</i> Italy PCT N _{Initial} =19, N _{Final} =19	<p>Population: Mean age=41.4yr; Gender: males=5, females=14; Disease course: RRMS; Mean EDSS=5.0; Mean disease duration: unspecified.</p> <p>Intervention: Participants underwent repetitive transcranial magnetic stimulation (rTMS) over the leg region of the primary motor cortex. <i>Experiment A:</i> Three rTMS sessions were completed: low frequency (1 train of 900 pulses at 1Hz for 15min), high frequency (18 trains of 50 stimuli at 5Hz for 15min), and sham (15min). Individuals received each rTMS session in a pseudorandomized order, with a 7d period between each. Outcomes were assessed at baseline, immediately following treatment, and 10 and 20min later. <i>Experiment B:</i> Participants returned 1wk later for high frequency rTMS (5Hz 1x/d for 5d, n=12) or to a sham condition (n=7) for 2wks. Outcomes were assessed at baseline, following one session, immediately following treatment, and 1wk and 2wks later.</p>	<p>Experiment A:</p> <ol style="list-style-type: none"> 1. There were no significant differences in MAS from baseline to 10 and 20min for all three groups (p>0.05). 2. Both 5Hz and 1Hz rTMS influenced significant changes in H/M amplitude from baseline (p<0.0001 for both), with an average 26% decrease and 40% increase, respectively. 3. There were no significant H/M amplitude changes for sham rTMS (p=0.33). <p>Experiment B:</p> <ol style="list-style-type: none"> 4. Individuals receiving 5Hz rTMS had a decrease in spasticity on MAS following 1 session, post treatment, and at 1wk (p<0.05), but not by 2wks (p>0.05). 5. 5Hz rTMS significantly decreased the H/M amplitude ratio after 1 session, post treatment, and 1wk later (p<0.05), but not at 2wks (p>0.05). 6. There was a significant between-group difference in H/M amplitude ratio post treatment (p<0.0001).

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
	Outcomes/Outcome Measures: Modified Ashworth Scale (MAS); H/M amplitude ratio.	7. There were no significant changes in MAS or H/M amplitude ratio in participants receiving sham rTMS ($p>0.05$).
Nielsen et al. 1996 <i>Treatment of spasticity with repetitive magnetic stimulation; a double-blind placebo-controlled study</i> Denmark RCT PEDro=9 N _{Initial} =38, N _{Final} =35	Population: <i>Repetitive Magnetic stimulation (n=21):</i> Median age=44yr; Gender: males=7, females=14; Disease course: unspecified; Severity: unspecified; Median disease duration=12yr. <i>Sham stimulation (n=17):</i> Median age=44yr; Gender: males=5, females=12; Disease course: unspecified; Severity: unspecified; Median disease duration=13yr. Intervention: Patients were randomly allocated to a group that received repetitive trans-spinal magnetic stimulation or the sham stimulation (placebo) 2x/d for 7d. Outcomes were assessed at baseline (test I), immediately after treatment (test II), 8d post treatment (test III), and 16d post treatment (test IV). Outcomes/Outcome Measures: Ashworth score; H-reflex; self-score of ease of daily activities related to spasticity.	1. There were no significant differences between groups in terms of participants' self-scores at test II. 2. The treatment was significantly associated with an 18% improvement in the Ashworth score ($p=0.005$), and scores remained unchanged in the sham stimulation group (test II). 3. The improvement in Ashworth scores in the treatment group compared to the control group was significantly different (-3.3 ± 4.7 vs. 0.7 ± 2.5 arbitrary units, respectively; $p=0.003$) at test II. 4. The treatment was significantly associated with an increase in the stretch reflex by 27% ($p=0.016$), and the threshold remained unchanged in the sham stimulation group (test II). 5. Compared to the sham stimulation, patients in the treatment group showed a significant improvement in the stretch reflex threshold (4.3 ± 7.5 deg/s vs. -3.8 ± 9.7 deg/s, respectively; $p=0.001$) at test II. 6. Compared to baseline scores, treatment remained significantly associated with an improvement in stretch reflex at test III, by 27% ($p=0.011$). 7. The improvement of the stretch reflex threshold after treatment was significantly different compared to sham stimulation at test III ($p<0.028$). 8. No significant effect of treatment was observed at test IV. 9. There were no statistically significant differences between the two groups with respect to the amplitude of stretch reflex, the maximum voluntary contraction of dorsi and plantar flexion at the ankle joint, and the H-reflex ratio.
Abdelkader et al. 2013 <i>Repetitive transcranial magnetic stimulation effect in multiple sclerosis spasticity (clinical and</i>	Population: Age range=16-42yr; Gender: males=12, females=9; Disease course: RRMS; Range EDSS=3.0-5.5; Mean disease duration: unspecified. Intervention: Individuals with lower limb spasticity received repetitive magnetic stimulation (rTMS) over the primary motor cortex of the leg for 2wks. Within rTMS,	1. Within Group A, there was a significant difference in muscle stretch on MAS ($p=0.000$) and on the Tardieu scale ($p=0.026$), and H/M ratio ($p=0.028$), compared to baseline. 2. Within Group B, there were no significant differences compared to baseline ($p>0.05$).

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
<i>electrophysiological evaluation): a preliminary Egyptian study</i> Egypt PCT N _{Initial} =21, N _{Final} =21	participants were divided into two groups. Group A (n=12) received 18 rTMS train stimulations at 5Hz (high) for 15min whereas Group B (n=9) received 1 rTMS train at 1Hz (low) for 15min. Outcomes were assessed at baseline and 2wks. Outcomes/Outcome Measures: Tardieu scales; Modified Ashworth Scale (MAS); H-reflex.	<ol style="list-style-type: none"> 3. MAS muscle stretch was the only outcome that significantly differed between Group A and Group B post treatment (2.92 vs. 4.0, respectively; $p=0.024$). 4. There was a significant negative correlation between MAS muscle stretch and muscle strength ($p=0.008$) and between Tardieu scale and MAS muscle strength ($p=0.041$). 5. A significant positive correlation existed between Tardieu scale and MAS muscle stretch ($p=0.001$). 6. EDSS was significantly negatively correlated with MAS muscle strength ($p=0.009$) and positively correlated with MAS muscle stretch ($p=0.036$) and the Tardieu scale ($p=0.015$).

Discussion

Two studies examined the effects of rTMS on treating spasticity in PwMS. This modality delivers a stimulus over the primary motor cortex and has previously been shown to modulate corticospinal tract excitability and the spinal H-reflex, a known measure of spasticity. Centonze et al. (2007) examined two rTMS protocols (within four separate experimental designs) in 19 subjects with RRMS (EDSS 3.0-6.0) with unilateral or predominantly unilateral lower limb spasticity. Clinical (MAS) and electrophysiological (H-reflex) measures of spasticity were used. Overall, the primary study findings indicated that rTMS over the primary motor cortex modulates spasticity and corticospinal tract excitability. In PwMS, a single session of rTMS did not have any clinical effect (decrease in MAS scores) on spasticity (Experiment A). A two-week, ten session series of 5Hz rTMS (Experiment D) did demonstrate a reduction in lower extremity spasticity as indicated by a reduction in MAS and H-reflex values. Furthermore, the reduction in H-reflex ratio was maintained one week after the intervention ended, indicating a beneficial prolonged reduction in spasticity. Abdelkader et al. (2013) also evaluated the use of rTMS and its effect on MS-related spasticity based on the results from Centonze et al. (2007). In this study, 21 subjects with RRMS (EDSS 3.0-5.5) and lower extremity spasticity underwent a two-week treatment series of both high frequency (5Hz) and low frequency (1Hz) rTMS protocols as described by Centonze et al. (2007). Spasticity was assessed clinically using the MAS and Tardieu scales and physiologically using the spinal H-reflex. Abdelkader et al. (2013) found statistically significant improvement on the MAS, Tardieu scales, and H-reflex in participants after treatment with 5Hz rTMS, and no improvement on spasticity after 1Hz rTMS, validating the findings previously reported by Centonze et al. (2007).

Nielsen et al. (1996) examined the effect of repetitive trans-spinal magnetic stimulation on spasticity as measured by the AS and H-reflex in 38 individuals with MS. The individuals were randomized to receive either active treatment or sham stimulation twice daily for one week. Stimulation was delivered across the thoracic spinal cord as determined by investigators. Following the intervention, individuals receiving

stimulation demonstrated statistically significant improvements in measures of spasticity including the AS and ankle stretch reflex as compared to controls. Interestingly, both the control (sham stimulation) and treatment stimulation groups reported significant improvement in self-reported spasticity compared to baseline (as measured by ease of activities of daily living) despite only the treatment group demonstrating clinical differences, leading to question a potential placebo effect.

Conclusion

There is level 2 evidence (from one prospective controlled trial; Centonze et al. 2007) that high frequency (5 Hz) repetitive transcranial magnetic stimulation (rTMS) may reduce spasticity compared to sham rTMS in persons with relapsing-remitting MS.

There is level 2 evidence (from one prospective controlled trial; Abdelkader et al. 2013) that high frequency (5 Hz) repetitive transcranial magnetic stimulation (rTMS) may reduce spasticity compared to low frequency (1 Hz) rTMS in persons with relapsing-remitting MS.

There is level 1b evidence (from one randomized controlled trial; Nielsen et al. 1996) that trans-spinal magnetic stimulation may reduce spasticity compared to sham stimulation in persons with MS.

Repetitive transcranial and trans-spinal magnetic stimulation may reduce spasticity in persons with MS.

2.3.2 Theta-Burst Stimulation

TBS is a form of transcranial magnetic stimulation first described in 2005. Originally used for stimulation of the motor cortex (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005), TBS may be a suitable intervention for reducing spasticity in people with MS (Di Lazzaro et al., 2005).

Table 8. Studies Examining Theta-Burst Stimulation for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Mori et al. 2010 <i>Effects of intermittent theta burst stimulation on spasticity in patients with multiple sclerosis</i> Italy	Population: Active ($n=10$): Mean age=44.4yr; Gender: males=4, females=6; Disease course: RRMS; Severity: unspecified; Mean disease duration=8.6yr. <i>Sham</i> ($n=10$): Mean age=44.3yr; Gender: males=3, females=7; Disease course: RRMS; Severity: unspecified; Mean disease duration=9.0yr. Intervention: Participants were randomized to receive active or sham intermittent theta-burst stimulation (iTBS). Treatment was	<ol style="list-style-type: none"> H/M ratio showed significant main effects of time ($F=2.36, p<0.05$) and treatment ($F=6.90, p<0.01$), and a significant time x treatment interaction ($F=2.63, p<0.05$). H/M ratio significantly decreased ($p<0.05$) with active iTBS vs. sham iTBS from T0 to T2 (74.6%), T3 (82.3%), T4 (72.4%), and T5 (80.7%) in the target

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
PCT N _{Initial} =20, N _{Final} =20	delivered 1x/d for 5d/wk over 2wks. iTBS consisted of 10 bursts, each burst composed of three stimuli at 50Hz, repeated at 5Hz every 10sec for a total of 600 stimuli. Outcomes of the lower limbs were assessed at baseline (T0), after first session (T1), after last session (T2), and at follow-ups of 1wk (T3), 2wks (T4), 3wks (T5), and 4wks (T6). Outcomes/Outcome Measures: Modified Ashworth Scale (MAS); H/M Ratio.	limb; no significant effect was seen in the contralateral limb. 3. MAS score showed a significant effect with active iTBS in the target limb ($\chi^2=24.29$, $p<0.001$) but not in the contralateral limb ($\chi^2=2.51$, $p>0.05$); no effect was seen in either limb with sham iTBS. 4. Mean MAS score significantly decreased ($p<0.05$) with active iTBS over sham iTBS from T0 (9.86) to T3 (6.86) and T4 (7.14).

Discussion

Only one prospective controlled trial has evaluated the effects of 10 sessions of intermittent TBS (iTBS) over two weeks in PwMS compared to sham iTBS. There was a subsequent decrease in spasticity post treatment as measured with the H/M ratio and the MAS scores (see Table 7). However, this trial had several limitations. First, it was carried out in only 20 participants with MS, 10 each in the intervention and sham groups; second, the level of severity was not specified. These limitations make it difficult to ascertain if these findings are indeed generalizable to the MS population.

Conclusion

There is level 2 evidence (from one prospective controlled trial; Mori et al. 2010) that intermittent theta-burst stimulation may reduce spasticity compared to sham stimulation in persons with relapsing-remitting MS.

Intermittent theta-burst stimulation may be an effective intervention to reduce spasticity in persons with relapsing-remitting MS.

2.3.3 Transcranial Direct Current Stimulation

tDCS is another form of non-invasive brain stimulation employing a constant, low current to the brain through electrodes on the scalp (Nitsche et al., 2008). Similar to rTMS, tDCS activates neurons in the stimulated area of the brain, and may have therapeutic benefits for people with neurological injury or disease (Stagg & Nitsche, 2011).

Table 9. Studies Examining Transcranial Direct Current Stimulation for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Iodice et al. 2015 <i>Anodal transcranial direct current stimulation of motor cortex does not ameliorate spasticity in multiple sclerosis</i> Italy RCT PEDro=8 N _{Initial} =20, N _{Final} =20	<p>Population: <i>Active (n=10):</i> Mean age=43.3yr; Gender: males=2, females=8; Disease course: RRMS; Mean EDSS=3.6; Mean disease duration: 7.0yr. <i>Sham (n=10):</i> Mean age=40.3yr; Gender: males=3, females=7; Disease course: RRMS; Mean EDSS=3.8; Mean disease duration=7.8yr.</p> <p>Intervention: Patients were randomized to receive active or sham anodal transcranial direct current stimulation (tDCS). tDCS was delivered to the primary motor cortex at 2mA for 20min/d over 5d. Outcomes were assessed at baseline and 5d.</p> <p>Outcomes/Outcome Measures: Modified Ashworth Scale (MAS); Multiple Sclerosis Spasticity Scale (MSSS-88).</p>	<ol style="list-style-type: none"> 1. Mean MAS score at 5d was lower in the active group than the sham group, but the difference was not statistically significant (4.1 vs. 4.4, p=0.60). 2. Mean MSSS-88 score at 5d was higher in the active group than the sham group, but the difference was not statistically significant (203.1 vs. 183, p=0.60). 3. There was no significant effect of time on scores of MAS (F=0.03, p=0.86) or MSSS-88 (F=0.013, p=0.91). 4. There was no significant time x intervention interaction on scores of MAS (F=1.461, p=0.242) or MSSS-88 (F=0.056, p=0.816).

Discussion

One study by Iodice et al. (2015) evaluated the effectiveness of anodal tDCS on lower extremity spasticity in MS. This study randomized 20 subjects with RRMS (EDSS 3.0-6.0) and lower extremity spasticity to an anodal tDCS or sham tDCS group. Each group underwent five daily tDCS sessions, with the anodal group receiving 2mA intensity for 20 minutes once a day. Spasticity was evaluated using the MAS and MSSS-88. The study did not find statistically significant changes for any outcome measures between the anodal and sham tDCS groups. These results contrast with previously reported findings regarding rTMS as demonstrated by Centonze et al. (2007) and Abdelkader et al. (2013); however, the authors hypothesized that the effect difference was due to the mechanism of action as tDCS alters the resting membrane potential of a nerve whereas rTMS triggers action potential propagation.

Conclusion

There is level 1b evidence (from one randomized controlled trial; Iodice et al. 2015) that transcranial direct current stimulation (tDCS) may not reduce spasticity compared to sham tDCS in persons with relapsing-remitting MS.

Transcranial direct current stimulation may not improve spasticity in persons with relapsing-remitting MS.

2.3.4 Transcutaneous Electrical Nerve Stimulation

TENS is an electromodality that delivers an electrical current to excite nerves via surface electrodes. While commonly used to modulate pain, TENS has been recently studied for potential application regarding spasticity.

Table 10. Studies Examining Transcutaneous Electrical Nerve Stimulation for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
<p>Miller et al. 2007</p> <p><i>The effects of transcutaneous electrical nerve stimulation (TENS) on spasticity in multiple sclerosis</i></p> <p>UK RCT Crossover PEDro=6 N_{Initial}=37, N_{Final}=32</p>	<p>Population: <i>Group 1 (n=16):</i> Mean age=46.8yr; Gender: unspecified; Disease course: unspecified; Mean EDSS=6.8; Mean disease duration=14.5yr. <i>Group 2 (n=16):</i> Mean age=47.1yr; Gender: unspecified; Disease course: unspecified; Mean EDSS=5.1; Mean disease duration=10.1yr.</p> <p>Intervention: Participants were randomized to receive transcutaneous electrical nerve stimulation (TENS; 100Hz, 0.125ms) for 60min/d (group 1) or 8hr/d (group 2) over 2wks. Following a 2wk washout period, participants received the alternative treatment for 2wks. Outcomes of the lower limbs were assessed before and after each treatment.</p> <p>Outcomes/Outcome Measures: Global Spasticity Scale (GSS); Penn Spasm Scale (PSS).</p>	<ol style="list-style-type: none"> GSS was a composite of the Ashworth Scale (AS), Patellar Tendon Reflex (PTR), and Clonus Score (CS). Changes in GSS were more greatly associated with changes in AS than PTR or CS. On GSS, participants showed a small, non-significant reduction with 60min/d TENS ($p=0.433$) and a larger, non-significant reduction with 8hr/d TENS ($p=0.217$). Reduction of ≥ 2 points was observed in 25% of participants with 8hr/d TENS and 12.5% with 60min/d TENS. On PSS, participants showed a significant reduction with 8hr/d TENS ($p=0.038$) and a non-significant reduction with 60min/d TENS ($p=0.281$). Participants reported subjective improvement of symptoms as follows: 87.5% for spasms, 73.3% for pain, and 73.3% for stiffness. Of those reporting improvements, complete relief was reported by 12.5% for spasms, 8.7% for pain, and 6.7% for stiffness. No improvement was reported by 12.5% for spasms, 30% for pain, and 27% for stiffness. There was no order effect: no significant difference between groups ($p=0.765$) or timings ($p=0.236$), and no significant interaction between groups ($p=0.299$).
<p>Armutlu et al. 2003</p> <p><i>The effect of transcutaneous electrical nerve stimulation on spasticity in multiple sclerosis patients: a pilot study</i></p>	<p>Population: Mean age=34.7yr; Gender: males=6, females=4; Disease course: PPMS=2, SPMS=8; Mean EDSS=4.86; Mean disease duration=6.2yr.</p> <p>Intervention: Transcutaneous electrical stimulation (TENS) was applied to participants with plantar flexor muscle spasticity. TENS was applied at the spinal cord level of the spastic muscle group under observation at 100Hz with 0.3msec pulse width, 20min/d for 4wks. Electromyography (EMG) feedback was</p>	<ol style="list-style-type: none"> TENS reduced spasticity in both extremities according to both EMG activity and MAS ($p<0.05$). However, there was no difference in the AI ($p>0.05$) following TENS. EMG amplitudes were significantly different following TENS compared to baseline ($p<0.05$).

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Turkey Pre-Post N _{Initial} =10, N _{Final} =10	assessed before and after each session and outcomes were assessed at baseline and post treatment. Outcomes/Outcome Measures: EMG feedback; Modified Ashworth Scale (MAS); Ambulation index (AI).	

Discussion

Two studies have examined the effects of TENS on spasticity in PwMS. A study by Armutlu and colleagues (2003) enrolled 10 participants with progressive MS (EDSS<6.0) and mild to moderate ankle plantar flexor spasticity. Each participated in daily TENS sessions (pulse width 300us, pulse frequency 100Hz), 20 minutes a day for four weeks; the TENS was placed over the same spinal cord level as the spastic muscle group. The study found statistically significant reductions (p<0.05) in myoelectric activity and MAS scores in both lower extremities after four weeks of treatment. While this study provides initial evidence that TENS has a positive effect on MS-related spasticity, further research is warranted. Miller and colleagues (2007) also assessed the impact of TENS on MS-related spasticity, specifically comparing the effect of two different application times. One treatment protocol administered 60 minutes of daily high frequency TENS (pulse frequency 100 Hz, pulse width 125us), while the second treatment protocol administered eight hours of the same high frequency TENS (pulse frequency 100Hz, pulse width 125us); both were applied directly over the affected quadriceps muscle at a “strong, but comfortable” sensation below motor threshold. Knee extensor spasticity was evaluated on the most affected limb using the Global Spasticity Scale (GSS) – a composite of the Ashworth Scale, Clonus score, and Patellar Tendon Reflex score – and Penn Spasm Scale (PSS). The study found reductions in mean GSS scores after both treatment protocols. A small, nonsignificant reduction was found after two weeks of 60-minute TENS application and a larger, but still nonsignificant, reduction was found after the eight-hour applications. The study also found a small, non-significant reduction in the PSS after the 60-minute protocol and a statistically significant reduction in PSS scores after the eight-hour applications.

Conclusion

There is level 1b evidence (from one randomized controlled trial; Miller et al. 2007) that electrical nerve stimulation using either a one-hour or eight-hour protocol may not reduce spasticity in persons with MS.

Transcutaneous electrical nerve stimulation may not reduce spasticity in persons with MS.

2.3.5 Subcutaneous Nerve Stimulation

SCNS, also known as peripheral nerve stimulation, involves implanting an electrode to deliver peripheral nerve stimulation directly. SCNS has been demonstrated to reduce neuropathic pain (de Leon-Casasola, 2009), and may be beneficial for reducing spasticity along similar pathways.

Table 11. Studies Examining Subcutaneous Nerve Stimulation for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Walker 1982 <i>Modulation of spasticity: prolonged suppression of a spinal reflex by electrical stimulation</i> USA PCT PEDro=4 N _{Initial} =13, N _{Final} =13	Population: MS participants (n=9). No further information provided. Intervention: Participants with MS (n=9) and post-laminectomy irritability (n=4) were randomly assigned to receive subcutaneous nerve stimulation (SCNS; n=9) or control SCNS (n=4) for 1hr 2x/d for 1wk. Outcomes were assessed at baseline and 30, 60, 90, and 120min following treatment. Outcomes/Outcome Measures: Clonus.	<ol style="list-style-type: none"> 1. None of the participants given control stimulation responded to treatment. 2. SCNS suppressed clonus for 2hr in all participants; clonus decreased steadily until 60min post treatment, remained constant until 90min, and then slightly increased to 120min. 3. Between-group analyses were not reported.

Discussion

In one study by Walker (1982), the effect of SCNS on upper extremity spasticity and ankle clonus was examined in individuals with upper motor neuron disorders. Of 13 participants, nine were diagnosed with MS, and four with post-laminectomy irritability resulting in ankle clonus that lasted for 40-60 beats as triggered by stretch. Nine participants underwent SCNS for one hour twice daily for one week while four participants underwent placebo stimulation at points distal to the tested nerves. The author noted that SCNS delivered to the radial, median (at the level of the wrist), and saphenous nerves resulted in inhibited ankle clonus. In 100% of individuals receiving SCNS, a slight inhibition of ankle spasticity was noted with maximal reflex suppression occurring one hour following treatment, with treatment effects lasting three hours. The author reports that the clonus reflex was inhibited contralaterally to the side stimulated in all cases.

Conclusion

There is level 2 evidence (from one prospective controlled trial; Walker 1982) that subcutaneous nerve stimulation may reduce spasticity compared to sham stimulation in persons with MS.

Subcutaneous nerve stimulation (SCNS) may reduce spasticity in persons with MS. SCNS does not seem to be harmful and may temporarily reduce clonus at the ankle.

2.3.6 Spinal Cord Stimulation

SCS involves delivering electrical stimulation to the spinal cord using an implanted device, often called a pacemaker (Oakley & Prager, 2002). SCS of the dorsal columns of the spinal cord has been used as a treatment for chronic pain and may also be an intervention useful for reducing spasticity.

Table 12. Studies Examining Spinal Cord Stimulation for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Koulousakis et al. 1987 <i>Application of SCS for movement disorders and spasticity</i> Germany Pre-Post N _{Initial} =20, N _{Final} =20	Population: MS participants (n=12): Mean age=46.9yr. No further information provided. Intervention: Participants received spinal cord stimulation by means of multipolar resume electrodes implanted into the spinal canal via laminectomy. Participants were regularly examined after 3, 6, and 12mo, and annually thereafter. Outcomes/Outcome Measures: Tonus; subjective and clinically objective improvement of movement disorder.	<ol style="list-style-type: none"> 4 and 8 MS participants had quadriparesis/tetraparesis and paraplegia, respectively, with slight to considerable increase in tonus. Of the MS participants with quadraparetic/tetraparetic spasticity, only 1, who had only a slight increase in tonus and could walk with canes, noticed an improvement of standing and walking ability. Another participant had a clinical decrease in spasticity, and 2 participants had no improvement. Of the MS participants with paraparetic spasticity, a slight to distinct decrease of spasticity was found in 6 participants. 2 participants with a slight increase in tonus preoperatively showed a normal tonus or even hypotonus postoperatively. 6 participants were satisfied with the result of the treatment, and reported advances in standing, walking, sitting up from bed into a wheelchair, and an increase in endurance which could also be observed by physiotherapists.
Scerrati et al. 1982 <i>Effects of spinal cord stimulation on spasticity: H-reflex study</i> Italy Pre-Post N _{Initial} =5, N _{Final} =5	Population: Age range=28-60yr; Gender: males=2, females=3. MS participants=4. No further information provided. Intervention: Spinal cord stimulation (SCS) electrodes were implanted epidurally at the T ₉₋₁₀ or T ₁ level. The intensity of stimulation was adjusted to evoke non-painful paresthesiae in the extremities and trunk caudal to the electrode sites. The frequency was between 50-120Hz, or 33Hz. The study was carried out in all participants in the first	<ol style="list-style-type: none"> During SCS all participants felt non-painful paresthesiae in both legs. 3 participants noticed a subjective feeling of relaxation, sense of well-being, and improvement of spasticity; the remaining 2 participants did not report a positive subjective impression of effectiveness. No objective changes with regard to clinical examination and to the motor ability or performance was observed,

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
	2wks after electrode implantation; in 3 it was repeated after 7, 11, and 15mo. Outcomes/Outcome Measures: H-reflex; clinical effects.	other than in 1 participant who showed the ability to move the right foot during stimulation. 4. The threshold of the H-reflex was reduced by SCS in 4 participants (3 with MS) from 7.5 to 16% and enhanced to 9% in the fifth (MS) participant. 5. The H_{max}/M_{max} ratio in 3 MS participants was above 0.5, and below this value in the remaining 2 participants. 6. SCS yielded a decrease of approximately 20% of the ratio in 3 participants and kept it unchanged in the remaining 2 participants. 7. SCS did not seem to produce any significant effect on either the early or late facilitation, while it constantly modified the depression period. 8. No significant modifications were noted in the 3 participants on whom the examination was repeated after months of SCS in comparison to that observed in the first 2wks.
Siegfried et al. 1981 <i>Electrical spinal cord stimulation for spastic movement disorders</i> USA Pre-Post N _{Initial} =164, N _{Final} =53	Population: MS participants (n=37): Age range=25-65yr; Gender: males=17, females=19; Disease course: unspecified; Severity: unspecified; Disease duration=1-30yr. Intervention: Participants received electrical stimulation implantations of the spinal cord. Outcomes were assessed at baseline and 1-5yr later. Outcomes/Outcome Measures: Spasticity.	1. Following treatment 2 participants showed no improvement, 12 showed fair improvement, 18 showed good improvement, and 3 showed very good improvement in spasticity.
Dimitrijevic et al. 1980 <i>Neurophysiological evaluation of chronic spinal cord stimulation in patients with upper motor neuron disorders</i> USA Pre-Post N _{Initial} =11, N _{Final} =11	Population: Age range=23-57yr; Gender: males=7, females=4. MS participants=6. No further information performed. Intervention: Individuals underwent spinal cord stimulation (100 μ V of 7-700Hz). Outcomes were assessed at baseline and up to 18mo post treatment with polyelectromyography recordings. Outcomes/Outcome Measures: Voluntary induced activity; clonus; vibration reflexes; segmental reflexes.	1. All participants had a reduction of spasticity in the examined muscles of the lower limbs after stimulation.
Read et al. 1980	Population: MS participants (n=15): Mean age=43.4yr; Gender: males=9, females=6; Disease course: chronic static, progressive	1. Cord stimulation had no effect in 2 patients and reduced tone without reduction in strength in 6 patients.

Author Year Title Country Research Design PE德罗 Sample Size	Methods	Results
<i>The effect of spinal cord stimulation on function in patients with multiple sclerosis</i> UK Pre-Post N _{Initial} =16, N _{Final} =16	spinal; Severity: unspecified; Mean disease duration=11.8yr. Intervention: Participants underwent a procedure of implanted vertebral electrodes. Stimulation was continuous throughout the 2wk treatment period with the current level adjusted by patient. Outcomes were assessed at baseline and post treatment. Outcomes/Outcome Measures: Tone.	2. One patient had normal leg tone throughout and in 2 tone increased during cord stimulation. 3. Three of the additional 5 patients had increased tone prior to cord stimulation and 2 of these were unable to walk more than two or three steps. During cord stimulation tone was decreased in all 3, and the 2 previously chair-bound patients could walk for distances of 50m and 20m.

Discussion

Five studies examined the use of SCS on a variety of symptoms including the reduction of spasticity in PwMS.

In a study by Read et al. (1980), the authors examined 16 ambulatory patients with chronic static or progressive spinal MS. All participants underwent a procedure to implant electrodes in the conus medullaris. There was continuous stimulation for two weeks with the intensity adjusted by each subject to maintain a comfortable paresthesia. Cord stimulation resulted in reduced tone in nine subjects, increased tone in two subjects, and there was no change in tone in two subjects. Additionally, the authors noted that one subject had normal leg tone throughout the study. Additionally, two participants who were wheelchair dependent were able to walk for short distances (20m and 50m) during the stimulation period.

Dimitrijevic et al. (1980) examined the neurophysiologic effects of chronic SCS in participants with upper motor neuron disorders. Eleven individuals were followed over the course of 18 months; six subjects had a diagnosis of MS and five had a chronic spinal cord injury. Spasticity was measured via subjective patient report and polyelectromyography (PEMG) of muscle activity were recorded over each subject's lower trunk and lower limb muscles. PEMG analysis demonstrated consistent repeatable and definitive changes in motor control in all subjects following continuous stimulation. The authors reported that the most noticeable results included a reduction in tonic responses to various passive stretch as well as less overflow to other local muscles.

Siegfried, Lazorthes, and Broggi (1981) examined 53 subjects with spastic movement disorders who underwent chronic spinal electrical stimulation over a period of one to five years. Of the 53 participants studied, 37 of the candidates who underwent the implantation procedures were diagnosed with MS and all had severe to very severe lower extremity spasticity. Motor function assessments were performed one to five years post electrical stimulator placement. Of those individuals, two subjects showed no change in spasticity, 12 with fair improvement in spasticity, 18 with good improvement, and three with very good improvement.

Koulousakis et al. (1987) investigated the impact of SCS on clinical and subjective reports of spasticity and quality of life in 20 subjects with movement disorders. Of those, 12 were diagnosed with MS; four had

quadripareisis/tetraparesis and eight had paraparesis. Each of the participants underwent placement of multipolar electrodes implanted in the spinal canal via laminectomy. Continuous stimulation was provided, and subjects were monitored three, six, and 12 months post implantation and annually for an additional three years. Investigators examined muscle tone, gait pattern (if ambulatory), and subjective and clinical improvements of movement disorder although the assessments used were not disclosed. Of the four subjects with MS with quadripareisis/tetraparesis, one noted improvement in standing and walking although they only had a slight increase in tone initially. One subject was found to demonstrate a decrease in clinically measured spasticity and improvements in speech and nursing care, however subjectively reported “no improvement” due to an unreasonable expectation of study findings as reported by the authors. Two others with quadripareisis/tetraparesis were noted to have no improvement in spasticity or quality of life. Of the eight subjects with paraparesis, seven were followed for the study duration; six of seven subjects had a slight to distinct decrease in spasticity with reports of improved mobility including sitting, transfers, standing and walking. All seven reported increased endurance noted clinically by investigators.

In one small study, Scerrati and colleagues (1982) investigated the effects of SCS on the H-reflex in five subjects with spinal spasticity; four of the participants were diagnosed with MS. Each subject underwent placement of the stimulation electrodes via epidural at the T9-10 or T1 level with the stimulation level between 50-120Hz in three subjects and 33Hz in two subjects; the stimulation was intended to provoke a non-painful paresthesia in all subjects. H-reflex was obtained by measuring percutaneous stimulation of the posterior tibial nerve. During SCS, three of the subjects reported a subjective feeling of relaxation and improvement in spasticity and two subjects reported no impression of effectiveness. Clinically, no objective changes were observed upon examination or in motor ability other than one subject who was able to move the right foot during stimulation. During SCS, the H-reflex threshold was reduced to 7.5% (from 16%) in four participants (three with MS) and enhanced to 9% in the fifth (MS) participant. Furthermore, the Hmax/Mmax ratio was decreased by approximately 20% in three subjects and unchanged in two subjects. As a result, the heterogeneity of the subjects studied, and non-uniformity of the results leads to an inconclusive decision regarding the effectiveness of SCS in persons with MS.

Conclusion

There is level 4 evidence (from four pre-post studies; Koulousakis et al. 1987; Siegfried et al. 1981; Dimitrijevic et al. 1980; Read et al. 1980) that spinal cord stimulation may reduce spasticity in persons with MS.

Spinal cord stimulation may be a beneficial modality for treating spasticity in persons with MS.

2.4 Orthoses

Many individuals with MS may, at some point in their disease course, adopt the use of some type of lower limb orthosis as an assistive device during transferring, standing, and walking activities or to improve seated positioning. The orthosis serves to protect an individual’s joints and maintain biomechanical alignment as well as offer support to PwMS who have weaker trunks and legs (Lehman, 1979). In general,

lower limb orthoses tend to be prescribed to PwMS to achieve the following goals: to assist in compensating for fatigable weakness with the view to improve walking endurance, to reduce the energy-cost of walking by improving gait parameters and reducing biomechanical disadvantages (decreasing the excursion of the centre of mass during the gait cycle), and to reduce the risk of falls. Some orthoses afford an individual to weight-bear on the lower extremities and ambulate, which may decrease muscle tone and spasticity.

Table 13. Studies Examining Orthoses for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
<p>Sutliff et al. 2008</p> <p><i>Efficacy and safety of a hip flexion assist orthosis in ambulatory multiple sclerosis patients</i></p> <p>USA</p> <p>Pre-Post</p> <p>N_{Initial}=24, N_{Final}=21</p>	<p>Population: Mean age=52.8yr; Gender: males=9, females=12; Disease course: RRMS=48%, SPMS=14%, PPMS=24%, PRMS=14%; Severity: unspecified; Mean disease duration=14.9yr.</p> <p>Intervention: Participants were fitted with a hip flexion assist orthosis on their weaker side, trained to use the device, and given a wear schedule. There were two baseline evaluations and further assessments at follow-up testing at 8 and 12wks.</p> <p>Outcomes/Outcome Measures: Modified Ashworth Scale (MAS).</p>	<p>1. Lower extremity MAS scores did not change significantly between baseline and 8wk or 12wk follow-up visits.</p>

Discussion

One study by Sutliff et al. (2008) examined the efficacy and safety of a hip flexion assist orthosis (HFAO) on spasticity in ambulatory MS patients. The study examined 21 ambulatory PwMS (EDSS not specified) with unilateral or predominantly unilateral hip flexor weakness in a pre-post study design where spasticity, as measured by the MAS, was a secondary outcome measure. After an initial evaluation, each participant was fitted and trained to use a semi-custom novel lightweight active HFAO and instructed on a wear schedule. Each participant wore the HFAO during ambulation activities (daily duration not specified) daily over the course of 12 weeks. The study found no significant effect of the HFAO on spasticity.

Many factors must be considered when choosing an appropriate orthosis, including cosmesis. In the case of hip flexion assist devices, the only device which has been studied in PwMS with the view to assessing impact on spasticity, these are the most commonly used orthotic strategy to compensate for pure proximal lower limb weakness or a combination of weakness and tone-inhibited hip flexion from severe quadriceps spasticity. Given that these devices are typically worn over clothing and highly visible leading to poor cosmesis, require some effort to don, and may be costly, many eligible users decline a trial. More typically, PwMS are prescribed ankle-foot orthoses, which help compensate for distal lower limb weakness.

Conclusion

There is level 4 evidence (from one pre-post study; Sutliff et al. 2008) that hip flexion assist orthoses may not improve spasticity in persons with MS.

Hip flexion assist orthoses may not be an effective intervention to reduce lower limb spasticity in persons with MS. There is no evidence related to the utility of other types of orthoses for reducing spasticity in persons with MS.

2.5 Radial Shock Wave Therapy

Radial shock wave therapy (RSWT) is a modality which utilizes kinetic energy generated by a ballistic source to create pressure waves over a given target tissue. The pressure waves then cause cavitation bubbles within the target tissue producing a biological response thought to influence pathways in pain and hypertonicity (Ueberle, 2007). RSWT has been successfully used in rehabilitation to treat pain and muscle hypertonicity in persons with cerebral palsy (Gonkova, Ilieva, Ferriero, & Chavdarov, 2013; Vidal, Morral, Costa, & Tur, 2011) and stroke (Kim, Shin, Yoon, Kim, & Lee, 2013).

Table 14. Studies Examining Radial Shock Wave Therapy for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Marinelli et al. 2015 <i>Effect of radial shock wave therapy on pain and muscle hypertonia: a double blind study in patients with multiple sclerosis</i> Italy RCT PEDro=8 N _{Initial} =68, N _{Final} =68	Population: <i>Treatment (n=34):</i> Mean age=51.74yr; Gender: males=14, females=20; Disease course: unspecified; Mean EDSS=6.60; Mean disease duration: unspecified. <i>Control (n=34):</i> Mean age=51.00yr; Gender: males=16, females=18; Disease course: unspecified; Mean EDSS=6.15; Mean disease duration: unspecified. Intervention: Participants were randomized to receive active (treatment) or sham (control) radial shock wave therapy (RSWT). RSWT was received over 4 sessions with 1wk intervals in between, each delivering 2000 shots at 4Hz and 1.5bars. Outcomes of the lower limbs were assessed at baseline (T0), 1wk after the first session (T1), and 1wk (T2) and 4wks (T3) after the last session. Outcomes/Outcome Measures: Modified Ashworth Scale (MAS); H/M ratio.	<ol style="list-style-type: none">1. Mean MAS was significantly reduced from T0 to T2 with active treatment (2.68 to 1.90, p<0.0001) but not with control (2.56 to 2.44, p=0.20).2. In participants with active treatment, mean H/M ratio did not change significantly from T0 to T2 (0.57 to 0.56, p>0.05), but was significantly greater when compared to matched healthy controls (0.30, p=0.000002).

Discussion

One randomized controlled trial (RCT) by Marinelli and colleagues (2015) examined the effects of RSWT on pain and muscle hypertonia in PwMS. Sixty-eight subjects participated, with 34 receiving active RSWT and 34 receiving sham RSWT as the control group. The investigators administered RSWT once weekly for four weeks. Spasticity of the lower limbs were assessed at baseline, one week after the initial treatment session, one week following the final treatment session, and one month following the treatment session. In those participants who received the active treatment, investigators examined the H/M ratio which did not change over the course of treatment. However, mean MAS scores were significantly reduced over the course of the treatment series in those who received active treatment as compared to the control group.

Conclusion

There is level 1b evidence (from one randomized controlled trial; Marinelli et al. 2015) that radial shock wave therapy may reduce spasticity compared to sham stimulation in persons with MS.

Radial shock wave therapy may be effective for reducing spasticity in persons with MS.

2.6 Complementary and Alternative Treatment

Complementary and alternative medicine (CAM) approaches have been used as an adjunct to traditional therapies in Western medicine for many years (Jonas, Eisenberg, Hufford, & Crawford, 2013). CAM interventions include a heterogeneous mix of practices, such as acupuncture, reflexology, massage therapy, dietary modification, and the use of herbal medicines; however, there is limited data regarding the safety or effectiveness of these modalities. Although people with MS report use of CAM to manage symptoms (Olsen, 2009; Schwarz, Knorr, Geiger, & Flachenecker, 2008), few have been effectively evaluated for the management of spasticity.

2.6.1 Reflexology

Reflexology is a treatment modality involving manual stimulation of reflex points on the feet that are presumed to correspond to various areas of the body whereby treatment to those areas may positively influence the target tissues (Ernst & Köder, 1997). Reflexology has become a popular CAM treatment in the last century (Ernst & White, 2000). However, there has been little research regarding the safety or efficacy of this modality in individuals with MS.

Table 15. Studies Examining Reflexology for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
<p>Siev-Ner et al. 2003</p> <p><i>Reflexology treatment relieves symptoms of multiple sclerosis: a randomized controlled study</i></p> <p>Israel RCT PEDro=6 N_{Initial}=71, N_{Final}=53</p>	<p>Population: <i>Reflexology group (n=27):</i> Mean age=46.2yr; Gender: males=10, females=17; Disease course: unspecified; Severity: unspecified; Mean disease duration=11.9yr. <i>Control group (n=26):</i> Mean age=49.2yr; Gender: males=9, females=17; Disease course: unspecified; Severity: unspecified; Mean disease duration=13.4yr.</p> <p>Intervention: Participants were randomized to receive 11wks of reflexology or sham control (non-specific calf massage). Outcomes were assessed at baseline, 6wks, post treatment, and 3mo follow-up.</p> <p>Outcomes/Outcome Measures: Ashworth score.</p>	<ol style="list-style-type: none"> 1. There was no significant difference between reflexology and control groups at baseline (p>0.05). 2. The reflexology group demonstrated statistically significant improvement in spasticity, while this did not occur in the control group. 3. There was a significantly greater improvement in the reflexology group compared to the control group at 6wks (p=0.03) and at treatment completion (p=0.03). 4. There was no significant difference between reflexology and control groups at 3mo follow-up (p=0.06).

Discussion

A study conducted by Siev-Ner et al. (2003) examined the impact of reflexology treatment on MS symptoms. In this study, 53 PwMS were randomized to either a sham treatment group or a reflexology group with participants receiving weekly treatment sessions for 45 minutes over 11 weeks. Muscle tone, as measured by Ashworth scores, was evaluated as a primary outcome. The control group received non-specific calf massage (to control for touch therapy) while the experimental group received manual stimulation of reflex points on the feet. The study found a statistically significant decrease in Ashworth scores in the experimental group as compared to the control group at the end of the treatment period. However, one might question whether specific calf massage was an effective sham control and whether non-specific foot massage would have been superior. This must be considered a significant limitation in study design.

Conclusion

There is level 1b evidence (from one randomized controlled trial; Siev-Ner et al. 2003) that reflexology may reduce spasticity compared to a sham control (non-specific calf massage) in persons with MS.

Reflexology may reduce spasticity in persons with MS.

2.6.2 Acupuncture

Acupuncture, similar to reflexology, is a treatment modality originating in Eastern medicine that incorporates the use of specific pressure points on the body that correspond somatotopically to various body areas and target tissues. Classically, these points are accessed by specifically designed needles. In contrast to reflexology, substantially more is known about the pathophysiologic mechanisms involved in acupuncture induced analgesia. Reduction of nociceptive inputs may be crucial to improvement in spasticity. Historical research has reported that an “intact nervous system” is necessary for the anti-nociceptive effects (Levy & Matsumoto, 1975). Thus, total lesion burden and/or lesion location in PwMS may impact acupuncture efficacy. Previous research has demonstrated the benefits of acupuncture in stroke rehabilitation (Park, Hopwood, White, & Ernst, 2001; Vados, Ferreira, Zhao, Verdelino, & Wang, 2015).

Table 16. Studies Examining Acupuncture for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
<p>Miller 1996</p> <p><i>An investigation into the management of the spasticity experienced by some patients with multiple sclerosis using acupuncture based on traditional Chinese medicine</i></p> <p>UK</p> <p>RCT Crossover</p> <p>PEDro=5</p> <p>N_{Initial}=4, N_{Final}=4</p>	<p>Population: Age range=38-54yr; Gender: males=0, females=4. No further information provided.</p> <p>Intervention: Participants received acupuncture or usual care in pairs in a randomized order, followed by the alternate treatment. Outcomes were assessed before and after each treatment.</p> <p>Outcomes/Outcome Measures: Modified Ashworth Scale (MAS).</p>	<ol style="list-style-type: none"> 1. Mobile patients showed improvement in spasticity after acupuncture compared to their counterparts receiving usual care. 2. Wheelchair-bound patients showed no measurable improvement after acupuncture. 3. Results of statistical analyses were not reported.

Discussion

One study has evaluated acupuncture as a complimentary modality for reducing MS-related spasticity (Miller, 1996). Four participants (no disease course or severity noted) received usual care and acupuncture, in a randomized order, to their lower extremities. Two of the four were ambulatory and two said to be ‘wheelchair-bound/confined to their wheelchairs’. Spasticity, as measured by the MAS, was noted to improve in ambulatory participants receiving acupuncture compared to their counterparts receiving usual care. However, wheelchair-bound participants did not show measurable improvement in spasticity following treatment with acupuncture. One could speculate that the ability to adequately transmit along nociceptive pathways by virtue of a more intact central nervous system may be a key factor in being able to mount a response to acupuncture but the authors themselves make no hypotheses regarding the failure of the acupuncture treatment in the non-ambulatory (“wheelchair-bound”) patients.

More research would be necessary to draw further conclusions regarding the efficacy, tolerability, and safety of acupuncture in PwMS across the disease continuum.

Conclusion

There is level 2 evidence (from one randomized controlled trial; Miller 1996) that acupuncture may reduce spasticity compared to usual care in ambulatory persons with MS.

Acupuncture may reduce spasticity in ambulatory persons with MS.

2.6.3 Massage Therapy

Massage involves the manual manipulation of muscle, connective tissue, tendons, and ligaments, and is generally thought of as a modality to enhance a person's health and well-being. Recent evidence suggests that massage may impact factors that influence the experience of anxiety and depression, such as cortisol, serotonin, and dopamine (Field, Hernandez-Reif, Diego, Schanberg, & Kuhn, 2005). Massage therapy is the therapeutic application of massage with the goal of achieving a structural or physiological change in the body (Moyer, Rounds, & Hannum, 2004), such as increasing circulation, improving lymphatic drainage, lengthening shorted soft tissue, or reducing pain. Massage therapy has been evaluated related to the effectiveness for reducing spasticity in people with neurological conditions such as spinal cord injury (Manella & Backus, 2011) and cerebral palsy (Hernandez-Reif et al., 2005).

Table 17. Studies Examining Massage Therapy for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Backus et al. 2016 <i>Impact of massage therapy on fatigue, pain, and spasticity in people with multiple sclerosis: a pilot study</i> USA Pre-Post N _{Initial} =28, N _{Final} =24	Population: Mean age=47.4yr; Gender: males=6, females=22; Disease course: unspecified; Severity: unspecified; Mean disease duration=12.7yr. Intervention: Participants underwent massage therapy for 60min/wk for 6wks that consisted of effleurage, static compression strokes, friction, and petrissage. Outcomes were assessed at baseline and at 6wks. Outcomes/Outcome Measures: Modified Ashworth Scale (MAS).	<ol style="list-style-type: none"> Spasticity according to MAS was not increased or reduced for the right (p=0.23) or left (p=0.17) leg following massage therapy. There was a small negative effect size for MAS for both right and left leg.
Brouwer & de Andrade 1995	Population: Mean age=48.8yr; Gender: males=6, females=4; Disease course: unspecified; Severity: unspecified; Mean disease duration=13.5yr.	<ol style="list-style-type: none"> A significant decrease in H-reflex amplitude was found 30min following massage compared to baseline values (p<0.05).

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
<i>The effects of slow stroking on spasticity in patients with multiple sclerosis: a pilot study</i> Canada Pre-Post N _{Initial} =22, N _{Final} =21	Intervention: Participants with plantar flexor spasticity underwent light pressure stroke massage for 3min along the primary rami region. Electrophysiological responses were recorded at baseline, immediately following massage, and 30min post massage. Outcomes/Outcome Measures: H-reflex.	2. There was no significant change in other measures (compound muscle action potential amplitudes ($p>0.05$), T_{max} ($p=0.68$), or H_{vib} ($p=0.37$)) following massage compared to baseline. 3. Individuals that were not administered anti-spastic drugs tended to decline in mean T_{max}/M_{max} ratio after massage (no statistical tests performed).

Discussion

Two studies employed a pre-post design to evaluate the effectiveness of massage therapy for reducing spasticity in persons with MS. Backus et al. (2016) evaluated the impact of massage therapy delivered for 30 minutes a week for six weeks on spasticity in the lower extremities in 28 people with MS. They found that a defined routine consisting of a combination of effleurage, petrissage, friction, and static compression strokes did not lead to significant changes, and specifically did not reduce spasticity, as measured with the MAS. The authors reported that spasticity was not a primary outcome measure for this study, and the intervention was not focused specifically on extremities in which there was increased tone or spasticity. They also stated that some participants in the study did not have spasticity at the start of the study, and thus, a decrease in spasticity was not anticipated.

In contrast to the Backus et al. (2016) study, all participants in the Brouwer and de Andrade (1995) study had mild to moderate spasticity in their lower extremities, as this was an inclusion criterion. In this study, investigators used electrophysiological measures, i.e., the H-reflex, to determine whether the excitability of the alpha-motor neuron pool and pre-synaptic inhibition could be acutely modified in the plantar flexor muscles with three minutes of slow stroking. While participants reported that they felt more relaxed, and the H-reflex amplitude and alpha motoneuron excitability were significantly decreased for up to 30 minutes after the intervention, neither the pre-synaptic inhibition nor the mechanically induced stretch reflex changed significantly. This was a small study, without a control group, and thus further research is warranted.

Conclusion

There is conflicting evidence (from two pre-post studies; Backus et al. 2016; Brouwer & de Andrade 1996) regarding whether or not massage therapy improves spasticity in the lower extremities of persons with MS.

It is unclear if massage therapy improves spasticity in the lower extremities of persons with MS.

2.7 Combining or Comparing Non-pharmacological Modalities

In the management of spasticity in PwMS, multiple interventions are often trialed, either in combination or comparatively. While the previous sections have evaluated the effect of independent treatment modalities to improve spasticity in PwMS, several studies have examined the use of multiple non-pharmacological interventions for MS-related spasticity.

2.7.1 Exercise and Theta-Burst Stimulation

Table 18. Studies Examining Exercise and Theta-Burst Stimulation for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
<p>Mori et al. 2011</p> <p><i>Transcranial magnetic stimulation primes the effects of exercise therapy in multiple sclerosis</i></p> <p>Italy RCT PEDro=6 N_{Initial}=30, N_{Final}=30</p>	<p>Population: <i>Group 1 (exercise therapy (ET) and intermittent theta-burst stimulation (iTBS)) (n=10):</i> Mean age=39.1yr; Gender: males=7, females=3; Disease course: RRMS; Mean EDSS=3.6; Mean disease duration: unspecified. <i>Group 2 (ET and sham iTBS) (n=10):</i> Mean age=37.7yr; Gender: males=6, females=4; Disease course: RRMS; Mean EDSS=3.8; Mean disease duration: unspecified. <i>Group 3 (iTBS only) (n=10):</i> Mean age=38.3yr; Gender: males=5, females=5; Disease course: RRMS; Mean EDSS=3.5; Mean disease duration: unspecified.</p> <p>Intervention: Patients were randomized to receive either iTBS plus ET for 2wks, sham stimulation plus ET for 2wks, or iTBS alone. Outcomes were assessed at baseline and after treatment.</p> <p>Outcomes/Outcome Measures: Modified Ashworth Scale (MAS); Multiple Sclerosis Spasticity Scale (MSSS-88).</p>	<ol style="list-style-type: none"> 1. The stimulated leg had significantly improved MAS scores (2.1 vs. 1.3, p<0.05) and MSSS-88 scores (74.3 vs. 53.2, p<0.001) after treatment with iTBS plus ET compared to baseline, but not after sham stimulation plus ET. 2. The stimulated leg had significantly improved MAS scores (3.3 vs. 1.6, p<0.05), but not MSSS-88 scores, after treatment with iTBS alone compared to baseline. 3. For the unstimulated leg, there were no significant differences in MAS scores between baseline and after treatment for any of the groups. 4. iTBS plus ET produced more consistent beneficial effects compared to iTBS alone. 5. Results also indicated that when ET was continued alone for 4wks or longer at the end of the experimental program (after sham stimulation had ended), ET was significantly associated with a decrease in MAS (2.4 vs. 1.8, p<0.05) and MSSS-88 scores (69.4 vs. 59.5, p<0.05).

Discussion

One study has examined the use of exercise and TBS as a combined intervention to treat MS-related spasticity. Mori et al. (2011) examined the benefits of iTBS alone and combined with exercise therapy, with spasticity as a primary outcome of the study. Thirty participants with RRMS (EDSS 2.0-6.0) with unilateral or predominantly unilateral lower extremity spasticity were randomly assigned to one of three groups: 1) iTBS alone, 2) iTBS plus exercise therapy, and 3) sham iTBS plus exercise therapy. The high frequency (theta frequency 5Hz) iTBS (or sham stimulation) was delivered for approximately three

minutes (200 seconds) daily for five consecutive days for two weeks. The study found that iTBS alone and iTBS together with exercise therapy produced positive effects on spasticity, while exercise therapy alone did not. While both groups receiving iTBS saw a significant reduction in lower extremity spasticity, the group receiving iTBS and exercise therapy saw a reduction in both MAS and MSSS-88 scores while the iTBS alone group noted only a reduction in MAS scores. As a result, this study demonstrates that the combined modalities have a greater beneficial effect than iTBS alone.

Conclusion

There is level 1b evidence (from one randomized controlled trial; Mori et al. 2011) that intermittent theta-burst stimulation (iTBS) in combination with exercise therapy may reduce spasticity compared to iTBS alone in persons with relapsing-remitting MS.

Intermittent theta-burst stimulation, in combination with exercise therapy, may reduce spasticity in persons with relapsing-remitting MS.

2.7.2 Exercise and Massage Therapy

Table 19. Studies Examining Exercise and Massage Therapy for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Negahban et al. 2013 <i>Massage therapy and exercise therapy in patients with multiple sclerosis: a randomized controlled pilot study</i> Iran RCT PEDro=7 N _{Initial} =48, N _{Final} =48	Population: <i>Massage Therapy (n=12):</i> Mean age=36.33yr; Gender: males=2, females=10; Disease course: RRMS or SPMS; Mean EDSS=3.75; Mean disease duration: 148.7mo. <i>Exercise Therapy (n=12):</i> Mean age=36.67yr; Gender: males=2, females=10; Disease course: RRMS or SPMS; Mean EDSS=3.5; Mean disease duration: 102mo. <i>Massage-exercise Therapy (n=12):</i> Mean age=36.67yr; Gender: males=2, females=10; Disease course: RRMS or SPMS; Gender: males=2, females=10; Mean EDSS=3.75; Mean disease duration=115.3mo. <i>Control (n=12):</i> Mean age=36.83yr; Gender: males=2, females=10; Disease course: RRMS or SPMS; Gender: males=2, females=10; Mean EDSS=3.83; Mean disease duration: 86.58mo. Intervention: Participants were randomly and allocated to one of four groups: 1) massage therapy, 2) exercise therapy, 3) massage-exercise therapy, and 4) control. The massage, exercise, and massage-exercise therapy groups received 30min sessions 3x/wk of their respective intervention, for	<ol style="list-style-type: none"> 1. The massage group and exercise group had significantly improved MAS scores following intervention (p=0.006 and p=0.031, respectively) compared to baseline. 2. The combined massage-exercise group demonstrated a reduction in MAS scores; however, it did not reach statistical significance compared to baseline (p=0.530). 3. The control group had significantly worsened MAS scores following intervention compared to baseline (p=0.031). 4. The massage and exercise groups had significantly better MAS change scores than the control group (p<0.001 and p=0.002, respectively). 5. The combined massage-exercise group did not show a significantly different MAS change score compared to the control group (p=0.015). 6. No significant difference in MAS change scores were observed between the

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
	5wks. The massage therapy group received a standard Swedish massage. The exercise therapy group performed a combined set of strength, stretch, endurance, and balance training exercises. The massage-exercise therapy group performed active exercises for 15min, and additionally received a passage massage for another 15min. The control group received standard medical care and refrained from participating in any exercise program during the 5wk treatment period. Outcomes were assessed at baseline and after treatment. Outcomes/Outcome Measures: Modified Ashworth Scale (MAS).	massage group, exercise group, and combined massage-exercise group.

Discussion

Negahban et al. (2013) evaluated the comparative effectiveness of massage and exercise therapies alone or in combination for reducing a variety of symptoms, including spasticity, in PwMS. Forty-eight participants with RRMS or SPMS (EDSS 2.0-6.0) were randomized to one of four groups including 1) massage therapy alone, 2) exercise therapy alone, 3) massage and exercise therapy, and 4) control group (standardized medical care). Each group received interventions in 30-minute sessions three times per week for five weeks. The massage therapy group received the massage therapy to their bilateral lower extremities for 30 minutes. The exercise therapy group participated in a 30-minute standardized program consisting of stretching, strengthening, balance, and endurance training for their lower extremities. The combined therapy group received 15 minutes of active exercise in addition to 15 minutes of passive massage to the bilateral lower extremities. Spasticity was measured by the MAS. The massage and exercise groups demonstrated significant reductions in spasticity compared to baseline ($p=0.006$ and $p=0.031$, respectively). Additionally, the combined intervention group experienced a smaller reduction that was not statistically significant compared to baseline ($p=0.530$). The lack of significant change in the combination group may be due to less time spent on either intervention alone, with the participants receiving half the dosage of each modality. The massage and exercise groups demonstrated significantly better MAS change scores compared to the control group ($p<0.001$ and $p=0.002$, respectively). However, the combined intervention group did not have significantly different MAS change scores compared to the control group ($p=0.015$). Furthermore, no significant differences in spasticity were observed between the exercise, massage, and combined intervention groups.

Conclusion

There is level 1b evidence (from one randomized controlled trial; Negahban et al. 2013) that massage therapy in combination with exercise therapy may not reduce spasticity compared to standard medical care in persons with MS.

There is level 1b evidence (from one randomized controlled trial; Negahban et al. 2013) that massage therapy, exercise therapy, and combined massage-exercise therapy may not be more effective compared to one another for spasticity in persons with MS.

Combining massage therapy with exercise therapy may not reduce spasticity in persons with MS more than either therapy alone.

2.7.3 Therapeutic Standing and Exercise

The effect of therapeutic static weight bearing has been demonstrated to reduce spasticity in individuals with cerebral palsy (Pin, 2007) and spinal cord injury (Bohannon, 1993).

Table 20. Studies Examining Therapeutic Standing and Exercise for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Baker et al. 2007 <i>Therapeutic standing for people with multiple sclerosis: efficacy and feasibility</i> UK RCT Crossover PEDro=5 N _{Initial} =6, N _{Final} =6	Population: Mean age=45.6yr; Gender: males=1, females=5; Disease course: SPMS; Mean EDSS=7; Mean disease duration=17yr. Intervention: Individuals were randomized to either Group A (Oswestry-exercise) or Group B (exercise-Oswestry). Both conditions were completed for 3wks before crossing over to other condition. The Oswestry standing frame was used for 30min/d. Home exercise programs were individualized to each participant. Outcomes were assessed at baseline, 3wks, and 6wks. Outcomes/Outcome Measures: Ashworth scale (AS); Penn Spasm Frequency Scale (PSFS).	1. There were no significant between-group differences in AS or PSFS scores ($p>0.05$), although downward trends were observed for both interventions.

Discussion

A single randomized controlled trial by Baker et al. (2007) examined the efficacy of a home exercise program and therapeutic standing (via Oswestry standing frame support) on range of motion, spasticity, and spasm outcomes in PwMS. Six participants with SPMS (EDSS 7.0) and Ashworth scores of at least greater than or equal to two in their lower extremities participated in this randomized crossover study. Statistically significant improvements were noted in range of motion in participants' hips and knees with the standing intervention as compared to the exercise group. Additionally, there were downward trends in the reduction of Ashworth scores for knee flexion and ankle dorsiflexion in standing as well as a reduction in spasm frequency (although not severity) as measured by the Penn Spasm Frequency Scale in both the exercise and standing programs. Although the study did not demonstrate statistically significant

between-group changes in measures of spasticity and spasms, improvements were noted, indicating that further research is warranted.

Conclusion

There is level 2 evidence (from one randomized controlled trial; Baker et al. 2007) that supported standing may not improve spasticity compared to a home exercise program in persons with secondary progressive MS.

The use of supported standing may not improve spasticity more than a home exercise program in persons with secondary progressive MS.

2.7.4 Vibration and Exercise

Vibration is a modality delivered while a participant is sitting, standing, or lying on a large vibrating platform. Whole body vibration involves stimulating the entire body with the body situated in some fashion over a vibrating surface (Dolny & Reyes, 2008), and may be beneficial for reducing spasticity in people with neurological injury or disease (Huang, Liao, & Pang, 2017).

Table 21. Studies Examining Vibration and Exercise for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Schyns et al. 2009 <i>Vibration therapy in multiple sclerosis: a pilot study exploring its effects on tone, muscle force, sensation and functional performance</i> UK RCT Crossover PEDro=4 N _{Initial} =16, N _{Final} =12	Population: <i>Group 1 (n=8):</i> Mean age=45.8yr; Gender: males=3, females=5; Disease course: unspecified; Severity: unspecified; Mean disease duration=6.7yr. <i>Group 2 (n=8):</i> Mean age=49.5yr; Gender: males=1, females=7; Disease course: unspecified; Severity: unspecified; Mean disease duration=11.8yr. Intervention: Participants were randomized to either group 1 or group 2. Group 1 received 4wks of whole body vibration plus exercise 3x/wk, 2wks of no intervention, and then 4wks of exercise alone 3x/wk. Group 2 was given the two treatment interventions in the reverse order to group 1. Outcomes were assessed at baseline and after each treatment period. Outcomes/Outcome Measures: Modified Ashworth Scale (MAS); Multiple Sclerosis Spasticity Scale (MSSS-88).	1. MAS scores remained unchanged for each intervention, although increased tone tended to be associated with exercise alone compared to whole body vibration plus exercise. 2. MSSS-88 spasm scores were reduced after whole body vibration and exercise to a greater degree than after exercise alone (p=0.02).

Discussion

One study by Schyns et al. (2009) evaluated the use of whole body vibration as an adjunct to traditional exercise programming. In this study, 16 participants with MS were randomly assigned to either an exercise program performed with whole body vibration or the same exercise program without whole body vibration. Both groups of participants then underwent the alternate condition with a two-week rest period in between programs. Spasticity was measured before and after each intervention series using the MAS and MSSS-88. The vibration was delivered at 40Hz for 30 seconds (specific manufacturers' recommendations for stretching and strengthening exercises) while each participant was performing a series of 10 lower body exercises. The study found that MAS scores were unchanged after either intervention in both groups. MSSS-88 scores showed a statistically significant reduction in spasms after the combined exercise program with whole body vibration versus the exercise program alone. While there is insufficient evidence to conclude whether whole body vibration provides additional improvements in tone reduction, vibration did not have a deleterious effect on MS-related spasticity. The authors suggest that vibration may potentially be used as an adjunct to an exercise program for the reduction of spasticity given that there was a reduction in the MSSS-88 scores.

Conclusion

There is level 2 evidence (from one randomized controlled trial; Schyns et al. 2009) that whole body vibration in combination with exercise may not be more effective for improving spasticity compared to exercise alone in persons with MS.

Whole body vibration, in combination with exercise, may not reduce clinical measures of spasticity in persons with MS; however, it may have a positive impact on subjective measures of spasticity.

2.7.5 Functional Electrical Stimulation-Supported Lower Extremity Cycling

Functional electrical stimulation (FES)-supported lower extremity cycling is a modality using electrical stimulation to support an individual's lower extremity muscle contraction throughout a cycling motion. The use of FES cycling has been previously demonstrated to be effective to improve muscle function and cycling mobility in persons with spinal cord injury (Hunt et al., 2004; Petrofsky & Phillips, 1984) and stroke (Szecsi, Krewer, Muller, & Straube, 2008). Consequently, the use of FES may have beneficial applications in the treatment of MS-related spasticity.

Table 22. Studies Examining Functional Electrical Stimulation-Supported Lower Extremity Cycling for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Szecsi et al. 2009 <i>Functional electrical stimulation-assisted cycling of patients with multiple sclerosis: biomechanical and functional outcome - a pilot study</i> Germany Pre-Post N _{Initial} =12, N _{Final} =8	<p>Population: Mean age=50.9yr; Gender: males=11, females=1; Disease course: chronic progressive; Mean EDSS=6.5; Mean disease duration=15.25yr.</p> <p>Intervention: Participants underwent 6 functional electrical stimulation (FES)-supported ergometric cycling training sessions on a stationary ergometer, 3 sessions/wk for 2wks. The patients' quadriceps and hamstrings were stimulated during training. Data was collected before and after daily training sessions, and before and after the 2wk training period.</p> <p>Outcomes/Outcome measures: Modified Ashworth Scale (MAS).</p>	1. There was a significant reduction in muscle spasticity in the short term (pre/post training sessions; p=0.05), but no significant reduction in the long term (first/last training days; p=0.92).

Discussion

Szecsi et al. (2009) performed a pilot studying evaluating the effects of FES assisted lower extremity cycling on various biomechanical and functional outcomes in PwMS. Twelve participants (EDSS scores 4.0-8.0) with 'chronic progressive' MS (term not defined by authors) participated in six FES-supported cycling training sessions over two weeks. During the sessions, each participant completed 12-18 minutes of total training time with only six minutes of FES-supported pedaling, with the patient physically controlling the stimulation intensity delivered via a throttle mechanism. Spasticity was measured using the MAS. A statistically significant reduction in spasticity was noted immediately following the intervention (pre and post daily training sessions), however there was no significant longer term reduction in spasticity (before and after the two-week training period).

Conclusion

There is level 4 evidence (from one pre-post study; Szecsi et al. 2009) that spasticity may be acutely reduced following functional electrical stimulation-assisted lower extremity cycling in persons with chronic progressive MS.

Functional electrical stimulation-supported lower extremity cycling may reduce spasticity immediately following treatment in persons with chronic progressive MS.

2.7.6 Multidisciplinary Rehabilitation

Multidisciplinary or interdisciplinary rehabilitation is a model of care that involves the input of a variety of medical specialists and allied health professionals working together for the purposes of minimizing the participant’s symptom burden and improving all facets of independent functioning at the activity and social participation levels. This may be delivered as inpatient or outpatient care depending on the complexity of the rehabilitation needs of the individual. In the context of MS, inpatient care may be the preferred delivery model following an acute and debilitating relapse or for periods of transition from ambulatory to non-ambulatory status. Increasingly, outpatient programs to assist in the development of self-management skills are gaining traction in the field of MS. For more information on team rehabilitation, see Team-Based Rehabilitation: Functional and Quality of Life Outcomes.

Table 23. Studies Examining Multidisciplinary Rehabilitation for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Storr et al. 2006 <i>The efficacy of multidisciplinary rehabilitation in stable multiple sclerosis patients</i> Denmark RCT PEDro=8 N _{Initial} =106, N _{Final} =90	Population: <i>Control group (n=52):</i> Mean age=50.1yr; Gender: males=16, females=36; Disease course: RRMS=12 (23%), PPMS=11 (21%), SPMS=29 (56%); Mean EDSS=6.5; Mean disease duration=9.0yr. <i>Intervention group (n=38):</i> Mean age=53.0yr; Gender: males=16, females=22; Disease course: RRMS=5 (13%), PPMS=9 (24%), SPMS=24 (63%); Mean EDSS=6.5; Mean disease duration=9.0yr. Intervention: Individuals were randomized either to the control group and received no rehabilitation treatment, or to the intervention group and received rehabilitation treatment from the MS rehabilitation hospital in Haslev Denmark. No information regarding medications was provided. Outcomes/Outcome Measures: Visual Analog Scale (spasticity).	1. No significant difference was found between the control and the intervention groups for spasticity (p=0.99).

Discussion

Storr et al. (2006) evaluated the efficacy of a multidisciplinary inpatient rehabilitation program in stable PwMS. Ninety participants were randomized into either a control group or intervention group. The control group remained in their homes and was given no study-related treatment while the intervention group was admitted to a comprehensive multidisciplinary inpatient rehabilitation program lasting, on average, 35 days. Spasticity was measured subjectively as a secondary outcome via a VAS for spasticity. The intervention group received individualized 45-minute physical therapy sessions four to five times per week, 30-minute occupational therapy sessions three times per week, and 30 minutes of daily self-directed exercise training over three to five weeks. The study did not demonstrate any beneficial effect of

the rehabilitation program on any study related outcome measures. The authors hypothesized that this effect was due to a short duration intervention in clinically stable individuals for sustained exercise as compared to rehabilitating specific impairments. Additionally, the generalized nature of the rehabilitative programs may have contributed to a smaller effect. A highly personalized program directed towards specific rehabilitative needs may yield better results.

Conclusion

There is level 1b evidence (from one randomized controlled trial; Storr et al. 2006) that multidisciplinary inpatient rehabilitation may not improve spasticity compared to no treatment in clinically stable persons with MS.

Multidisciplinary inpatient rehabilitation may not improve subjective measures of spasticity in clinically stable persons with MS.

2.8 Surgery

In some individuals with spasticity, hypertonia may be so severe that contractures develop and can drastically impair functional positioning, mobility, and lead to harmful skin breakdown. When an individual develops severe spasticity that fails conventional conservative treatments, surgery may be necessary to prevent increasingly severe abnormal postures. Surgical options for the treatment of severe spasticity and contractures in PwMS include both orthopedic and neurological approaches, including multiple tenotomy, and longitudinal myelotomy, selective posterior rhizotomy, microsurgical dorsal root entry zone (DREZ)-otomy (MDT), and intrathecal injections, respectively. Intrathecal baclofen pump treatment is discussed in a separate module focusing exclusively on evidence for the pharmacological management of spasticity.

Table 24. Studies Examining Surgery for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Pope et al. 1991 <i>Surgery combined with continuing post-operative stretching and management for knee flexion contractures in cases of multiple sclerosis - a report of six cases</i> UK	Population: Age range=46-67yr; Gender: males=0, females=6. No further information provided. Intervention: Patients with severe spasticity in the lower limb underwent tenotomy as well as post-operative continuous passive motion and plaster of Paris immobilization. Outcomes were assessed at baseline and at 2wks, 3mo, and 9mo postoperatively. Outcomes/Outcome Measures: Contractures.	1. Knee contractures were significantly reduced in all participants in both legs following surgery (p<0.0005).

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Pre-Post N _{Initial} =6, N _{Final} =6		
Sindou & Jeanmonod 1989 <i>Microsurgical DREZ-otomy for the treatment of spasticity and pain in the lower limbs</i> France Pre-Post N _{Initial} =53, N _{Final} =53	<p>Population: Mean Age=41yr; Gender: males=23, females=30; MS participants=28. No further information provided.</p> <p>Intervention: Participants with MS (n=28), brain injury (n=10), and spinal cord injury (n=15) underwent microsurgical DREZ-otomy for spasticity. Follow-up times ranged from 1mo to 13yr.</p> <p>Outcomes/Outcome Measures: Spasticity; spasms.</p>	<ol style="list-style-type: none"> 1. Mean spasticity score at baseline was 3.6/4 (with 4 indicating severe spasticity). 2. Mean spasticity scores at follow-up were 1.04 (1mo), 1.56 (6mo), and 1.58 (1yr). 3. Mean spasm score at baseline was 2.52 (with 4 indicating severe spasms). 4. Mean spasm scores at follow-up were 0.93 (1mo), 0.97 (6mo), and 1.03 (1yr).
Sindou et al. 1982 <i>Results of selective posterior rhizotomy in the treatment of painful and spastic paraplegia secondary to multiple sclerosis</i> France Pre-Post N _{Initial} =15, N _{Final} =15	<p>Population: Age range=31-58yr; Gender: males=2, females=13; Disease course: unspecified; Severity: unspecified; Mean disease duration=12yr.</p> <p>Intervention: Participants underwent a selective posterior rhizotomy procedure. Participants were evaluated at baseline and postoperatively within a 1-8yr follow-up period.</p> <p>Outcomes/Outcome Measures: Spontaneous postures; spasms.</p>	<ol style="list-style-type: none"> 1. After surgery, 12/15 participants had a significant improvement in terms of spontaneous postures. 2. Results for spasms in flexion and pain crises, which were intense and frequent in all participants, were good in all but 1 participant.
Laitinen & Singounas 1971 <i>Longitudinal myelotomy in the treatment of spasticity of the legs</i> Finland Pre-Post N _{Initial} =9, N _{Final} =9	<p>Population: MS participants (n=5): Mean age=39.6yr; Gender: males=2, females=3; No further information provided.</p> <p>Intervention: Participants underwent a lateral longitudinal myelotomy at the level of the conus medullaris. Outcomes of the lower limbs were assessed before and 1-4yr after the operation.</p> <p>Outcomes/Outcome Measures: Spasticity.</p>	<ol style="list-style-type: none"> 1. Severe spasticity and associated pain were relieved in 8 participants. 2. 4/5 participants with MS had absent spasticity, and 1 still had spastic ankles, postoperatively.
Glazer & Mooney 1970 <i>Surgery of the extremities in patients with multiple sclerosis</i>	<p>Population: Gender: males=68, females=181. No further information provided.</p> <p>Intervention: Patients who received surgical procedures (e.g., tenotomy, neurectomy, fusion, release, transfer) were retrospectively analyzed.</p>	<ol style="list-style-type: none"> 1. 231 surgical procedures had postoperative data: 85 extremity operations, 44 nerve blocks, and 102 miscellaneous operations. 2. Only 61 extremity procedures (surgery or nerve block) were performed for MS-related issues.

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
USA Case Series N _{Initial} =249, N _{Final} =249	Outcomes/Outcome Measures: Spasticity; contractures.	<ol style="list-style-type: none"> 3. Spasticity was greatly relieved by 35 procedures, partially by 7, and slightly by 2. 4. Contracture was greatly relieved by 41 procedures, partially by 8, and slightly by 2.

Discussion

Several studies have investigated a wide range of surgical interventions for severe spasticity management in PwMS. Pope et al. (1991) examined the effect of surgery (tenotomy) and post-operative stretching and immobilization for the management of knee contractures in six cases of MS. Following surgery, bilateral knee contractures in all subjects were significantly reduced with a statistically significant increase in hip range of motion which was maintained at reassessment at two weeks, three months, and nine months postoperatively. Furthermore, a post-surgical stretching regimen using either continuous passive motion or plaster of Paris serial casting showed no statistically significant differences in maintaining gains. Functionally, the authors found no significant improvement in transfer time following surgery. As such, tenotomies to address contracture management is a viable option if the individual is no longer able to be managed by conservative care.

Laitinen and Singounas (1971) investigated lower extremity spasticity and lower extremity mobility in response to longitudinal myelotomy in nine participants, five of whom were diagnosed with MS. All patients except one had complete paraplegia with spasticity preoperatively. In all participants, severe spasticity and associated pain was immediately relieved postoperatively. Five patients experienced a recurrence of distal spasticity in the Achilles reflex without recurrence of hip or knee spasticity which the author attributed to the fact that the "lower end of the [surgical] incision had been made higher than it should have been." Postoperatively, two patients with MS regained some volitional movement in both limbs. A third patient (with MS) had been completely bedridden with paraplegia for eight years prior to the longitudinal myelotomy and was able to walk with the help of a knee supporting splint three months post surgery. As a result, myelotomy may be a viable option for treatment of severe spasticity of the lower extremities.

Glazer and Mooney (1970) reported on a retrospective case series of 249 patients with MS who underwent various surgical procedures including tenotomies, neurectomies, spinal fusions, tendon releases, and tendon transfers. Of the 231 procedures performed, only 61 extremity procedures in 42 participants (surgery or nerve block) were performed to alleviate MS-related issues. Spasticity was relieved to an extent in 44 extremity procedures; of the procedures performed, spasticity was greatly relieved by 35 operations, partially relieved by seven operations, and slightly relieved by two operations. Additionally, fixed contractures were relieved by 41 operations, partially relieved by eight operations, and slightly relieved by two operations. Overall, retrospective analysis demonstrated effective relief of spasticity and decrease in contractures leading to improved quality of life for PwMS.

Sindou and colleagues (1982) evaluated the effectiveness of selective posterior rhizotomy (SPR) in 15 subjects with advanced MS. All subjects demonstrated hypertonicity with irreducible abnormal postures in lower extremity triple flexion and adduction with significant associated pain that had been resistant to conservative treatments. Following SPR, 12 of the 15 subjects has significant improvement in spastic flexion of the hips and knees allowing for an improved spontaneous posture. Additionally, all but one participant demonstrated good improvements in flexion spasms. Given the result that 80% (12 out of 15) of participants experienced positive outcomes, SPR may be considered a valuable method for the treatment of paraplegia with significant hypertonicity and postural dysfunction.

Sindou and Jeanmonod (1989) evaluated the long-term effects of MDT to treat harmful spasticity in one or both lower extremities in 53 bedridden patients with intractable spasticity; 28 of the 53 study participants were diagnosed with MS. All patients underwent surgical procedures via microsurgical laminectomy to access the appropriate rootlets within the conus medullaris. Spasticity was measured on a scale developed by the authors ranging from zero (best – normal tone) to four (severe), similar to the MAS. Preoperatively, severe flexor spasticity was present in 49 out of 53 subjects and severe extensor spasticity in three out of 53 subjects. Additionally, 38 of the participants had severe flexion spasms. Postoperatively, 75% of the subjects had good or excellent outcomes for resolution of their spasticity with mean scores at baseline of 3.6/4 reduced to follow up scores of 1.04 (one month post), 1.56 (six months post) and 1.58 (one year post) with no significant changes noted in continued follow up to 13 years post-operatively. Additionally, 82.2% of subjects experienced good or excellent outcomes for reduction of flexion spasms. Regarding flexion spasms, these subjects had mean scores at baseline of 2.52/4 reduced to follow up scores of 0.93 (one month post), 0.97 (six months post) and 1.03 (one year post) with no significant changes noted in continued follow up to 13 years post-operatively. Given these results, MDT is potentially a viable option for managing severe spasticity that is not responsive to more conservative treatments.

Conclusion

There is level 4 evidence (from four pre-post studies and one case series; Pope et al. 1991; Sindou & Jeanmonod 1989; Sindou et al. 1982; Laitinen & Singounas 1971; Glazer & Mooney 1970) that orthopedic surgical interventions and neurosurgical interventions involving the spinal cord may reduce spasticity in persons with MS.

Both orthopedic surgical and neurosurgical interventions may be effective for reducing severe spasticity in persons with MS.

3.0 Combining or Comparing Pharmacological and Non-pharmacological Modalities

In the management of spasticity in PwMS, multiple interventions are often trialed, either in combination or comparatively. Several studies have examined the use of various combinations of pharmacological and non-pharmacological interventions for MS-related spasticity.

3.0.1 Baclofen and Transcutaneous Electrical Nerve Stimulation

Table 25. Studies Examining Baclofen and Transcranial Electrical Nerve Stimulation for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Shaygannejad et al. 2013 <i>Comparison of the effect of baclofen and transcutaneous electrical nerve stimulation for the treatment of spasticity in multiple sclerosis</i> USA RCT PEDro=5 N _{Initial} =58, N _{Final} =52	<p>Population: <i>Transcutaneous Electrical Nerve Stimulation (TENS) group (n=26):</i> Mean age=39.5yr; Gender: males=9, females=17; Disease course: RRMS=20, SPMS=5, PPMS=1; Mean EDSS=2.8; Mean disease duration=7.2yr. <i>Baclofen group (n=26):</i> Mean age=38.9yr; Gender: males=6, females=20; Disease course: RRMS=18, SPMS=8; Mean EDSS=2.6; Mean disease duration=5.3yr.</p> <p>Intervention: Participants were randomized to receive either baclofen (10mg 2x/d, increasing to 25mg over the following 3wks) or self-applied TENS (20-30min/session (as needed) for 4wks). Outcomes were assessed at baseline and at 4wks.</p> <p>Outcomes/Outcome Measures: Modified Ashworth Scale (MAS).</p>	<ol style="list-style-type: none"> 1. There was a significant improvement in MAS scores in the right and left leg after treatment in both the TENS group and baclofen group compared to baseline (both p<0.001). 2. TENS treatment was significantly more effective at reducing MAS scores in both the right (p<0.05) and left (p<0.01) legs compared to the baclofen group.

Discussion

One RCT compared the effects of baclofen and TENS on lower extremity spasticity in PwMS (Shaygannejad et al., 2013). Fifty-two patients (EDSS≤6.0 and MAS scores of ≤3) were randomized to a four-week course of oral baclofen (10mg bid titrated up to 25mg bid) or four-week course of self-applied TENS to the gastrocnemius daily for 20-30 minutes any time a spasm occurred. Spasticity was measured with the MAS. Both groups demonstrated a statistically significant reduction in lower extremity spasticity following treatment, with the TENS group demonstrating a greater reduction in MAS scores (mean decrease of 1.04 points (95% CI, 0.81, 1.28)) compared to the baclofen group (mean decrease of 0.58 points (95% CI, 0.37, 0.78)). The mean difference in MAS scores at follow-up was significantly lower in the TENS group compared to the baclofen group (p<0.05), in both legs. Furthermore, the TENS group maintained a greater reduction in spasticity after the four-week follow up as noted by a lower mean difference in scores compared to baseline.

Conclusion

There is level 2 evidence (from one randomized controlled trial; Shaygannejad et al. 2013) that transcutaneous electrical nerve stimulation may lead to greater reductions in spasticity compared to oral baclofen in persons with MS.

Transcutaneous electrical nerve stimulation may reduce lower extremity spasticity in persons with MS to a greater degree than oral baclofen.

3.0.2 Baclofen and Exercise

Table 26. Studies Examining Baclofen and Exercise for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
<p>Brar et al. 1991</p> <p><i>Evaluation of treatment protocols on minimal to moderate spasticity in multiple sclerosis</i></p> <p>USA</p> <p>RCT Crossover</p> <p>PEDro=3</p> <p>N_{Initial}=38, N_{Final}=30</p>	<p>Population: Age range=24-54yr; Gender: males=8, females=22; Disease course: unspecified; Minimum EDSS=5.5; Mean disease duration: unspecified.</p> <p>Intervention: Participants were randomized to one of the following treatment groups: i) baclofen, ii) stretching exercises, iii) stretching exercises with baclofen, or iv) placebo.</p> <p>Outcomes/Outcome Measures: Cybex flexion score; Ashworth Scale (AS).</p>	<ol style="list-style-type: none"> 1. Compared to the placebo group, the baclofen treatment and combination therapy were each significantly associated with an improvement in Cybex flexion scores ($p<0.05$). 2. There were no significant differences between baclofen and combination therapy on flexion scores, although there was a trend indicating less spasticity in favour of combination therapy. 3. AS scores indicated that the baclofen and combination therapy groups were more effective than placebo and stretching exercises alone, although these findings were not statistically significant.

Discussion

Brar et al. (1991) examined three treatment regimens involving baclofen and exercise for MS-related spasticity. Thirty PwMS (EDSS≤5.5 with mild to moderate lower extremity spasticity) participated in a randomized crossover study with the following treatment groups: baclofen alone, a stretching program with placebo, a stretching program with baclofen, and placebo alone. Participants' spasticity, as a primary outcome measure, was measured using Cybex isokinetic knee flexion scores and MAS scores. The authors found that spasticity significantly decreased in the baclofen and combination therapy groups compared to placebo (flexion scores). A trend toward decreased spasticity was noted in the combination therapy group compared to the baclofen only group, although this was not statistically significant.

Conclusion

There is level 2 evidence (from one randomized controlled trial; Brar et al. 1991) that oral baclofen combined with a stretching program may reduce spasticity compared to placebo in persons with MS.

There is level 2 evidence (from one randomized controlled trial; Brar et al. 1991) that oral baclofen combined with a stretching program may not reduce spasticity compared to baclofen alone in persons with MS.

Oral baclofen in combination with a stretching program may reduce spasticity more than placebo in persons with MS, but may not be more effective than baclofen alone.

3.0.3 Dantrolene Sodium, Physical Therapy, and Surgery

Table 27. Studies Examining Dantrolene Sodium, Physical Therapy, and Surgery for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
<p>Reyes et al. 1978</p> <p><i>Management of leg contractures in multiple sclerosis</i></p> <p>USA</p> <p>Pre-Post</p> <p>N_{Initial}=5, N_{Final}=5</p>	<p>Population: Mean age=51yr; Gender: males=1, females=4; Disease course: unspecified; Severity: unspecified; Mean disease duration=20yr.</p> <p>Intervention: Participants were treated by a combination of tenotomy, plastic procedures to close pressure sores, physiotherapy, and peroral administration of dantrolene sodium (300-500mg daily).</p> <p>Outcomes/Outcome Measures: Spasticity; contractures.</p>	<ol style="list-style-type: none"> All 5 participants showed a reduction in spasticity and contracture under dantrolene sodium therapy, 75-125mg by mouth four times daily. Long-term success of surgical release procedures was facilitated by drug-induced decrease in spasticity. At the last follow-up, 3 participants had been returned to the community, and the remaining 2 had been transferred to a nursing home. No participants redeveloped contractures, and muscle tone remained improved. No untoward effects of dantrolene sodium, either clinical or laboratory, could be detected.

Discussion

Reyes et al. (1978) investigated the effect of a combined program for MS-related spasticity, including anti-spasticity medication (dantrolene sodium), surgical procedures (tenotomy and plastic surgery to close pressure wounds), and physical therapy (passive range of motion exercises to manage lower extremity spasticity and contractures). Five participants were included who had severe lower extremity spasticity in hip flexors, adductors, and knee flexors, contracture formation, and pressure sores due to spasticity-related positioning challenges. The primary objective of the study was life-preserving medical management given the extent of tissue breakdown in these individuals. Spasticity, as a contributory factor, was only measured as a secondary outcome subjectively (no outcome measure noted), with subjective improvement alongside improved passive range of motion scores following surgical procedures. After each patient underwent tenotomies of their adductors and hamstrings, therapy programs consisted of daily passive range of motion two-three times per day in conjunction with oral

dantrolene sodium (75-125mg four times daily). Upon long term follow up (three years), all patients had maintained positive changes in muscle tone with continued daily passive range of motion and dantrolene sodium, which allowed for improved positioning in bed as well as in wheelchairs.

Conclusion

There is level 4 evidence (from one pre-post study; Reyes et al. 1978) that a combination of oral dantrolene sodium and physical therapy interventions following surgical management of contractures may improve spasticity in persons with MS.

A combination of oral dantrolene sodium and physical therapy interventions following surgical management of contractures may improve spasticity in persons with severe MS.

3.0.4 Botulinum Toxin and Physical Therapy

Table 28. Studies Examining Botulinum Toxin and Physical Therapy for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Giovannelli et al. 2007 <i>Early physiotherapy after injection of botulinum toxin increases the beneficial effects on spasticity in patients with multiple sclerosis</i> Italy RCT PEDro=6 N _{Initial} =40, N _{Final} =38	Population: <i>Physiotherapy group (n=20):</i> Mean age=46.4yr; Gender: males=2, females=18; Disease course: SPMS; Mean EDSS=5.8; Mean disease duration: unspecified. <i>Control group (n=18):</i> Mean age=48.1yr; Gender: males=2, females=16; Disease course: SPMS; Mean EDSS=6.0; Mean disease duration: unspecified. Intervention: Participants were randomized to receive physiotherapy plus botulinum toxin A or botulinum toxin alone (control group). Patients were assessed at baseline and at 2, 4 and 12wks. Outcomes/Outcome Measures: Modified Ashworth Scale (MAS); Visual Analog Scale (VAS) (spasticity).	<ol style="list-style-type: none"> 1. The physiotherapy group showed a significantly greater improvement in MAS scores at 2wks, 4wks, and 12wks compared to the control group (all p<0.01). 2. Significant differences between the groups were also found for VAS spasticity scores at 4wks and 12wks (p=0.01), but not at 2wks (p=0.41).

Discussion

Giovanelli et al. (2007) examined the benefits of early physical therapy programming after local upper and lower extremity botulinum toxin type A injections. The study randomized 38 participants with SPMS (EDSS unspecified, MAS scores of at least 3) to either a control group of botulinum toxin only or a treatment group consisting of botulinum toxin followed by active and passive exercise and stretching programs. The

exercise and stretching programs were performed daily for 15 consecutive days immediately following injection with botulinum toxin. Spasticity measures, MAS and VAS, were assessed at baseline, and at two, four, and 12 weeks after injection. The study found statistically significant decreases in both groups after botulinum toxin. The experimental group was found to have a significantly better combined positive effect as the group was noted to have a reduction in spasticity that remained at four and 12 weeks whereas the control group was noted to have an initial reduction in spasticity that increased at four and 12 weeks. Indeed, post-procedure instructions to persons receiving botulinum toxin for the purposes of spasticity management/hypertonicity that include post-injection stretching, especially between days 3-21 post injection, would be considered standard of care by most injectors.

Conclusion

There is level 1b evidence (from one randomized controlled trial; Giovannelli et al. 2007) that early physiotherapy following botulinum toxin type A may be more effective for reducing spasticity compared to botulinum toxin alone in persons with secondary progressive MS.

Botulinum toxin, when followed by early physiotherapy, may provide greater reduction in spasticity than botulinum toxin alone in persons with secondary progressive MS.

3.0.5 Botulinum Toxin and Segmental Muscle Vibration

Segmental muscle vibration is a modality in which specific target muscles are placed under vibratory stimulation to inhibit muscle activation via the surface placement of a mechanical device producing low amplitude/high frequency bursts presumed to stimulate muscle spindle afferents, with effectiveness noted in stroke (Noma, Matsumoto, Etoh, Shimodozono, & Kawahira, 2009).

Table 29. Studies Examining Botulinum Toxin and Segmental Muscle Vibration for Spasticity in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Paoloni et al. 2013 <i>Does giving segmental muscle vibration alter the response to botulinum toxin injections in the treatment of spasticity in people with multiple sclerosis? A single-blind randomized controlled trial</i>	Population: <i>Group A (n=14):</i> Mean age=54.9yr; Gender: males=6, females=8; Disease course: SPMS; Median EDSS=5.25; Mean disease duration: unspecified. <i>Group B (n=14):</i> Mean age=47.4yr; Gender: males=5, females=9; Disease course: SPMS; Median EDSS=4.75; Mean disease duration: unspecified. <i>Group C (n=14):</i> Mean age=50.6yr; Gender: males=4, females=10; Disease course: SPMS; Median EDSS=5.50; Mean disease duration: unspecified. Intervention: Patients were randomized to either group A (segmental muscle vibration	<ol style="list-style-type: none"> 1. There was a statistically significant effect of time on knee MAS scores for each of the groups (p<0.001). Post-hoc analyses showed within-group differences in all groups between T0 and T1 and between T0 and T2 (p<0.05). Within group C, patients had higher knee MAS scores at T2 compared to T1 (p<0.05). 2. There were no significant differences between groups at T1 (p=0.26) or T2 (p=0.29) for knee MAS scores. 3. There was a statistically significant effect of time on ankle MAS scores for each of

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Italy RCT PEDro=8 N _{Initial} =42, N _{Final} =42	group), group B (botulinum toxin A plus segmental muscle vibration group), or group C (botulinum toxin A group). Outcomes were assessed at baseline (T0) and at 10wks (T1) and 22wks (T2). Outcomes/Outcome Measures: Modified Ashworth Scale (MAS).	the groups (p<0.001). Post-hoc analyses showed within-group differences in all groups between T0 and T1 and between T0 and T2 (p<0.05). In group C, patients had higher ankle MAS scores at T2 compared to T1 (p<0.05). 4. There were no significant differences between groups at T1 (p=0.26) or T2 (p=0.29) for ankle MAS scores.

Discussion

Paoloni et al. (2013) examined the effect of segmental muscle vibration after botulinum toxin injection for the treatment of spasticity in PwMS. In this study, 42 participants with SPMS (EDSS 2.0-6.0) were randomized to one of three groups: 1) segmental vibration to lower extremity muscles three times per week for four weeks, 2) botulinum toxin followed by segmental vibration, or 3) botulinum toxin alone. All groups also participated in general physical therapy sessions three times per week for four weeks. The study found that all three groups demonstrated statistically significant decreases in both knee and ankle MAS scores over time compared to baseline. Furthermore, the group that received a combination of botulinum toxin and vibration therapy demonstrated statistically significant decreases in knee and ankle spasticity scores that continued at 10 weeks and 22 weeks following treatment. The group receiving botulinum toxin alone demonstrated the shortest effects of any group, as indicated by higher MAS scores at 22 weeks post intervention, suggesting an unsurprising re-increase in muscle tone known to occur given the typical efficacy period of botulinum toxin injections. However, no significant differences were observed between groups in both knee and ankle MAS scores at any time point.

Conclusion

There is level 1b evidence (from one randomized controlled trial; Paoloni et al. 2013) that segmental muscle vibration, and combined segmental muscle vibration and botulinum toxin, may be more effective compared to botulinum toxin type A for spasticity in persons with secondary progressive MS.

Segmental muscle vibration, or a combination of segmental muscle vibration with botulinum toxin, may provide greater reduction in spasticity in persons with secondary progressive MS compared to botulinum toxin alone.

4.0 Summary

There is level 1b evidence (from one randomized controlled trial; Tarakci et al. 2013) that a group exercise training program targeting lower extremity flexibility, strength, and balance may improve spasticity compared to no intervention in persons with MS.

There is level 4 evidence (from one pre-post study; Giesser et al. 2007) that locomotor training using body weight supported treadmill training may improve spasticity in persons with secondary progressive MS.

There is conflicting evidence (from two prospective controlled trials; Sosnoff et al. 2010; Sosnoff et al. 2009) regarding whether or not unloaded leg cycling reduces spasticity compared to quiet sitting in persons with MS.

There is level 2 evidence (from one prospective controlled trial; Sosnoff et al. 2010) that unloaded leg cycling may reduce spasticity more as compared to unloaded arm cycling in persons with relapsing-remitting MS.

There is level 2 evidence (from one prospective controlled trial; Motl et al. 2007) that unloaded leg cycling may be an effective adjuvant to pharmacological spasticity management compared to quiet sitting in persons with MS.

There is level 2 evidence (from one randomized controlled trial; Velikonja et al. 2010) that mixed fitness recreational activities such as sports climbing or yoga may not reduce spasticity in persons with MS.

There is level 1b evidence (from one randomized controlled trial; Castro-Sanchez et al. 2012) that an aquatic Ai-Chi exercise program may reduce spasticity compared to land-based breathing and relaxation exercises in persons with MS.

There is level 1b evidence (from two randomized controlled trials; Nilsagard et al. 2006; Chiara et al. 1998) that cryotherapy may not reduce spasticity compared to ambient temperature in persons with MS.

There is level 2 evidence (from one prospective controlled trial; Centonze et al. 2007) that high frequency (5 Hz) repetitive transcranial magnetic stimulation (rTMS) may reduce spasticity compared to sham rTMS in persons with relapsing-remitting MS.

There is level 2 evidence (from one prospective controlled trial; Abdelkader et al. 2013) that high frequency (5 Hz) repetitive transcranial magnetic stimulation (rTMS) may reduce spasticity compared to low frequency (1 Hz) rTMS in persons with relapsing-remitting MS.

There is level 1b evidence (from one randomized controlled trial; Nielsen et al. 1996) that trans-spinal magnetic stimulation may reduce spasticity compared to sham stimulation in persons with MS.

There is level 2 evidence (from one prospective controlled trial; Mori et al. 2010) that intermittent theta-burst stimulation may reduce spasticity compared to sham stimulation in persons with relapsing-remitting MS.

There is level 1b evidence (from one randomized controlled trial; Iodice et al. 2015) that transcranial direct current stimulation (tDCS) may not reduce spasticity compared to sham tDCS in persons with relapsing-remitting MS.

There is level 1b evidence (from one randomized controlled trial; Miller et al. 2007) that electrical nerve stimulation using either a one-hour or eight-hour protocol may not reduce spasticity in persons with MS.

There is level 2 evidence (from one prospective controlled trial; Walker 1982) that subcutaneous nerve stimulation may reduce spasticity compared to sham stimulation in persons with MS.

There is level 4 evidence (from four pre-post studies; Koulousakis et al. 1987; Siegfried et al. 1981; Dimitrijevic et al. 1980; Read et al. 1980) that spinal cord stimulation may reduce spasticity in persons with MS.

There is level 4 evidence (from one pre-post study; Sutliff et al. 2008) that hip flexion assist orthoses may not improve spasticity in persons with MS.

There is level 1b evidence (from one randomized controlled trial; Marinelli et al. 2015) that radial shock wave therapy may reduce spasticity compared to sham stimulation in persons with MS.

There is level 1b evidence (from one randomized controlled trial; Siev-Ner et al. 2003) that reflexology may reduce spasticity compared to a sham control (non-specific calf massage) in persons with MS.

There is level 2 evidence (from one randomized controlled trial; Miller 1996) that acupuncture may reduce spasticity compared to usual care in ambulatory persons with MS.

There is conflicting evidence (from two pre-post studies; Backus et al. 2016; Brouwer & de Andrade 1996) regarding whether or not massage therapy improves spasticity in the lower extremities of persons with MS.

There is level 1b evidence (from one randomized controlled trial; Mori et al. 2011) that intermittent theta-burst stimulation (iTBS) in combination with exercise therapy may reduce spasticity compared to iTBS alone in persons with relapsing-remitting MS.

There is level 1b evidence (from one randomized controlled trial; Negahban et al. 2013) that massage therapy in combination with exercise therapy may not reduce spasticity compared to standard medical care in persons with MS.

There is level 1b evidence (from one randomized controlled trial; Negahban et al. 2013) that massage therapy, exercise therapy, and combined massage-exercise therapy may not be more effective compared to one another for spasticity in persons with MS.

There is level 2 evidence (from one randomized controlled trial; Baker et al. 2007) that supported standing may not improve spasticity compared to a home exercise program in persons with secondary progressive MS.

There is level 2 evidence (from one randomized controlled trial; Schyns et al. 2009) that whole body vibration in combination with exercise may not be more effective for improving spasticity compared to exercise alone in persons with MS.

There is level 4 evidence (from one pre-post study; Szecsi et al. 2009) that spasticity may be acutely reduced following functional electrical stimulation-assisted lower extremity cycling in persons with chronic progressive MS.

There is level 1b evidence (from one randomized controlled trial; Storr et al. 2006) that multidisciplinary inpatient rehabilitation may not improve spasticity compared to no treatment in clinically stable persons with MS.

There is level 4 evidence (from four pre-post studies and one case series; Pope et al. 1991; Sindou & Jeanmonod 1989; Sindou et al. 1982; Laitinen & Singounas 1971; Glazer & Mooney 1970) that orthopedic surgical interventions and neurosurgical interventions involving the spinal cord may reduce spasticity in persons with MS.

There is level 2 evidence (from one randomized controlled trial; Shaygannejad et al. 2013) that transcutaneous electrical nerve stimulation may lead to greater reductions in spasticity compared to oral baclofen in persons with MS.

There is level 2 evidence (from one randomized controlled trial; Brar et al. 1991) that oral baclofen combined with a stretching program may reduce spasticity compared to placebo in persons with MS.

There is level 2 evidence (from one randomized controlled trial; Brar et al. 1991) that oral baclofen combined with a stretching program may not reduce spasticity compared to baclofen alone in persons with MS.

There is level 4 evidence (from one pre-post study; Reyes et al. 1978) that a combination of oral dantrolene sodium and physical therapy interventions following surgical management of contractures may improve spasticity in persons with MS.

There is level 1b evidence (from one randomized controlled trial; Giovannelli et al. 2007) that early physiotherapy following botulinum toxin type A may be more effective for reducing spasticity compared to botulinum toxin alone in persons with secondary progressive MS.

There is level 1b evidence (from one randomized controlled trial; Paoloni et al. 2013) that segmental muscle vibration, and combined segmental muscle vibration and botulinum toxin, may be more effective compared to botulinum toxin type A for spasticity in persons with secondary progressive MS.

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