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Spasticity Following Spinal Cord Injury

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We would like to acknowledge the late Sandra J Connolly OT

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Key Points

Introduction

Although consensus has not yet been reached on clinically meaningful, feasible and effective outcome measures relevant to the treatment of spasticity and patient reported outcomes, development and inclusion of such a multidimensional test battery is required for understandable interpretations of and between future studies.

Non-pharmacological Interventions for Spasticity

Hippotherapy may result in short-term reductions in spasticity.

A combination of neural facilitation techniques and Baclofen may reduce spasticity.

Rhythmic passive movements may produce short-term reductions in spasticity.

Prolonged standing or other methods of producing muscle stretch may result in reduced spasticity.

Electrical passive pedaling systems may result in short-term reduction in spasticity.

Active exercise interventions such as hydrotherapy, FES-assisted cycling and walking and robot-assisted exercise (including specific exercises combined) may produce short-term reductions in spasticity.

Electrical stimulation applied to individual muscles may produce a short-term decrease in spasticity; however, there is also some concern that long-term use of electrical stimulation may increase spasticity.

Ongoing (TENS) transcutaneous electrical nerve stimulation programs result in short-term reductions in spasticity which may last for up to 24 hours.

Use of TENS and standard physical therapy showed a reduction in clinical spasticity in the subacute phase of rehabilitation.

Penile vibration and rectal probe stimulation may be effective at reducing lower limb muscle spasticity for several hours.

Other forms of afferent stimulation including taping, massage, cryotherapy, helium-neon irradiation, whole-body vibration, and galvanic vestibular stimulation may result in immediate spasticity reduction but require more research to understand effects and intervention parameters.

Spinal cord stimulation may provide spasticity relief over a few months but long-term effectiveness and feasibility is less certain.

Repetitive transcranial magnetic stimulation may provide spasticity relief and improve walking speed over the short-term but long-term effectiveness is unknown.

Treatment with intermittant theta-burst stimulation is likely to reduce upper extremity spasticity for up to 1 week.

Neuro-Surgical Interventions for Spasticity

Dorsal longitudinal T-myelotomy may result in reduced spasticity.

Human neural stem cell transplantation in chronic SCI does not reduce spasticity secondary to SCI.

Intrathecal injection of autologous mesenchymal stem cells in people with chronic SCI is unlikely to result in persistent spasticity reduction.

Pharmacological Interventions for Spasticity

Oral baclofen reduces muscle spasticity in people with SCI.

Oral baclofen is inferior to botulinumtoxin A injection and oral tolperisone by 6 weeks of spasticity treatment in people with SCI.

Diazepam is effective for the treatment of spasticity secondary to SCI.

Bolus or long-term intrathecal baclofen decreases spasticity and may improve functional outcomes with low complication rates and is a cost-effective intervention.

Tizanidine is likely useful in treating SCI spasticity.

Clonidine may be effective in treating SCI spasticity but more evidence is required to support its routine use.

Fampridine-SR is not significantly efficacious for the treatment of spasticity in chronic SCI.

Intravenous Fampridine is not significantly efficacious for the treatment of spasticity in chronic SCI.

Cyproheptadine may be useful in treating SCI spasticity but requires additional confirmatory trials using rigorous study design.

Gabapentin may be useful in treating SCI spasticity but requires additional confirmatory research.

Traditonal Chinese medicine, intravenous orphenadrine cirate, riluzole, and L-threonine may be effective in treating SCI-related spasticity.

Levitiracetam, diazepam, dantrolene and naloxone may not be effective for treating SCI-related spasticity, but would benefit from confirmatory studies.

Nabilone has been shown to be effective in reducing spasticity but additional research is needed.

Oral detra-9-tetrahydrocannabinol (dronabinol) may help to reduce spasticity but requires additional evidence from controlled studies.

Botulinum neurotoxin may improve focal muscle spasticity in people with SCI.

Phenol block may improve pain, range of motion and function related to shoulder spasticity in individuals with tetraplegia.

Phenol block may reduce hip adductor spasticity in individuals with paraplegia and tetraplegia.

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1 Executive Summary

Although the majority of people with Spinal Cord Injury (SCI) have spasticity, it is not always detrimental or predictable, and may affect muscles across different joints to varying degrees. Therefore, treatment must be carefully selected to ensure that overall function is optimized for a specific individual. To create an individualized treatment plan, clearly established clinical and functional goals combined with the use of clinical and patient-reported outcomes, validated for use in SCI, is essential.

Early in-patient rehabilitation will employ physical therapy to manage spasticity through to discharge with a post-discharge plan for ongoing management. Spasticity related pharmacotherapies are usually needed and also initiated during hospitalization. More invasive treatments such as surgery or neurolysis are offered to treat severe focal spasticity that remain resistant to less invasive treatment, later post-injury. Botulinum Toxin (BTX) injections are commonly used to treat persistent and severe focal spasticity.

As part of a full rehabilitation program, active exercise interventions such as hydrotherapy, Functional Electrical Stimulation (FES)-assisted cycling and walking and robot-assisted exercise are trialed and can provide short-term spasticity relief. Other options for short-term spasticity relief include Transcutaneous Electrical Nerve Stimulation (TENS), various forms of afferent stimulation, direct spinal cord and transcranial stimulation, and drugs such as benzodiazepines for nocturnal spasticity. However, the most common consistent management of spasticity relies on oral or intrathecal baclofen with tizanidine as a potential alternative pharmacological option. Various other drugs, including cannabinoids, may also be effective but require additional confirmatory research. Finally, while many still hold out hope for stem cell therapy for spasticity, it has not been shown to be affective.

Gaps in the Evidence

There is need for a psychometrically-validated outcome assessment for spasticity related to quality of life that probes the interactions between the spasticity, chronic pain and depression.

A clinically meaningful, feasible and effective outcome measures relevant to the treatment of spasticity and individual reported outcomes.

Confirmatory trials are needed for pharmacotherapies for people with spasticity resistant to existing first or second line treatments (baclofen (oral or intrathecal), or tizanidine).

Confirmatory trials are needed for non-pharmacological options to offer short term relief of spasticity for mild spasticity or as adjunct treatments to pharmacotherapies.

Confirmatory trials are needed to confirm that stem cell transplantation of human neural stem cells is not effective for the treatment of spasticity (and SCI in general).

2 Introduction

2.1 Definition

Spasticity is traditionally defined as "[…] 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). Spasticity is quite commonly confused with tremor, rigidity, clonus, dystonia and various movement disorders (i.e., athetoid, ballisms, and chorea). One of the earliest examples of this confusion is the term "spastic rigidity" used to refer to "excessive muscular contraction" first published in 1843 (Little WJ). Attempts to clarify this confusion have resulted in the most recent definition published by Pandyan et al. (2005) (adapted from Tardieau et al. 1954) as follows: *"disordered sensori-motor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscle".* This definition is intended to be more inclusive of clinical signs and symptoms of "spasticity" but has yet to be validated for clinical relevance.

Regardless of the definitions presented, each eludes to various inter-related components of the upper motor neurone syndrome (i.e., tone, clonus, spasms, spastic dystonia and co-contractions). Therefore, a thorough clinical assessment of spasticity should always be undertaken as follows (Kheder & Nair 2012): 1) differentiate spasticity from other causes of increased tone, 2) identify potential triggers, 3) measure spasticity, 4) assess spasticity's impact on function, and 5) gather input from individuals , caregivers, therapists and other rehabilitation professionals. Spasticity is not static and therefore, assessments should be done regularly and combined with establishing goals of treatment to make decisions regarding treatment strategy (Rekand et al. 2012).

2.2 Pathophysiology

Recent studies indicate that, besides changes in motoneuron activation (involuntary supraspinal descending inputs and inhibited spinal reflexes etc.), changes in muscle properties also contribute to the clinical appearance of limb spasticity and rigidity, which are frequently linked symptoms. In clinical practice, signs of exaggerated tendon tap reflexes associated with muscle hypertonia are generally thought to be responsible for spastic movement disorders. Therefore, most antispastic treatments are directed at the reduction of reflex activity. In recent years, researchers have noticed a discrepancy between spasticity as measured in the clinic and functional spastic movement disorders, which is primarily due to the different roles of reflexes in passive and active states, respectively. We now know that central motor lesions are associated with loss of supraspinal drive and defective use of afferent input with impaired behaviour of short-latency and long-latency reflexes. These changes lead to paresis and maladaptation of the movement pattern. Secondary changes in mechanical muscle fiber, collagen tissue, and tendon properties (e.g., loss of sarcomeres, subclinical contractures) result in spastic muscle tone, which in part compensates for paresis and allows functional movements on a simpler level of organisation. Antispastic drugs can accentuate paresis and therefore should be applied with caution in mobile individuals (Dietz & Sinkjaer 2007).

Phadke et al. (2013) completed a review of articles published between 1989 and 2012 (n=24) using the EMBASE, CINAHL, and PEDro databases. The review examined the effect of triggers on spasticity. The authors found that the quality of the studies was moderate and included non-randomized trials, randomized trials with no effect and/or low study subject numbers or case reports. The authors found that factors increasing spasticity included pregnancy, posture, cold, circadian rhythm, and skin conditions as measured via objective clinical tests. Studies that relied on individual self-reports, revealed that bowel and bladder related issues, menstrual cycle, mental stress, and tight clothing were suspected to increase spasticity. There was no literature that reported on the increase in spasticity in response to heterotopic ossification, hemorrhoids, deep vein thrombosis, fever, sleep patterns and pain and conditions, even though these are thought to increase spasticity.

2.3 Impact

It has been estimated that 53% (Walter et al. 2002) to 78% (Adams & Hicks 2005; Maynard et al. 1990; Levi et al. 1995) of individuals report spasticity secondary to chronic SCI. Spasticity has been reported to be more frequent in cervical and incomplete injuries (Mumtaz et al. 2014). Approximately 41% (Levi et al. 1995) of individuals with spasticity secondary to SCI list it as one of the major medical obstacles to community and workplace re-integration (Canadian Paraplegic Association 1996). Although, spasticity is not typically thought to get worse with age and time, uncontrolled spasticity is thought to have an impact on emotional adaptation, dependency, secondary health problems and environmental integration (Krause 2007).

2.4 Determining Impact of Treatment

During initial inpatient rehabilition, spasticity that was not optimally managed was found to be, after pain and fatigue, a primary medical reason for increased length of stay (Dijkers & Zanca 2013; Hammond et al. 2013). Van Cooten et al. (2015) postulate that early, active rehabilitation would serve to reduce functional hindrance due to spasticity. Identification of specific spasticity components, during the subacute and chronic stages of SCI, that impact directly on gait, lower limb muscle function and activities of daily living could also be helpful in the refinement and customization of ongoing neurorehabilitation treatment strategies (Bravo-Esteban et al. 2013).

Spasticity in SCI varies with location and degree depending on the injury pathophysiology. Not all spasticity is bad and for this reason, an assessment of treatment goals must be considered with various management strategies and cost factors in mind. Sometimes, increased spasticity is beneficial for transfers and mobility, and the reduction of tone may negatively impact those activities of daily living. For example, in the acute rehabilitation setting, the absence of spasticity was an independent risk factor for the development of deep vein thrombosis (Do et al. 2013).

The goal should not be to modify the excitability and rigorousness of reflexes, but to overcome functional impairments related to “spasticity” (Dietz 2000). Therefore, the decision to treat “spasticity” should not only be based on the findings gained by the examination in passive (lying bed, sitting in the wheelchair) but also in active conditions (like walking, doing transfer etc.). As

well, spasticity can be protective against skeletal muscle atrophy that in turn could indirectly affect functional independence, ambulation and incidence of fracture (Gorgey & Dudley 2008). Spasticity has also been reported to increase glucose uptake and thereby reduce the risk of diabetes in SCI (Bennegard & Karlsson 2008). Furthermore, recent reports identifying spasticity related enhancement/detraction of sexual activity in males/females respectively (Anderson et al. 2007a; Anderson et al. 2007b), again exemplifies the importance of individualized treatment choices. Incrementally applying the less invasive and cost-efficient treatments, as is common practice (Kirshblum 1999), will likely lead to a combination of treatments necessary to achieve the most successful outcome specific for each individual. Simultaneously with the completion of an assessment that clearly delineates the treatment goals, objective measures of spasticity that include individual reported outcomes are important to identify in order to confidently monitor the success of treatment choice(s). Spasticity treatment as it pertains to the various domains of everyday life should be considered (Mahoney et al. 2007).

2.5 Outcome Measurement and Spasticity

The studies reviewed in this chapter involve a variety of outcome measures, of which only some are widely used clinically (e.g. Spinal Cord Injury Spasticity Evaluation Tool (SCI-SET), Ashworth Scale (AS) and Modified Ashworth Scale (MAS). However, there are many outcome measures used in published trials that not well understood by the majority of clinicians which cause confusion when comparing studies and treatments. It is important to develop agreement on clinically meaningful outcome measures for demonstrating the efficacy of an experimental therapeutic intervention (Steeves et al. 2007).Outcome measure feasibility is another important consideration given that clinicians commonly do not have consistent access to specialized equipment, nor have sufficient time to administer highly technical methods in a clinical setting (e.g. Cybex; Franzoi et al. 1999). Very few studies included measures addressing quality of life despite the need to ensure that treatments are well tolerated as well as functionally and practically effective for individuals. However, Balioussis et al. (2014) provided a review of psychometric data for SCI specific spasticity outcome measures that assess its impact on quality of life. These authors conclude that Individual reported impact of spasticity measure is the current best option because it accounts for more affective reactions in the presence of spasticity compared to SCI-SET with less available psychometric data. Balioussis et al. (2014) also put forth that despite good clinical feasibility, the AS and MAS known poor inter-rater and intersession reliability may shed doubt on their applicability for SCI, especially with respect to quality of life. Having a psychometrically-validated outcome assessment for spasticity related quality of life will be beneficial, especially for understanding of interactions between the clustering of spasticity with chronic pain and depression in people with SCI.

The gold-standard for clinical testing is the double-blind, randomized, placebo-controlled study design, particularly for the measurement of short-term treatment effects. However, the results of a well-designed trial are more easily interpreted if the outcome measures used follow outcome measure standards as outlined by Pierson (1997). In summary, effective outcome measures should be selected based on 1) understandability for administration/scoring/interpretation and validity/reliability; 2) relevancy to the clinical situation and population measured; 3) having a reasonable risk-benefit ratio; 4) requirement for strict adherence to test conditions and

procedures; and 5) practicality in terms of personnel, time, equipment, cost, space and impact on the subject. No single outcome measure can capture the multi-dimensional nature of spasticity. Therefore, it is important, not only to choose an effective outcome measure but also to choose effective outcome measures to monitor the range of medical outcomes as suggested by Goldberg (1991): 1) technical outcome (i.e., reduction of spasm frequency); 2) functional outcome; 3) individual satisfaction and; 4) cost effectiveness. Consensus has not yet been reached on clinically meaningful, feasible and effective outcome measures relevant to the treatment of spasticity and individual reported outcomes.

Some of the measures that have been tested for various aspects of spasticity and for validity and/or reliability include the Ashworth (Ashworth 1964) and MAS (Bohannon & Smith 1987; Haas et al. 1996) spasticity scales, the PSFS (Penn 1988; Priebe 1996), the Pendulum test (Nance 1994), the Spinal Cord Assessment Tool for Spasticity (SCATS; Benz et al. 2005), the Spastic Paraplegia Rating scale (Schüle et al. 2006), and the SCI-SET(Adams et al. 2007). Please refer to the SCIRE chapter, Outcome Measures, for a more in-depth discussion on these measures.

Key Points

Although consensus has not yet been reached on clinically meaningful, feasible and effective outcome measures relevant to the treatment of spasticity and patient reported outcomes, development and inclusion of such a multidimensional test battery is required for understandable interpretations of and between future studies.

2.6 Overview of Treatments

Physical therapy, surgery, and pharmacotherapy including neurolysis are among the most common treatment options currently employed to manage spasticity in SCI. Physical therapy is initiated during rehabilitation and usually continues post-discharge either formally or through individual education and caregiver administration. Pharmacotherapies are thought to be the most efficacious for treatment of the velocity-dependent increase in hyperexcitable tonic stretch reflexes, one component of the upper motor neuron syndrome defined by Lance (1980). Surgery and neurolysis may be appropriate choices to treat focal spasticity. A combination treatment regimen can be individualized and appears to be a common approach in clinical practice.

3 Non-pharmacological Interventions for Spasticity

As noted above, there are a wide variety of approaches in treating spasticity. It is generally accepted practice to employ more conservative approaches initially and gradually administer more invasive treatments with the understanding that no one approach is likely to be universally successful for all individuals (Kirshblum 1999). However, some have contended that this stepwise approach is not necessarily the ideal. For example, Gormley Jr. et al. (1997) have asserted that in the hands of an experienced clinical team, it may be decided that aggressive measures are needed early on, based on the individual presentation and the many factors that may influence spasticity. More recently, D'Amico et al. (2014) have suggested that "increasing

the excitation of the spinal cord with spared descending and/or peripheral inputs by facilitating movement, instead of suppressing it pharmacologically, may provide the best avenue to improve residual motor function and manage spasticity after SCI." Regardless, in general most clinicains feel that active exercise and physical therapy modalities should be the first line of treatment before adding pharmacological (e.g., oral medications, BTX, or intrathecal agents), orthopaedic, or neurosurgical options (Kirshblum 1999; Rekand et al. 2012). It is important that the clinical team have a thorough understanding of these factors as these may impact assessment and treatment decisions. For example, it is generally accepted that posture has a major impact on the clinical presentation of spasticity (Kakebeeke et al. 2002) and there are suggestions from clinical experience that consideration of the wheelchair and seating equipment being prescribed plays an important part in the management of spasticity. Regardless, effective clinical management requires an individualized and often a combinational approach, thereby necessitating a broad knowledge of the various options available. In the present section, non-pharmacological interventions are outlined-from the more conservative options such as passive and active movement-based interventions, to those based on forms of electrical and other types of stimulation and finally to more invasive neurosurgical interventions.

For the purpose of this review we have classified the various non-pharmacological approaches into six general categories. These include interventions based on i) passive movement, ii) active movement, iii) direct muscle electrical stimulation, iv) various forms of afferent stimulation, v) direct spinal cord stimulation and vi) repetitive transcranial magnetic stimulation. It should be noted that although we have tried to be as specific as possible within these distinctions, there may be some overlap across the categories for specific modalities. For example, passive movements produce afferent outflow and may have also been classified as a form of afferent stimulation. Hydrotherapy, classified as an active movement-based intervention given the buoyancy and viscous properties of water in aiding active movement exercise (Kesiktas et al. 2004), often involve passive movements as well as the contributions of afferent stimulation associated with heated water. We have tried to categorize the approaches based on the primary intent of the authors in describing the various interventions. In addition, when considering final conclusions, we have tried to be as specific as possible within each category, despite the obvious need to bring together evidence from different sources.

3.1 Passive Movement or Stretching

It has been reported that self-stretching, regular physiotherapy and physical activities affect spasticity and should be considered as a therapeutic approach prior to antispastic medication and surgical procedures (Merritt 1981). In particular, therapies based on physical interventions are advantageous as they generally have fewer related adverse events although they also typically have short-lasting effects. Movement therapies can be differentiated into passive or active maneuvers that are assumed to affect both spinal neuronal circuits and fibro-elastic properties of the muscles, thereby potentially reducing spasticity. An underlying physiologic paradigm that explains why passive movements have an influence on spasticity in individuals with a lesion of the upper motor neuron is equivocal (Katz 1991).

3.1.1 Passive Stretching

Passive movement may be accomplished by therapist/care-giver or self-mediated limb movement focusing on muscle stretching or on preserving full range of motion over joints that may be immobilized (Harvey et al. 2009). Alternatively, a mechanical device may be employed such as a motorized therapy table (Skold 2000) or exercise cycle (Kakebeeke et al. 2005; Kiser et al. 2005; Rayegan et al. 2011). These mechanical devices have the advantages for research purposes of producing repeatable movements over a specific range and also in standardizing other parameters (e.g., frequency, speed). However, they are commonly not accessible for routine clinical use and may present an obstacle for multicentre trials.

Neurodevelopmental Therapy (NDT)

One class of therapies employed by physiotherapists and occupational therapists which utilize passive (and active) movement and stretching represent those developed mostly for stroke rehabilitation such as Bobath (neurodevelopmental) therapy and proprioceptive neuromuscular facilitation or other approaches such as those advocated by Rood or Brunnstrom. Although normalization of movement (sometimes associated with spasticity reduction) is at the basis of most of these approaches, it is noted that advocates for Bobath define this approach as more of a continually evolving, problem-solving concept that forms a framework for specific clinical practice (Raine 2007). Anecdotally, these approaches appear to be in widespread practice although there are no reports that document the extent of their actual use in clinical practice within SCI rehabilitation. Li et al. (2007) recently conducted an Randomized Controlled Trial (RCT) involving the use of three of these approaches (Bobath, Rood, Brunnstrom) in combination with baclofen therapy to reduce spasticity.

3.1.2 Hippotherapy

Another approach to spasticity reduction is hippotherapy, which involves the rhythmic movements, associated with riding a horse, to regulate muscle tone (Lechner et al. 2003; Lechner et al. 2007). Although the specific mechanisms by which an antispastic effect may be achieved with hippotherapy is unknown, it is postulated that it may be brought about by the combination of sensorimotor stimulation, psychosomatic effects and the specific postural requirements, and passive and active movements necessary for riding a horse.

3.1.3 Prolonged Standing

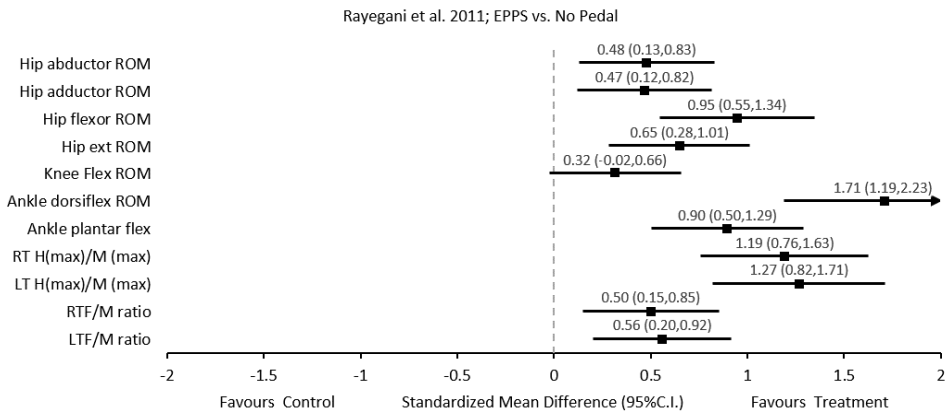
Although it has been suggested by some that repetitive movements are deemed necessary for obtaining a clinical effect (Rosche et al. 1997), there have been several reports of reduced spasticity associated with regular periods of passive standing (Odeen & Knutsson 1981; Bohannon 1993; Kunkel et al. 1993; Dunn et al. 1998; Eng et al. 2001; Shields & Dudley-Javoroski 2005). The majority of these are individual case reports (Bohannon 1993; Kunkel et al. 1993; Shields & Dudley-Javoroski 2005) or user satisfaction surveys (Dunn et al. 1998; Eng et al. 2001) and have not been included in Table 2 (i.e., other than Odeen & Knutsson 1981) which outlines the specific investigations of effectiveness of these “passive” approaches. The individuals examined in all three case reports reported reductions in lower limb spasticity

associated with passive standing despite the fact that different procedures and devices were used across the reports including a tilt table (Bohannon 1993), a standing frame (Kunkel et al. 1993) and a stand-up wheelchair (Shields & Dudley-Javoroski 2005). In addition, a significant number of people have indicated they receive benefit with respect to reduced spasticity in response to surveys about prolonged standing programs. Specifically, Eng et al. (2001) and Dunn et al. (1998) reported that 24% and 42%, respectively, of individuals engaged in this activity find it beneficial in reducing spasticity. However, it should be noted that in each of these studies some individuals also reported an increase in spasticity with this activity (13% and 3% respectively).

Table 1. Studies of Passive Movement-based Approaches for Reducing Spasticity

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Fang et al. 2015 Taiwan RCT Crossover PEDro=5 N=10	**Population:** Mean age:30.1yr; Gender: males=8, females=2; Injury etiology: SCI=10; Level of injury: C2-C6=2, T3-T7=6, L2-L11=2; Mean time since injury:5.7yr. **Intervention:** Individuals wore robot-assisted passive exercise devices on their ankle joints. Individuals were randomly assigned in a crossover design to one of three interventions: high speed cyclic passive exercise (50 cycles/min), low speed cyclic passive exercise (20 cycles/min), or electrical stimulation-induced contractions (ES) for 8 min, 1x/wk for 3 wk. They were allocated to the other interventions 2 wk later. Outcomes were assessed before each intervention and at 10, 20 min after each intervention. **Outcome Measures:** H reflex, M waves, Total resistance during cyclic stretching, Isometric torque.	1. The amplitude of the H reflex was significantly reduced at 10- and 20-min post high-speed cyclic passive exercises ($p<0.05$), and 20 min post low-speed cyclic passive exercises ($p<0.05$). 2. There were no significant changes in M waves after any of the interventions ($p>0.05$). 3. For individuals whom received ES, and then the high speed cyclic passive exercise, the total resistance during cyclic stretching increased significantly ($p<0.05$). 4. Isometric torque decreased significantly after 8 min of ES and the reduction persisted up to 20 min ($p<0.05$).
Chang et al. 2013 Taiwan RCT PEDro=6 N=14	**Population:** *Control (N=7)*: Mean age: 31.1 yr; Mean time since injury: 20.4 mo. *Experimental (N=7)*: Mean age: 35.3 yr; Mean time since injury: 29.1 mo; Chronicity: chronic. **Intervention:** Subjects received continuous passive motion training for 60 min/day, 5 days/wk for 4 wk. PAD recordings were measured	1. Before intervention, the H-reflex was not significantly depressed at 1 Hz or 5 Hz, but was significantly depressed in both groups at 10 Hz ($p<0.05$). 2. PAD increased significantly ($p=0.038$) after CPM intervention compared with pretest conditions.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	from pairs of soleus H-reflexes elicited at 0.1 Hz, 1 Hz, 5 Hz and 10 Hz. **Outcome Measures:** Modified Ashworth Scale (MAS), Postactivation depression (PAD).	3. MAS scores decreased significantly (p=0.013) after CPM intervention compared with pretest conditions. 4. The control group did not exhibit significant changes in either PAD or MAS after 4 wk. 5. One subject who completed 12 wk of training displayed further increases in PAD at 1 Hz and 5 Hz stimulation frequencies, but no further increases in PAD were seen at the 10 Hz stimulation frequency.
Rayegani et al. 2011 Iran RCT PEDro=3 $N_{Initial}$=74, N_{Final}=64	**Population:** Mean age: 43.0 yr; Gender: males=60, females=4; Level of injury: cervical=11, upper thoracic=22, lower thoracic=29, lumbar=2; Level of severity: AIS A=63, AIS B=1. **Intervention: Individuals** were randomly allocated to either the passive cycling group (n=37) or the controlled physical therapy group (n=37). The passive cycling intervention consisted of individuals sitting in their wheelchair while a motor passively moved their legs for up to 20 min/set, 3 sets/day for 2 mo (weekly regiment unspecified). The physical therapy included stretching, range of motion (ROM) and strengthening exercises (no further details provided). **Outcome Measures:** Level of SCI, Kondal scale (for muscle strength), Modified Ashworth Scale (MAS), goniometer measurements (for passive range of motion (ROM) in the hip, knee and ankle) and electrodiagnostic parameters (H-reflex, H (max)/M (max), and F-wave parameters).	1. MAS scores significantly decreased in the passive cycling group post intervention (p=0.003). 2. Range of motion of the hip, ankle dorsiflexion and plantar flexion increased significantly post intervention in the passive cycling group (hip: p=0.005; ankle dorsi: mean difference=10°, p=0.000; ankle plantar: mean difference=9.4643, p=0.000) no significant change was observed in the knee flexion ROM in the passive cycling group (p=0.111). 3. The F/M ratio (p<0.027) and the H max/M max (p=0.000) decreased significantly in the passive cycling group post intervention. 4. H-reflex amplitude was not significantly different post intervention in either group. 5. No significant differences were observed in the physical therapy group in regards to MAS scores and ROM of the hip, knee flexion, ankle dorsiflexion or plantar flexion.
	Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- to post-intervention and pre-intervention to retention.	

<table>
<tr><th>Author Year
Country
Research Design
Score
Total Sample Size</th><th>Methods</th><th>Outcome</th></tr>
<tr><td></td><td colspan="2"> 
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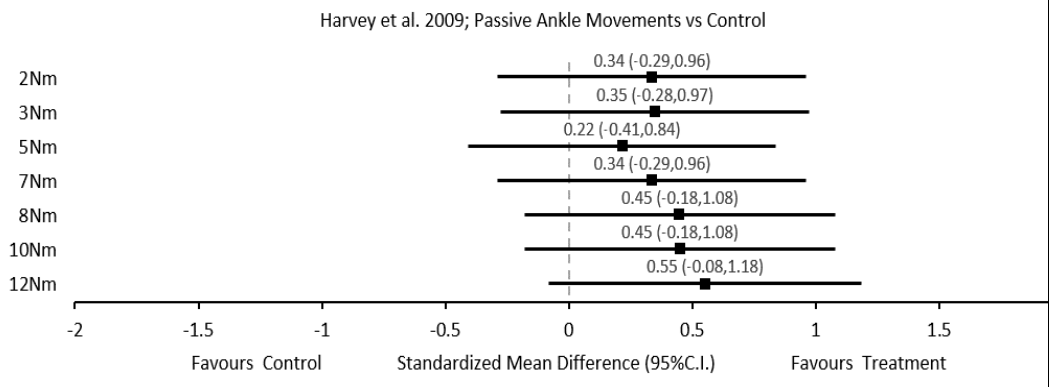
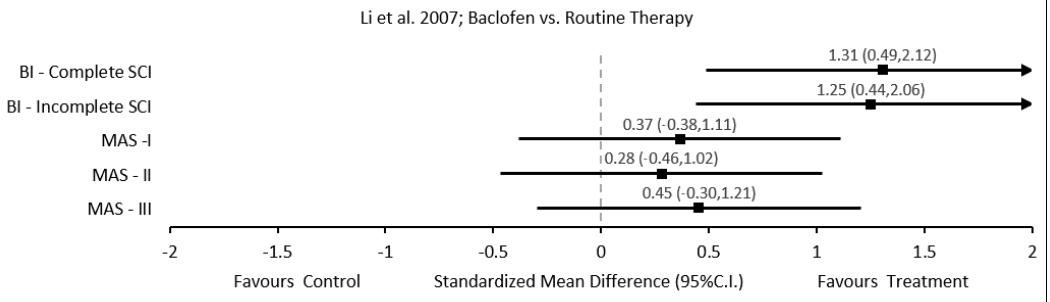
<tr><td rowspan="2">Harvey et al. 2009
Australia
RCT
PEDro=6
N=20</td><td>Population: Injury etiology: SCI=20; Level of injury: C2-C7.
Intervention: Passive movement of the experimental ankle, 5 days/wk for 6 mo.
Outcome Measures: Passive dorsiflexion of ankles; Modified Ashworth Scale (MAS) of the hamstring and plantar-flexor muscles; Global Impression of Change scale.</td><td>1. Passive dorsiflexion increased for the experimental ankle (88±9 versus 91±10) and decreased for the control (89±8 versus 87±9) (p=0.002), overall difference of 4.0°.
2. There was no significant difference in the MAS scores between ankles
3. Subjects reported a median of 2-4 points on the 15-pt Global Impression of Change scale for the experimental ankle, and 0 for control.</td></tr>
<tr><td colspan="2">Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- and post-intervention data.
 
</td></tr>
<tr><td>Li et al. 2007
China
RCT</td><td>Population: SCI: Mean age: 56.0 yr; Gender: males=17, females=11; Level of injury: paraplegic, thoracic; Level of severity: complete=16, incomplete=12; Mean</td><td>1. More subjects had reduced spasticity (reduced MAS scores) with neural facilitation and baclofen Grade I (n=2 to 12 from pre-to post), Grade II (n=7 to 2) and</td></tr>
</table>

<table>
<tr><th>Author Year
Country
Research Design
Score
Total Sample Size</th><th>Methods</th><th>Outcome</th></tr>
<tr><td rowspan="2">PEDro=6
N=28</td><td>time since injury: 38 days; Chronicity: acute.
Intervention: Control Group: Routine Therapy (undefined). Intervention group: Routine Therapy+oral baclofen (initial dose 5 mg, increase by 5mg every 5 days to maximum of 60mg) + neural facilitation (Rood, Brunnstrom & Bobath techniques) for 1-2 40 min sessions 6 d/wk for 6wk
Outcome Measures: Modified Ashworth Scale (MAS), BI tested pre-post 6 wk intervention.</td><td>Grade III (n=5 to 0) in the intervention group, as compared to the control group, Grade I (n=1 to 6), Grade II (n=7 to 4) and Grade III (n=6 to 4) (p<0.05).
2. Significantly higher BI scores were found for the intervention versus control group in complete SCI (45.35±12.01 versus 30.86±11.20) and incomplete SCI (57.98±11.54 versus 42.14±12.75) (p<0.05).</td></tr>
<tr><td colspan="2">Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- and post-intervention data.
 
</td></tr>
<tr><td>Lechner et al. 2007
Switzerland
RCT Crossover
PEDro=4
$N_{Initial}$=12,
N_{Final}=11</td><td>Population: SCI: Mean age: 44.0 yr; Gender: males=12, females=0; Level of injury: paraplegia=8, tetraplegia=4; Level of severity: AIS A-B; Mean time since injury: 13.1yr; Chronicity: chronic.
Intervention: 1) Control–no intervention; 2) Intervention H–hippotherapy intervention; 3) Intervention S–sitting on a rocker board driven by motor adjusted to mimic a horse's rhythm and amplitude; 4) Intervention R–sitting astride a bobath roll. Twice-weekly sessions for 4wk.
Outcome Measures: Ashworth Scale (AS), Visual Analog Scale (VAS)-self rating of spasticity, Mental well-being Bf-S.</td><td>1. Overall, significant reductions in spasticity were observed as indicated by AS sum score changes caused by Hippotherapy versus none for the control condition or other interventions (p<0.05).
2. Significant differences were found when comparing pre versus post-session AS scores, in all 3 intervention groups [H (p=0.004), R (p=0.003), S (p=0.005)] but not for the control condition (p=0.083).
3. Overall, significant spasticity reductions (VAS-self rated spasticity) were found for hippotherapy versus intervention R (p<0.05) and S (p<0.05) but not for the control condition.</td></tr>
</table>

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		4. Significant spasticity reductions were found in the VAS scores before and after intervention sessions for interventions H (p=0.004), R (p=0.014) and the control condition (p=0.021) but not S (p=0.181). 5. Improved mental well-being (i.e., reduced Bf-S scores) was seen with hippotherapy (p=0.048) but not with R (p=0.933) or S (p=0.497). 6. There were no long-term effects (i.e., 4 days post-intervention) for any intervention.
Kakebeeke et al. 2005 Switzerland Pre-Post N=10	**Population:** Age range: 23-60 yr; Gender: males=9, females=1; Level of injury: C6-T12; Level of severity: AIS A-B; Time since injury range: 1-25 yr. **Intervention:** Passive cycling with motorized cycle for 30 min at 40 RPM (1 session) versus no cycling. **Outcome Measures:** Torque resistance to movement on isokinetic dynamometer, Subjective subject assessment collected just prior and following cycling (or control).	1. Six out of ten subjects estimated that their spasticity was less after cycling and 3/10 estimated it was less after no cycling. 2. No effect on objective assessment of spasticity was noted as indicated by no differences with torque before and after cycling or before and after the control (no cycling) condition.
Lechner et al. 2003 Switzerland Pre-Post N=32	**Population:** Mean age: 37.0 yr; Gender: males=28, females=4; Level of injury: C4-T12; Level of: AIS: A-D; Time since injury range: 1 mo-6 yr. **Intervention:** Hippotherapy-K® (HTK; Kuenzle 2000): An average of 11 sessions (5-24) each lasting 25-30 min. Sheepskin (no saddle) on Icelander horse. **Outcome Measures:** Ashworth Scale (AS) of 8 limb movements bilaterally for a summed score of 16-80. Measures were taken pre- and post each session and the proportion of scores with a +ve or -ve change was recorded.	1. 93% of intervention sessions led to lower AS scores immediately after sessions. 2. Significant decrease in muscle tone as indicated by reduced AS scores in the lower limbs ($p<0.001$). 3. There was no carry-over effect from session to session as there was no longitudinal trend or trend of the before and after session differences. 4. No significant difference between para/tetraplegic subjects (p=0.4).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Sköld, 2000 Sweden Pre-Post N=45 (Passive stretches performed on n=12)	**Population:** Age range: 17-47 yr; Gender: males=39, females=6; Level of injury: cervical, thoracic; Level of severity: AIS A-D; Time since injury range: 3-26 yr, (Passive stretches performed on n=12, thoracic AIS C, D). **Intervention:** Repetitive passive movements of standardized range of motion in three different positions administered with motorized table, 10 min per position, 20-30 move-ments/min, 2 sessions/wk for 6 wk. **Outcome Measures:** Self-reported Visual Analog Scale (VAS): "no spasticity" to "most imaginable spasticity", Modified Ashworth Scale (MAS), collected just prior and after each intervention session.	1. Spasticity decreased after each intervention session as indicated by VAS ($p<0.001$) and MAS ($p<0.001$). 2. Spasticity reductions were maintained in VAS values (albeit to a lesser degree) after intervention was discontinued for four days ($p<0.018$).
Odeen & Knutsson, 1981 Sweden Pre-Post N=9	**Population:** Age range: 21-67 yr; Gender males=8, females=1; Time since injury: >3 yr. **Intervention:** Standing in forced dorsiflexion or plantarflexion (i.e., load applied) versus stretch applied to plantar flexors while supine. 30 min sessions. **Outcome Measures:** Torque resistance and angular displacement to sinusoidal ankle movement as measured by strain gauge transducer and potentiometer respectively. EMG recorded for some subjects as well. All collected just prior and following intervention.	1. Average reduction in resistance to passive movement at 1 cycle/s was 32%, 26% and 17 % for standing in dorsiflexion, standing in plantarflexion and supine dorsiflexion respectively. 2. Greater reductions were seen at one cycle/sec than at 0.25 cycle/sec, although significant reductions were still seen for both conditions of dorsiflexion stretch (i.e., standing and supine) at the slower test speed.

Discussion

The most prevalent therapeutic intervention involving passive movement to reduce spasticity is therapist or caregiver-mediated muscle stretching.

Fang et al. (2015) conducted a crossover RCT using a custom-made robot-assisted passive device for ankle hypertonia in individuals with chronic SCI. Study subjects (n=10) were randomly

assigned in a crossover design to one of three interventions: high speed cyclic passive exercise (50 cycles/min), low speed cyclic passive exercise (20 cycles/min), or electrical stimulation-induced contractions for 8 minutes, one time per week for 3 weeks, with a 2 week washout between conditions. H-reflexes, M-waves, total resistance during either slow or fast cyclic stretching, or isometric torque were assessed before each intervention and at 10 and 20 minutes after each intervention.

The amplitude of the H reflex was significantly reduced at 10- and 20-minutes post high-speed cyclic passive exercises ($p<0.05$), and 20 minutes post low-speed cyclic passive exercises ($p<0.05$) but not after repeated ES-elicited contractions. M-waves did not change with any condition ($p>0.05$). For study subjects who received ES, and then the high speed cyclic passive exercise, the total resistance during cyclic stretching increased significantly ($p<0.05$). Isometric torque did not decrease after either low or high speed cyclic passive exercise, although it did after 8 minutes of electrical stimulation along with reduction of reflex excitability which persisted up to 20 minutes ($p<0.05$). A key finding was that the change in the total resistance was specific to the testing speed in that resistance decreased with the low-speed cyclic stretch test after electrical stimulation-induced contractions ($p<0.05$) and after low-speed but not high-speed cyclic passive exercise ($p<0.05$). For the high-speed cyclic stretch test, the total resistance decreased only after high-speed cyclic passive exercise ($p<0.05$). Clinical implications are that there may be some specificity related to the intended speed of movement and stretching or exercise (i.e, range of speed of exercises or stretching to reduce spasticity should consider intended range of speed of functional activities). In previous studies, it was observed that MAS scores decreased after 1 hour of repeated stretching of the ankle joint completed at a relatively high speed in individuals with chronic SCI which is comparable to the reduction of total resistance during the high-speed cyclic stretch test seen in this study.

Chang et al. (2013) conducted an RCT (n=14) to investigate whether five, 1 hour sessions per week over four weeks of continuous passive motion of the ankle could increase post-activation depression , as measured by pairs of soleus H-reflexes elicited at 0.1 Hz, 1 Hz, Hz and 10 Hz in persons with chronic SCI. Before treatment, the H-reflex was not significantly depressed at 1 Hz or 5 Hz, but was significantly depressed in both groups at 10 Hz ($p<0.05$). post-activation depression increased significantly ($p=0.038$) after continuous passive motion treatment compared with pretest conditions. MAS scores also decreased significantly ($p=0.013$) after continuous passive motion treatment compared with pretest conditions. The control group did not exhibit significant changes in either post-activation depression or MAS after four weeks. One subject who completed 12 weeks of training displayed further increases in post-activation depression at 1 Hz and 5 Hz stimulation frequencies, but not at the 10Hz stimulation frequency.

Harvey et al. (2009) conducted an RCT (n=20), with blinded assessment, in which persons with chronic SCI received 6 months of passive ankle movement (i.e., plantar and dorsi-flexion) on one ankle (i.e., experimental condition) but not the other (i.e., control condition.) Although spasticity was only a secondary outcome measure in this trial, there was no apparent benefit of passive movement as indicated by no statistically significant changes in the MAS score (p not reported) for the hamstring and ankle plantar flexors. It should be noted that the participants in this study appeared to have predominately none or only mild spasticity as the initial MAS score ranged from zero to two with a median score of one. Notably, there were no participants with a

score of two following treatment and there were subjective reports of reduced spasticity. Unfortunately, no further details were reported about spasticity given that the primary outcome measure for this study was range of motion, for which a four-degree improvement was noted between the experimental and control conditions. This finding was statistically significant ($p=0.002$) but deemed to not be clinically significant.

Kakebeeke et al. (2005) employed externally applied repetitive cycling movements to the lower limbs with a specifically adapted motorized exercise bicycle. This study employed a prospective controlled design with each subject acting as his or her own control (i.e., cycling versus no cycling one week apart). However, it involved only a single intervention session, not accounting for an order effect and no clinically relevant outcome measures were employed. In addition to a self-report measure of "more", "less" or "equal" amounts of spasticity, a Cybex II isokinetic dynamometer was used to measure torque resistance to two different speeds of knee flexion/extension. The majority of subjects tested (60%) reported subjectively that their spasticity was reduced following cycling; however, some subjects (30%) also indicated it was reduced following the control (no cycling) condition. No changes were seen for either condition with the objective torque resistance response to movement. Given the mixed results of this study and uncertainty of the clinical relevance of the outcome measures, the findings of this study are deemed equivocal. Motorized cycle has been studied as a continuous intervention by Rayegani et al. (2011) who had subjects using the cycle for 20-minute intervals, three times a day for a 2-month period. This study also utilized a relevant outcome measure (Modified Ashworth) which identified that the passive cycling group showed a significant decrease ($p=0.003$) in spasticity. Hip, knee and ankle range of motion also significantly improved.

Rayegani et al. (2011) also employed a motorized cycle as part of an RCT ($n=74$; 10 subjects lost during follow up) to examine the effects on spasticity. Study subjects were randomly assigned to either a passive cycling group ($n=37$) or a physical therapy group ($n=37$), which received stretching, ROM and strengthening exercises. The treatment received 20 minutes of passive cycling for three sets per day over 2 months (# of times per week unspecified). Spasticity was assessed with MAS and electrodiagnostic parameters (H-reflex, H (max)/M (max), and F-wave). MAS scores significantly decreased post-intervention in the passive cycling group ($p=0.003$), but not with physical therapy. In the passive cycling group, the F/M ratio ($p<0.027$) and the H max/M max ($p=0.001$) decreased significantly. The H-reflex amplitude was not significantly different post intervention in either group.

Sköld (2000) employed a pre-post study design along with clinically relevant outcome measures (i.e., MAS, Visual Analog Scale (VAS)) to assess the effect of standardized, repetitive passive movements of prone and supine hip flexion/extension and lumbar lateral flexion elicited by a motorized table in persons with American Spinal Injury Association Impairment Scale (AIS)-C and D paraplegia. These subjects were drawn from a larger study examining self- versus clinically-rated spasticity fluctuations. There was a significant reduction in the MAS and also a significant decrease in the self-report measure of spasticity immediately following passive movement. In addition, these reductions in spasticity were partially maintained as indicated by self-report assessments (but not clinical evaluations) conducted 4 days following the discontinuation of the intervention.

Passive stretching and active movements conducted with careful attention to postural positioning comprise important elements of the neural facilitation techniques (i.e., Bobath, Rood, Brunnstrom) examined by Li et al. (2007) in combination with baclofen therapy to reduce spasticity. These investigators utilized an RCT (n=24) of individuals with thoracic SCI to examine the effect of a six-week course of this combination of therapies to demonstrate significant spasticity reductions ($p<0.05$) and concomitant increases in ADL independence as compared to traditional rehabilitation approaches. Unfortunately, what constituted "traditional" rehabilitation was not described in this paper, which presumably would constitute stretching and movement, and the relative contribution of baclofen versus the neural facilitation techniques was also not assessed so it is uncertain as to the degree of effectiveness associated with these manual techniques.

Lechner et al. (2003 and 2007) have conducted two separate investigations demonstrating a short-term effect of hippotherapy on decreasing spasticity of the lower extremity. The more rigorous of these studies involved a small sample (n=12) crossover RCT during which each subject received twice weekly 25 minute sessions over four weeks of a) hippotherapy treatment, b) sitting on a rocker board driven by motor adjusted to mimic a horse's rhythm and amplitude; c) sitting astride a bobath roll to mimic the postural demands associated with hippotherapy as compared to a similar period of pre-treatment (control). The results of this study indicated that hippotherapy had a short-term effect on decreasing spasticity of the lower extremity, as demonstrated by significant decreases in muscle tone (i.e., reduced AS scores, $p<0.05$) and self-reported spasticity ($p<0.05$) in comparison to the other interventions. Significant differences were found when comparing pre-versus post AS scores for all three intervention groups (i.e., hippotherapy, $p=0.004$; rocker board, $p=0.003$; bobath roll, $p=0.005$) but not for the control condition ($p=0.083$). In addition, improved mental well-being (i.e., reduced Befindlichkeits-Skala scores) was seen with hippotherapy ($p=0.048$) but not with sitting on the rocker board ($p=0.933$) or bobath roll ($p=0.497$). Neither study showed a carry-over effect from session to session or beyond 4 days (Lechner et al. 2003; Lechner et al. 2007). As noted previously, it is difficult to know the primary mechanism for this antispastic effect, although the latter study suggests that it is the combination of sensorimotor stimulation, psychosomatic effects, specific postural requirements and passive and active movements that provide therapeutic benefits as individual aspects of this treatment (i.e., posture or rhythmic movements alone) demonstrated more modest beneficial effects than the full hippotherapeutic approach (Lechner et al. 2007).

Odeen and Knutsson (1981) employed a tilt table on nine subjects with spastic paraparesis due to spinal cord lesions to examine whether benefits of reduced spasticity with passive activity were due to increased muscle load or muscle stretch. These investigators examined the effect of various conditions on resistance to passive sinusoidal ankle movement by loading the tibialis anterior or gastrocnemius by having the subject stand at an angle of 85º with the ankle dorsi-or plantar flexed by 10-15 degrees or by applying stretch to the gastrocnemius muscles while supine. All procedures tested resulted in reduced resistance to passive movement (i.e., reduced tone or spasticity) with the most significant reductions noted for standing in forced dorsiflexion with load applied (i.e., stretch applied to calf muscles, $p<0.001$) (Odeen & Knutsson, 1981).

Conclusion

There is level 1b evidence (from one RCT; Fang et al. 2015) that passive ankle movements may not reduce lower limb muscle spasticity in persons with initial mild spasticity.

There is level 2 evidence (from one RCT; Lechner et al. 2007) that hippotherapy may reduce lower limb muscle spasticity immediately following an individual session.

There is level 2 evidence that electrical passive pedaling systems have an effect on spasticity and hip, knee and ankle range of motion.

There is limited level 1b evidence from a single study that a combination of a 6 week course of neural facilitation techniques (Bobath, Rood and Brunnstrom approaches) and baclofen may reduce lower limb muscle spasticity with a concomitant increase in ADL independence. More research is needed to determine the relative contributions of these therapies.

There is level 4 evidence from a single study that rhythmic, passive movements may result in a short-term reduction in spasticity.

There is level 4 evidence from a single study that externally applied forces or passive muscle stretch as are applied in assisted standing programs may result in short-term reduction in spasticity. This is supported by individual case studies and anecdotal reports from survey-based research.

Key Points

Hippotherapy may result in short-term reductions in spasticity.

A combination of neural facilitation techniques and Baclofen may reduce spasticity.

Rhythmic passive movements may produce short-term reductions in spasticity.

Prolonged standing or other methods of producing muscle stretch may result in reduced spasticity.

Electrical passive pedaling systems may result in short-term reduction in spasticity.

3.2 Interventions Based on Active Movement (Including FES-assisted Movement)

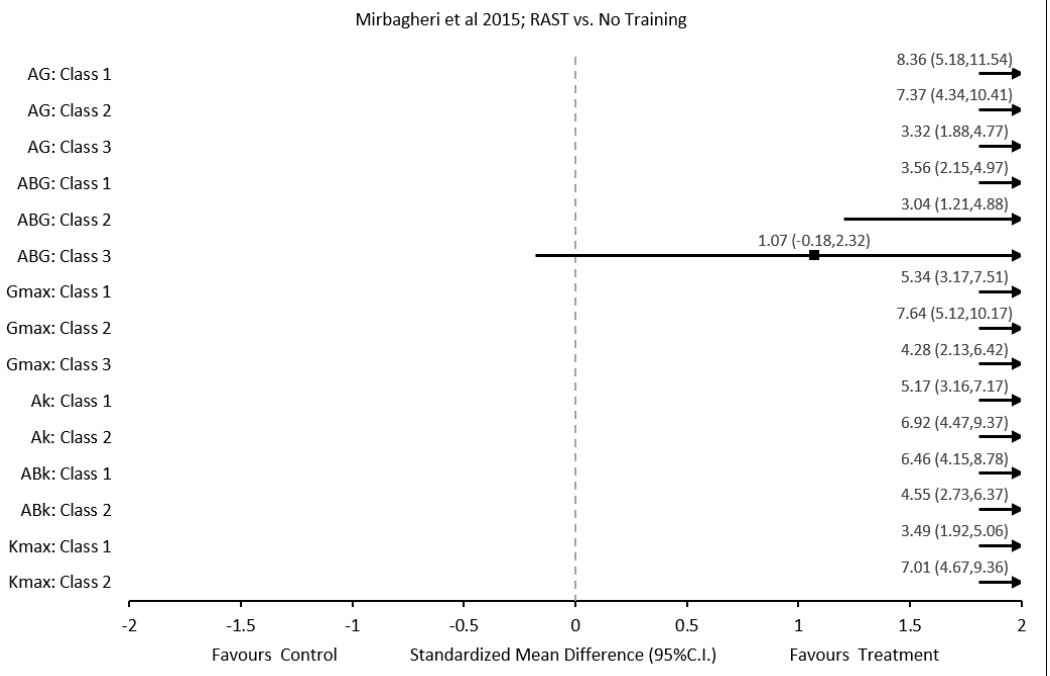
Physical therapy approaches are often advocated as the first treatment choices for reducing spasticity and are deemed as the foundation upon which other therapies are built (Merritt 1981; Kirshblum 1999; Rosche 2002). Despite these contentions, there is a relative paucity of literature addressing the efficacy of either the passive techniques noted in the previous section or approaches involving active movement in individuals with SCI. In practice, active movement approaches may be conducted using a variety of exercise forms that may also provide benefits

beyond spasticity reduction (e.g., strength, endurance, gait re-training). The studies meeting the criteria for the present review involve exercises performed in a therapeutic pool (i.e., hydrotherapy) (e.g., Kesiktas et al. 2004), those associated with FES-assisted cycling (e.g., Krause et al. 2008), locomotor training programs, whether assisted by FES (e.g., Granat et al. 1993; Kapadia et al. 2014; Mirbagheri et al. 2002), or a FES-powered orthosis (e.g., Mirbagheri et al. 2015; Thoumie et al. 1995).

Table 2. Studies of Active Movement-based Approaches for Reducing Spasticity

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Robot-Assisted Exercise		
Fang et al. 2015 Taiwan RCT Crossover PEDro=5 N=10	**Population:** SCI: Mean age: 30.1 yr; Gender: males=8, females=2; Level of injury: C2-C6=2, T3-T7=6, L2-L11=2; Mean time since injury: 5.7 yr. **Intervention:** Individuals wore robot-assisted passive exercise devices on their ankle joints. Individuals were randomly assigned in a crossover design to one of three interventions: high speed cyclic passive exercise (50 cycles/min), low speed cyclic passive exercise (20 cycles/min), or electrical stimulation-induced contractions (ES) for 8 min, 1 x/wk for 3 wk. There were allocated to the other interventions 2 wk later. Outcomes were assessed before each intervention and at 10, 20 min after each intervention. **Outcome Measures:** H reflex, M waves, Total resistance during cyclic stretching, Isometric torque.	1. The amplitude of the H reflex was significantly reduced at 10- and 20-min post high-speed cyclic passive exercises ($p<0.05$), and 20 min post low-speed cyclic passive exercises ($p<0.05$). 2. There were no significant changes in M waves after any of the interventions ($p>0.05$). 3. For individuals whom received ES, and then the high speed cyclic passive exercise, the total resistance during cyclic stretching increased significantly ($p<0.05$). 4. Isometric torque decreased significantly after 8 min of ES and the reduction persisted up to 20 min ($p<0.05$).
Mirbagheri et al. 2015 USA RCT PEDro=6 N=46	**Population:** *Intervention group:* Mean age: 46.4 yr; Gender: males=16, females=7; Mean time since injury: 10.1 yr. *Control group:* Mean age: 47.9 yr; Gender: males=15, females=8; Mean time since injury: 8.9 yr. *All subjects:* Level of injury: C2-T9; Level of severity: AIS C or D. **Intervention:** Subjects were randomly allocated to either the intervention group or the control group. All participants in the intervention group received 1-hr sessions of robotic-assisted step training (RAST), 3x/wk for	1. Using GGM, three classes were identified for each of the reflex parameters and two classes were identified for the intrinsic parameters. Classes were numbered by increasing baseline value. 2. The reflex stiffness parameters showed significant decreases, evident because β was significantly lower than zero for all classes ($p<0.05$). 3. Rates of change for reflex stiffness became more negative

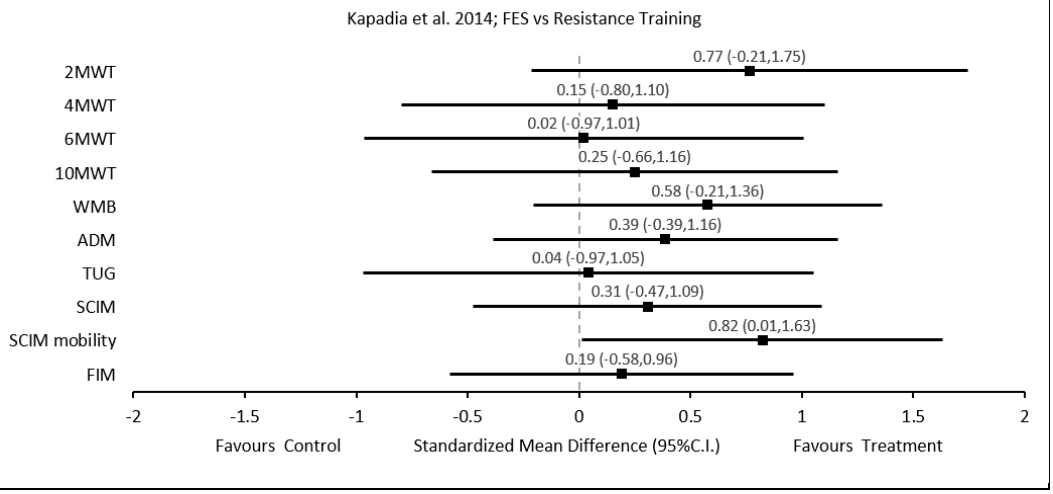
Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	4 wk. Each session included up to 45 min of training. To measure the neuromuscular properties of the ankle joint of all 46 subjects, ankle perturbations were applied to one of the subject's ankles to elicit the stretch reflex. Ankle position and torque were recorded. Evaluations were performed at baseline (prior to training) and after 1, 2, and 4 wk of RAST. The measured joint torque due to perturbations was then separated into intrinsic (musculotendinous) and reflex contributions using a parallel-cascade system identification technique. This analysis was performed for each ankle position yielding stiffness versus joint angle curves for each subject (intrinsic=*K*, reflex=*G*). Growth mixture modelling (GMM) was used to stratify groups based on similar intrinsic/reflex recovery patterns of neuromuscular parameters for both RAST and control groups. Random coefficient regression (RCR) was then used within each class to model the recovery pattern as an exponential function of time, and to determine whether the change in the parameter value was significant. The linearly transformed RCR function was: $\ln C(t)=\ln C_0 + \beta t$. **Outcome Measures:** Stiffness parameters [*A*=offset or intercept, *AB*=slope, G_{max}/K_{max}=maximum value of *G/K* over the passive range of motion (PROM)], correlation between mean baseline values and rates of change ($C_o * \beta$), and the exponential trend parameter, β.	with increasing class number. There was a strong correlation between the mean baseline values and rates of change (r^2=0.94, p=0.0001). 4. The intrinsic stiffness parameters showed significant decreases, evident because β was significantly lower than zero for all classes (p<0.05). 5. Rates of change for reflex stiffness became more negative with increasing class number. There was a strong correlation between the mean baseline values and rates of change (r^2=0.84, p=0.01). 6. Three classes were identified by GMM and RCR for the control group. β was not significantly different from zero for any of these classes (p>0.05 for all).
	Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- and post-intervention data.	

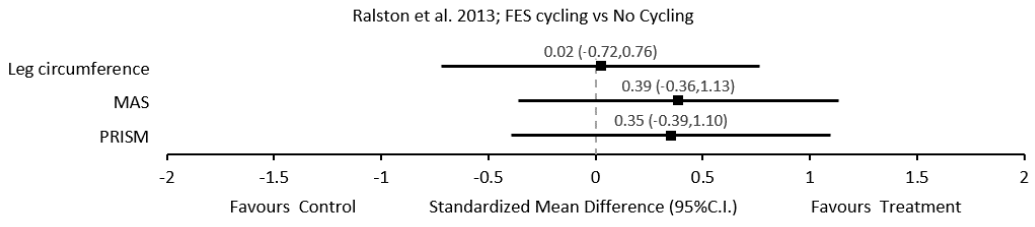
Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		
Mirbagheri et al. 2013a USA Prospective Controlled Trial N=46	**Population:** *Intervention group (n=23):* Mean age: 46.4 yr; Gender: males=16, females=7; Injury etiology: SCI=23. *Control group (n=23):* Mean age: 47.9 yr; Gender: males=15, females=8; Injury etiology: SCI=23. **Intervention:** Each of the subjects in the intervention group participated in 1-hr LOKOMAT training sessions 3x/wk for 4 wk, with each session containing up to 45 min of training. Neuromuscular properties were evaluated (for both intervention and control groups) at four time points- prior to the start of training, and 1, 2, and 4 wk after the start of training. For the neuromuscular assessments, a custom joint-stretching device was used to measure position and torque of the ankle joint. A Parallel-Cascade System Identification Technique was used to separate total ankle torque into the sum of the intrinsic (muscular) pathway and the reflex pathway. From which, intrinsic (K) and reflex (G)	1. Three classes were identified for the reflex slope, and two classes were identified for the intrinsic slope of the intervention group. Classes were numbered by increasing baseline value. 2. Statistically significant values of reduction in reflex stiffness slope ($p<0.05$): a. Class one: 5.2 N-m.s/rad^2 b. Class two: 16.3 N-m.s/rad^2 c. Class three: 32.1 N-m.s/rad^2 3. Statistically significant values of reduction in intrinsic slope ($p<0.05$): a. Class one: 46.5 N-m.s/rad^2 b. Class two: 38.7 N-m.s/rad^2

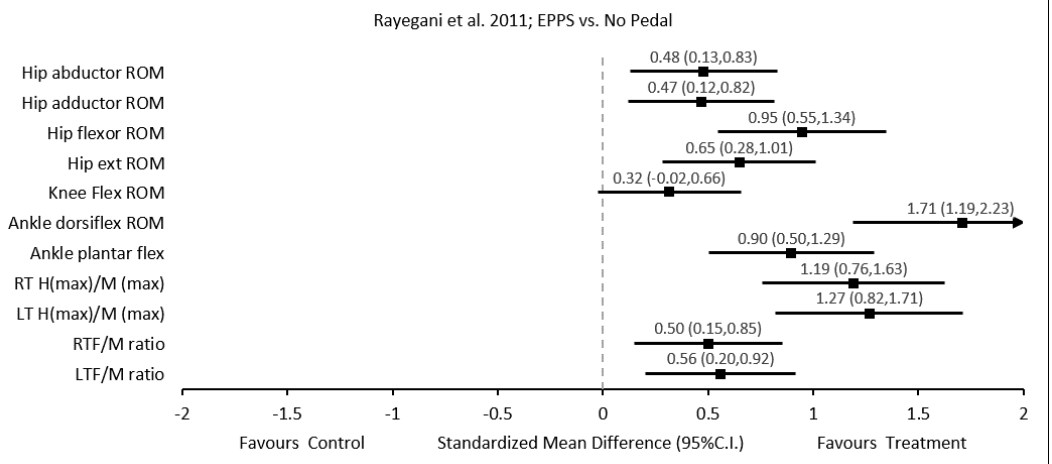
Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	stiffness were calculated and plotted against ankle angle. Subjects were stratified using growth mixture modelling (GMM) based on similar intrinsic and reflex recovery patterns/the slopes of the exponential fit (M_k and M_G). **Outcome Measures:** M_k and M_G.	4. Control subjects presented no significant change in either reflex slope or intrinsic slope over time (p=NS for all groups).
Exoskeleton Walking Device		
Juszczak et al. 2018 USA Pre-Post N=45	**Population**: SCI (n=45): Mean age=35±12.65yr; Gender: males=37, females=8; Level of injury: T1-T8=27, T9-L2=18; Mean time since injury=3.9±5.13yr; AIS scale: A=30, B=5, C=10. **Intervention:** Participants received 3-4 gait training sessions/wk over 8 wk while using the Indego Powered Exoskeleton. At the outset, sessions consisted of learning how to sit and stand, as well has how to ambulate indoors on smooth surfaces while using the exoskeleton. As participants became more proficient, training shifted towards managing doors, ramps, sidewalk curbs, and various indoor and outdoor surfaces. Outcome measures were assessed before and after each training session. **Outcome Measures:** Modified Ashowrth Scale (MAS); self-reported spasticity.	1. Self-reported spasticity indicated significant decreases in spasticity at the end of the study compared to the beginning (p<0.001). 2. However, the majority of participants (n=28, 62.2%) did not experience in mAS score when comparing pre to post trial. 26.7% (n=12) showed decreases in spasticity according to the mAS; 11.1% (n=5) showed increases in spasticity.
Aach et al. 2014 Germany Pre-Post N=8	**Population:** Mean age: 48.0 yr; Gender: males=6, females=2; Level of severity: AIS A=4, AIS B=1, AIS C/D=3. **Intervention:** All individuals underwent body weight supported treadmill training 5x/wk for 90 days using the hybrid assistive limb (HAL) exoskeleton (mean number of sessions=51.75). **Outcome Measures:** Walking index for SCI II (WISCI II), Treadmill-associated walking distance, speed, and time, 10-m walk test (10MWT), Timed-up and go test (TUG test), 6-min walk test (6MWT).	1. The mean improvement of the WISCI II was not statistically significant (p>0.05). At baseline the mean WISCI II was 10±4.34 which increased to 11.13±6.68 after training. 2. Mean walking speed increased from 0.91±0.41 m/s at baseline, to 1.59±0.5 m/sec post-intervention. 3. The mean walking time increased from 12.37±4.55 min at baseline, to 31.97±9.45 min post- intervention.

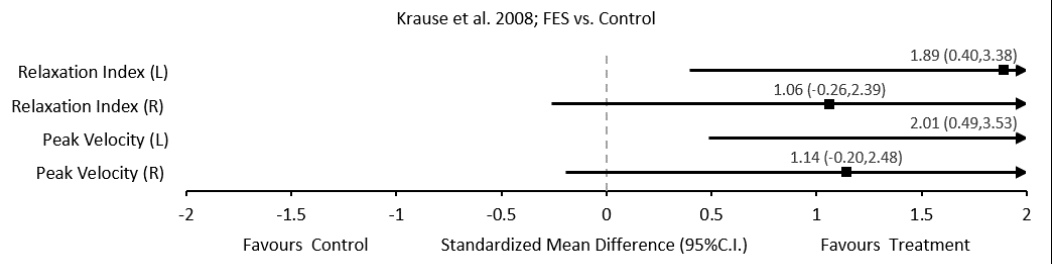
Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		4. The mean walking distance increased from 195.9±166.7 m at baseline, to 954.13±380.4 m post- intervention. 5. The 10MWT speed significantly increased from 0.28±0.28 m/sec at baseline to 0.5±0.34m/s post-intervention ($p<0.05$). 6. The TUG test significantly decreased from 55.34±32.20 sec at baseline to 38.18±25.98 sec post- intervention ($p<0.05$). 7. The 6MWT distance significantly increased from 70.1±130m at baseline to 163.3±160.6m post- intervention ($p<0.05$).
Kressler et al. 2014 USA Case Series N=3	**Population:** Mean age: 30.3 yr; Gender: males=2, females=1; Injury etiology: complete SCI=3; Level of injury: T9/10=1, T7=1, T1/2=1; Level of severity: AIS A=3. **Intervention:** Individuals performed over-ground bionic ambulation (OBA) training using a bionic device (Esko). **Outcome Measures:** 10-m walk test (10MWT), 2-minute walk test (2MWT), Spinal Cord Assessment Tool for Spastic Reflexes, Spinal reflex excitability, Recordings of electromyographic activity, Electroencephalography (EEG), Graded exercise test, Heart rate monitor, International SCI Basic Pain Dataset, Multidimensional Pain Inventory (SCI version) Subscale for pain severity, Neuropathic Pain Symptom Inventory.	1. All participants increased the number of steps taken and distance walked per session in the device. 2. Functional walking capacity increased two-to three-fold for subjects one, two and four over the training period. 3. No changes in clinical measures of spasticity beyond what is attributable to typical variability observed. 4. With training, participants were able to achieve walking speeds and distances in the OBA device similar to those observed in persons with motor-incomplete SCI (10-m walk speed, 0.11-0.33 m/s; 2-min walk distance, 11-33 m). 5. The energy expenditure required for OBA was similar to walking in persons without disability (i.e., 25%-41% of peak oxygen consumption). 6. The unchanged energy cost resulted in improved walking economy for all participants.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		7. Subjects with lower soleus reflex excitability walked longer during training, but there was no change in the level or amount of muscle activity with training. 8. No change in cortical activity patterns. 9. All participants reported an average reduction in pain severity over the study period ranging between-1.3 and 1.7 on a 0-to-6 numeric rating scale.
Del-Ama et al. 2014 Switzerland Case Series N=3	**Population:** Not Reported. **Intervention:** To determine the effects of electrical-muscle stimulation (EMS)-induced hybrid gait training (interventions with a hybrid bilateral exoskeleton for 4 days). **Outcome measures:** 6-minute walk test (6MWT), 10-minute walk test (10MWT), Manual muscle test (MMT) for the lower limbs, Ashworth Scale (AS).	1. All subjects responded favorably to the hybrid walking intervention as indicated by statistically significant improvements in walking tests after 1-2 wk of the intervention. 2. Participants demonstrated statistically significant improvements after the intervention on muscle controlling hip and knee joints as shown by improved MMT scores. 3. There were improvements in knee flexor and extensor muscle groups (intervention wk I-II). 4. Participants demonstrated an improvement in spasticity as marked by differences in Ashworth and Penn scales: average relative increments in AS was -0.2±0.4 and Penn Spasm Frequency Scale was -0.4±0.5 after the intervention. 5. Statistics are not provided to support statistical significance statements. Data was presented graphically.
Functional Electrical Stimulation		
Kapadia et al. 2014 Canada RCT	**Population:** Mean age: 55.3 yr; Gender: males=26, females=8; Injury etiology: motor vehicle accident=9, fall=15, gunshot wounds=1, sports=5, other=4; Level of injury: paraplegia=8,	1. Both groups significantly improved over time on the 6MWT (p=0.002), and there were

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
PEDro=5 N=34	tetraplegia=26; Level of severity: AIS C-D=8, AIS C-D=26; Mean time since injury: 9.5 yr. **Intervention:** Individuals were randomly assigned to the intervention or control groups. In the intervention group individuals received functional electrical stimulation (FES) on their quadriceps, hamstrings, dorsiflexors, and plantarflexors while performing ambulation exercises on a body weight supported treadmill. The control group received conventional resistance and aerobic training. Both groups received 45 min sessions, 3x/wk for 16 wk. Outcomes were assessed at baseline, 16 wk, 6 mo, and 12 mo. **Outcome Measures:** 6-minute walk test (6MWT), 10-meter walk test (10MWT), Timed up and go test (TUG), Spinal cord independence measure (SCIM), Modified Ashworth Scale (MAS), Pendulum test.	no significant differences between groups (p=0.096). 2. The 10MWT had no significant time effects (p=0.084) or between groups differences (p=0.195). 3. Both groups had significant improvements in the TUG over time (p=0.016), and there were no significant differences between groups (p=0.528). 4. Over time the intervention group had significantly greater improvements on the SCIM compared to the control group (p<0.01). 5. MAS scores significantly worsened for both groups in the right quadriceps over time (p= 0.015), and there were no significant differences between groups (p=0.942). 6. The pendulum test had no significant time effects (p<0.05) or between groups differences (p<0.05).
	Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- and post-intervention data. 	

<table>
<tr><th>Author Year
Country
Research Design
Score
Total Sample Size</th><th>Methods</th><th>Outcome</th></tr>
<tr><td rowspan="2">Ralston et al. 2013
Australia
RCT Crossover
PEDro=7
N=14</td><td>Population: Median age: 25.0 yr; Gender: males=11, females=3; Injury etiology: suprathoracic SCI=14; Level of severity: AIS A=13, AIS B=1.
Intervention: Individuals were randomized to receive either the experimental or control intervention first. Each intervention persisted for 2 wk with a 1 wk washout period in between interventions. The experimental intervention consisted of cycling with functional electrical stimulation (FES) for 30-45 min/day, 4 days/wk. FES was directed to the quadriceps, hamstrings and gluteals of each leg. During the control intervention, individuals received no FES cycling. All individuals also received usual care consisting of standard inpatient physiotherapy and occupational therapy including treatment for poor strength, restricted joint mobility, limited fitness, reduced dexterity, pain and functional skills training.
Outcome Measures: Urine output, lower limb swelling, Ashworth Scale (AS) spasticity and individuals' perception of treatment effect (Patient reported impact of spasticity measure-PRISM and Global impression of change scale-GICS).</td><td>1. Urine output was increased by 82mL with FES cycling compared to the control.
2. With FES cycling:
• Lower limb swelling was lower (-0.1 cm between group difference)
• Spasticity was lower (-1.9 points between groups difference on AS)
• PRISM was lower (-5 points between groups difference)
3. 12 individuals reported improvements with FES cycling on the GICS with a median improvement of 3 points.
4. Two individuals reported adverse events: an increase in spasticity and the precipitation of a bowel accident.</td></tr>
<tr><td colspan="2">Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- and post-intervention data.
 
</td></tr>
<tr><td></td><td>Population: Mean age: 43.0 yr; Gender: males=60, females=4; Level of injury: cervical=11, upper thoracic=22, lower</td><td>1. MAS scores significantly decreased in the passive cycling group post intervention (p=0.003).</td></tr>
</table>

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Rayegani et al. 2011 Iran RCT PEDro=3 $N_{Initial}$=74, N_{Final}=64	thoracic=29, lumbar=2; Level of severity: AIS A=63, AIS B=1. **Intervention: Individuals** were randomly allocated to either the passive cycling group (n=37) or the controlled physical therapy group (n=37). The passive cycling intervention consisted of individuals sitting in their wheelchair while a motor passively moved their legs for up to 20 min/set, 3 sets/day for 2 mo (weekly regiment unspecified). The physical therapy included stretching, range of motion (ROM) and strengthening exercises (no further details provided). **Outcome Measures:** Level of SCI, Kondal scale (for muscle strength), Modified Ashworth Scale (MAS), Goniometer measurements (for passive range of motion in the hip, knee and ankle) and electrodiagnostic parameters (H-reflex, H (max)/M (max), and F-wave parameters).	2. Range of motion of the hip, ankle dorsiflexion and plantar flexion increased significantly post intervention in the passive cycling group (hip: p=0.005; ankle dorsi: mean difference=10°, p=0.000; ankle plantar: mean difference=9.4643, p=0.000) no significant change was observed in the knee flexion ROM in the passive cycling group (p=0.111). 3. The F/M ratio (p<0.027) and the H max/M max (p=0.000) decreased significantly in the passive cycling group post intervention. 4. H-reflex amplitude was not significantly different post intervention in either group. 5. No significant differences were observed in the physical therapy group in regard to MAS scores and ROM of the hip, knee flexion, ankle dorsiflexion or plantar flexion.
	Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- to post-intervention and pre-intervention to retention. 	
Krause et al. 2008 Germany RCT Crossover	**Population:** Mean age: 46.0 yr; Gender: males=3, females=2; Level of injury: thoracic=5; Level of severity: AIS A=5.	1. A reduction in spasticity was seen after each intervention although the effect was significantly greater for FES-

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
PEDro=5 N=5	**Intervention:** In a crossover design, individuals with SCI were randomly assigned to FES induced leg cycling movement group versus passive-movement with cycle ergometer. interventions were delivered over a single session of 60-100 min. **Outcome Measures:** Pendulum test (Relaxation index, peak velocity), Ashworth Scale (AS) conducted within 30 min prior or following intervention.	assisted versus passive movement. 2. The relaxation index and peak velocity were significantly greater in the active session with FES than (68%, 50%, p=0.01); passive movement session increase was not significantly different (12%, 1%). 3. In the active FES session significant increase in relaxation index and peak velocity was seen in both the left and right leg, while in the passive session such an increase was only present in the left leg relaxation index. 4. Reduction in the MAS was seen after both active FES (p<0.001) and the passive movement session (p<0.05).
	Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- and post-intervention data. 	
Reichenfelser et al. 2012 Austria Prospective Controlled Trial N=36	**Population:** *Intervention group (n=23)*: Mean age: 40.0 yr; Gender: males=20, females=3; Level of injury: paraplegia=16, tetraplegia=7; Level of severity: AIS B-D; Mean time since injury: 9 mo. *Control group (n=13)*: Mean age: 35.0 yr; Gender: males=9, females=4. **Intervention:** Intervention group subjects performed training sessions 3x/wk over an average timespan of 2 mo. A training session consisted of pre-training (MAS assessment, transfer to the functional electrical stimulation	1. Monthly increase in power output averaged over all subjects was 4.4 W at 30 rpm and 18.2 W at 60 rpm. 2. Group A showed the highest decrease in passive resistance overall. 3. Groups B and C showed very similar results of decreased passive resistance. However, the difference between these two groups increases at higher rpm. Passive resistance decreases

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	(FES) cycling system, and electrode attachment), training, and post-training phases (electrode detachment, transfer, and MAS assessment). The intervention group was stratified based on each patient's averaged MAS scores over all training sessions (Group A: MAS>1, n=8, Group B: MAS<1, n=15). Control group (Group C) participants performed the training session twice. **Outcome Measures:** Active power output (30 and 60 rpm), Spasticity (instantaneous decrease in passive resistance to the pedalling motion due to FES cycling training/average decrease in Modified Ashworth Scale (MAS) scores).	more in Group C across the various rpm.
Sadowsky et al. 2013 USA Cohort N=45	**Population:** Mean age: 36.0 yr; Gender: males=38, females=7; Level of injury: C1-T1=28, T2-L5=17; Level of severity: AIS A=31, AIS B=9, AIS C=5; Mean time since injury: 85.8 mo. **Intervention: Individuals** underwent lower extremity Functional Electrical Stimulation (FES) during cycling (using ERGYS2 FES cycle ergometers) to determine long term effects on physical integrity and functional recovery. Individuals non-randomly grouped into intervention (n=25) and control (n=20) and did not differ significantly by important characteristics at baseline. **Outcome Measures:** International Standards for Neurological Classification of Spinal Cord Injury, American Spinal Injury Association Impairment scale (AIS), Composite Motor–Sensory Score (CMSS), Spasticity and strength were measured quantitatively, total thigh, muscle, intra-and intermuscular fat volumes, Medical Outcomes Study 36-Item Short Form Survey, Functional Independence Measure (FIM), Multi-	1. Spasticity as indicated by the ratio of maximal resistance torque to the maximal voluntary-plus-stimulated torque in the same muscle was ~40–50% greater in the control group than the FES group for all comparisons at the knee joint ($p<0.05$) but not significantly different at the ankle ($p=0.60$). 2. Motor function improvement was observed in 20 of 25 (80%) FES subjects but in only 9 of 20 (45%) controls ($p=0.02$). 3. CMSS improved in 20 of 25 (80%) FES subjects compared with eight of 20 (40%) controls ($p=0.006$). 4. There was no significant difference in AIS grades following FES during cycling. 5. The FES and control groups showed no significant difference ($p=0.24$) in total thigh volume. 6. Total thigh fat measured by MRI was 44% less in the FES group than in the controls (462 versus 828 cc; $p=0.003$).

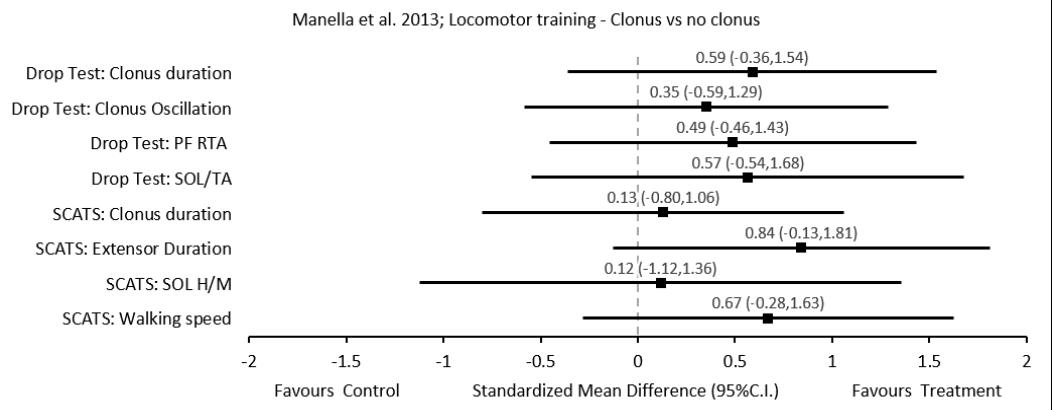
Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	field questionnaire that captures neurogenic bowel habits.	7. Strength values were significantly greater in the trained muscles of the FES group (quadriceps, p=0.006; hamstrings, p=0.011) than in the controls, but not in the untrained ankle (triceps surae muscles, p=0.234). 8. Quality of life and daily function measures were significantly higher in FES group. 9. Mean bowel function scores were significantly higher in the FES group than in the controls (36.7 FES versus 33.6 control; p=0.04).
Kuhn et al. 2014 Germany Pre-Post N=30	**Population:** Mean age: 44.0 yr; Gender: males=30, females=0; Level of injury: C4-C7=13, T4-T12=11, L1-L5=6; Level of severity: AIS A=10, AIS B=3, AIS C=15, AIS D=2; Median time since injury: 2 mo. **Intervention: Individuals** participated in functional electrical stimulated (FES) cycling programs. FES was targeted to the hamstrings, quadriceps and gluteal muscles. Sessions were 20 min, 2x/wk for 4 wk. Outcomes were assessed at before and after each session. **Outcome Measures:** Circumferential measurement, Muscular ultrasound, Manual muscle test, Modified Ashworth Scale (MAS), Walking index for spinal cord injury II (WISCI II), Timed up and go (TUG) test, 6-minute walk test (6MWT).	1. No significant changes in circumferential measurement (p>0.05). 2. AIS A and AIS B individuals had significant improvements on muscular ultrasound measurements after their first session (p=0.016). Additionally, all participants had significant improvements on their muscular ultrasound measurements after their last session (AIS A + B, p=0.019; AIS C+D, p=0.006). 3. Manual muscle strength was significantly increased in the hamstrings (p<0.001), quadriceps (p<0.001), and gluteal muscles (p<0.001) from the first to last session. 4. MAS scores had significant improvements (p=0.002); where improvements were significant in hip abduction (p=0.016), knee flexion (p=0.003), knee extension (p=0.001), and dorsal extension (p=0.001). 5. Of the seven participants whom demonstrated walking ability, there were significant

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		improvements in WISCI II (p=0.04) and 6MWT (p=0.03) scores from the first to last session. 6. TUG scores did not improve (p=0.5).
Manella et al. 2013 USA Pre-Post N=12	**Population:** *Tibialis Anterior (TA) activation group (n=6)*: Mean age: 44.2 yr; Gender: males=6, females=0; Median level of injury: C7; Level of severity: AIS D=6; Mean time since injury: 10.8 yr. *Soleus (SOL) H-reflex suppression group (n=6)*: Mean age: 45.2 yr; Gender: males=4, females=2; Median level of injury: C5; Level of severity: AIS D=6; Mean time since injury: 10.8 yr. **Intervention: Individuals** were randomly assigned to either the TA or SOL groups. In the TA group, operant conditioning training via electromyography feedback was performed to induce voluntary TA activation to enhance supraspinal drive. While in the SOL group, training was performed to modulate reflex pathways at the spinal cord level. Training was performed in both groups 3x/wk for 5wk. Individuals were assessed the wk before and after completion of training. **Outcome Measures:** Maximal voluntary contraction % (MVC%), H-reflex during dorsiflexion % (HDF%), Ankle clonus drop test (Mean clonus duration, Plantar flexion threshold angle (PF RTA)), Timed toe tapping tests, Voluntary dorsiflexion (DF) active range of motion (ROM), ASIA lower extremity motor scores), Foot clearance, Walking speed, Walking distance, SOL H-reflexes % (Presynapic inhibition, reciprocal inhibition, and low-frequency post-activation depression), SOL/TA co-activation ratio.	1. The TA group had significant improvements in: MVC% amplitude (p=0.01), foot clearance (p=0.05) and walking distance (p=0.02). 2. The SOL group had significant decreases for HDF% (p=0.09), and SOL/TA co-activation (p=0.02) over time. 3. None of the other outcome measures had significant changes (p>0.05).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Mazzoleni et al. 2013 Italy Pre-Post N=5	**Population:** Mean age: 43.0 yr; Gender: males=4, females=1; Injury etiology: suprathoracic SCI=5; Level of severity: AIS A=1, B=2, C=2. **Intervention:** All individuals received cyclo-ergometer training in conjunction with functional electrical stimulation (FES) 3 days/wk for 20 wk. Training consisted of pedaling on the cycle for 15-30 min/day with the pedaling time increasing as individuals progressed through the intervention period. FES was delivered to the quadriceps, femoral biceps and gluteus during cyclo-ergometer training. The motor either assisted movements if muscles weren't trained enough or provided a resistance when muscles are able to achieve the minimum power. Individuals also received a rehabilitation program during the intervention period consisting of exercises to increase movement of the head, trunk and arm. **Outcome Measures:** ASIA lower extremity motor control, Spinal cord independence measure (SCIM), Modified Ashworth Scale (MAS), 4-point spasms scale, Muscle area measurements at 5, 10 and 15 cm above the knee and kinetic measurements during cycling (mean speed, maximum speed, resistance, mean power, maximum power and distance).	1. Thigh circumference at 10 cm and 15 cm above the kneecap increased significantly from baseline to post intervention ($p<0.05$). 2. The distance travelled during cycling increased significantly from baseline to post intervention ($p<0.05$). 3. No significant changes were observed in mean speed, max speed, resistance, mean power, max power, MAS and the spasms scale from baseline to post intervention.
Mirbagheri et al. 2002 Canada Pre-Post $N_{Initial}$=9, N_{Final}=5	**Population:** Age range: 25-49 yr; Gender: males=5, females=4; Level of injury: C5-L1; Level of severity: AIS C-D=5; Time since injury range: 3.1-12.3 yr. **Intervention:** FES-assisted walking for as much time as possible during daily living (~1-3 hr/day) for 16-18 mo following 4 wk of training. **Outcome Measures:** Reflex and intrinsic stiffness (mathematical modelled responses of torque	1. Spasticity was reduced in those that did FES-assisted walking as indicated by reductions in decreased reflex ($p<0.001$) and intrinsic ($p<0.001$) stiffness. 2. Spasticity increased for the non-FES subject as indicated by increased reflex stiffness and no change in intrinsic stiffness. 3. The MAS either showed no change following the training

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	resistance to movement), Modified Ashwoth Scale (MAS) collected prior to and following the 16-18 mo trial.	period or was not collected (this was not clearly presented by the authors).
Thoumie et al. 1995 France Pre-Post N=21	**Population:** Age range: 20-53 yr; Gender: males=20, females=1; Level of injury: C8-T12; Time since injury range: 4-72 mo. **Intervention:** Fitting of a Reciprocating Gait Orthosis II (RGO) hybrid (FES-assisted) system and subsequent locomotor training program of 2, 1 hr sessions/wk for 3-14 mo. **Outcome Measures:** Spasticity (subjective self-report scale) collected prior to and following the 3-14 mo trial.	1. No group analysis reported for spasticity measure–No marked changes reported, decrease in spasticity for 7 subjects at 0.5-5 hr and increase in spasticity for 4 subjects at 0.5-1 hr. No long-term effects were observed.
Granat et al. 1993 Scotland Pre-Post N=6	**Population:** Age range: 20-40 yr; Gender: males=3; females=3; Injury etiology: SCI=6; Level of injury: C4 to L1; Level of severity: Frankel grade C=3, D=3; Time since injury range: 2-18 yr. **Intervention:** FES-assisted locomotor training for at least half an hr each day for a minimum of 5 days/wk for a minimum of 3 mo. **Outcome Measures:** Spasticity (Ashworth Scale (AS) and Pendulum Test), Manual muscle tests using Oxford Scale, Maximum voluntary contraction, Upright motor control, Gait Performance (Energy Cost), postural stability (Centre of Pressure), Modified Barthel Index. Spasticity tests were conducted at least 24 hr after FES use.	1. Significant reductions in spasticity as indicated by increased relaxation index of pendulum test ($p<0.05$). 2. No changes were evident with Ashworth scale. 3. Gait and muscle strength changes are elaborated in Chapter entitled “Lower Limb Rehabilitation”.
Effects of Standing		
Sadeghi et al. 2016 Canada Prospective Controlled Trial N=10	**Population:** Mean age: 40.4 yr; Gender: males=9, females=1; Injury etiology: SCI=10. **Intervention:** Individuals underwent two different standing training interventions (dynamic and static). These interventions were given for 20 min and separated by 1 wk. Outcomes were assessed immediately before	1. Non-significant decrease in spasticity in both dynamic and static standing trials for individuals with SCI as measured by MAS, VAS or EMG. 2. There was no statistical difference in spasticity between dynamic and static standing training in individuals with SCI

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	standing training, 5 min after, and 1 hr afterwards. **Outcome Measures:** Modified Ashworth Scale (MAS), Visual Analog Scale (VAS), Electromyography (EMG).	as measured by MAS, VAS or EMG.
Body Weight Support Treadmill Training versus Tilt Table Standing		
Manella & Field-Fote 2013 USA RCT PEDro=5 N=18	**Population:** Mean age: 35.1 yr; Gender: males=16, females=2; Injury etiology: motor incomplete SCI=18; Level of severity: AIS C=9, AIS D=9. **Intervention:** Individuals were randomized to receive 1/4 body-weight supported locomotor training interventions: treadmill based training with manual assistance (TM-n=4), treadmill based training with stimulation of the common peroneal nerve (TS-n=6), lokomat robotic assistance (LR-n=3) or over ground training with stimulation of the common peroneal nerve (OG-n=5). Individuals underwent locomotor training for 1 hr/day, 5 day/wk for 12 wk. Body-weight was supported through the use of a harness in all interventions. Peroneal stimulation was delivered to assist with stepping (flexor reflex response in TS, ankle dorsiflexion in OG). Manual assistance was provided for TM and LR. Results were reported as clonus versus no-clonus (not by different intervention groups) based on number of beats recorded during the drop test. **Outcome Measures:** Drop test (thigh manually raised up a point 10 cm above the knee, the leg is then released and contacts a 10 cm raised platform, eliciting a passive plantar flexion stretch to cause clonus), spinal cord assessment of spastic reflexes (SCATS: measures ankle clonus-plantar	1. Extensor spasm duration significantly decreased in the clonus group (mean difference=-13.20 sec, p=0.05). 2. Overground walking speed increased significantly in the clonus group (mean difference=0.06 m/sec, p<0.01). 3. The clonus duration observed from the drop test (mean difference=-3.99 sec, p=0.06) and the plantar flexion reflex threshold angle (mean difference=-5.82°, p=0.09) decreased non-significantly. 4. The no clonus group showed no significant changes in any outcome measure.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	flexors are stretched by ankle dorsiflexion and clonus duration recorded-and extensor spasm duration-leg is flexed at the hip and knee then rapidly extended), electromyographic (EMG) recordings during drop test (recordings of the soleus, medial gastrocnemius and tibialis anterior), soleus H-reflex (after stimulating the posterior tibial nerve) and over ground walking speed (patients walked 6m at self-selected pace, speed during central 2m recorded).	
	Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- and post-intervention data. 	
Adams et al. 2011 Canada RCT Crossover PEDro=5 N=7	**Population:** Gender: males=6, females=1; Inury etiology: SCI=7; Chronicity: chronic. **Intervention:** Twelve sessions of body-weight supported treadmill training (BWSTT) and tilt-table standing (TTS). **Outcome Measures:** Modified Ashworth Scale (MAS), Soleus H/M ratio, Four self-report questionnaires, Spinal Cord Assessment Tool for Spinal reflexes, Spinal Cord Injury Spasticity Evaluation Tool (SCI-SET), Penn Spasm Frequency Scale (PSFS), Quality of life (Quality of Life Index Spinal Cord Injury Version–III), Functional mobility (FIM Motor Subscale).	1. Extensor spasms exhibited a decrease in extensor spasms following TTS but not after BWSTT (ES=0.68). 2. There was a greater reduction in passive resistance to movement (Ashworth; ES=0.69) and flexor spasms (ES=0.57) after BWSTT compared to TTS. 3. Following BWSTT, there was a greater reduction in the H/M ratio compared to TTS (ES=0.50). 4. Findings suggested that extensor spasms were reduced after TTS (ES=0.95) with a greater reduction after TTS than BWSTT (ES=0.79). However,

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		flexor spasms were observed to be reduced to a greater extent after BS TT as compared to TTS (ES=0.79). 5. There were no observed changes in the H/M ratio following either BWSTT or TTS. 6. There were no group changes in SCI-SET scores or PSFS scores. 7. BWSTT was associated with an improved quality of life and positive changes in FIM motor Subscale scores (ES=0.50 and ES=1.24). *No comments were made on statistical significance of findings.
Dynamic Standing		
Boutilier et al. 2012 Canada Pre-Post $N_{Initial}$=9, N_{Final}=8	**Population:** Mean age: 44.1 yr; Gender: males=7, females=1; Injury etiology: SCI=9; Chronicity: chronic. **Intervention:** Participants underwent a 4 wk dynamic standing program using a Segway (3x/wk, 30 min sessions). **Outcome measures:** Modified Ashworth Scale (MAS), Spinal Cord Injury Spasticity Evaluation Tool (SCI-SET), Pain Outcomes Questionnaire (POQ-VA), Fatigue Severity Scale (FSS).	1. Individual muscle MAS scores decreased after the intervention in at least 2/3 muscle groups for every subject. 2. There was a statistically significant reduction in MAS sum immediately from pre-to post training ($p<0.001$) though there was no significant improvement over time. 3. Spasticity evaluations using the SCI-SET showed an improvement in SCI-SET scores from -0.91±0.30 at initial visit, to -0.63±0.24 for midway and at the final visit from -0.57±0.24, although these differences were not statistically significant. 4. There was a statistically significant reduction in pain over time ($p<0.05$) for the three visits (initial 42.75±8.49, midway 40.88±10.10 and final 32.88±7.17). 5. There was no significant difference between initial and final visits for fatique, though mean fatigue scores did

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		improve (mean=4.2±0.42 to 3.7±0.54).
	Upper Limb	
Cortes et al. 2013 Spain Pre-Post N=10	**Population:** Mean age: 44.8 yr; Gender: males=8, females=2; Injury etiology: SCI=10; Level of injury: tetraplegia=10; Chronicity: chronic. **Intervention:** Subjects received a 6 wk wrist-robot training intervention from the InMotion 3.0 Wrist robot, for 1 hr/day, 3 days/wk, for a total of 18 training sessions per participant. **Outcome measures:** Upper extremity motor score (UEMS), Modified Ashworth Scale (MAS), Visual Analog Scale (VAS).	1. There was a statistically significant improvement in kinematic variables for aim and smoothness after the training program (aim: pre 1.17±0.11 radians, post: 1.03±0.08 radians, p=0.03) 2. 6 wk of robotic training was not associated with a statistically significant change in motor strength of the trained arm (p=0.4) or in the untrained left arm (p=0.41). 3. There were no significant changes in upper limb spasticity in the right trained arm (p=0.43) and left untrained arm following training (p=0.34). 4. There were no changes observed in pain levels following training (p=0.99). 5. There were no changes in any neurophysiological parameters after the 6 wk training (MEP amplitude, p=0.28; latency, p=0.28).
	Hydrotherapy	
Kesiktas et al. 2004 Turkey Pre-Post N=20	**Population:** *Hydrotherapy group (n=10):* Mean age: 32.1 yr; Gender: males=8, females=2; Level of injury: C5-6=3, T8-9=7; Level of severity AIS: A/B-C/D=3/3/4; Mean time since injury: 7.7 yr. *Control group (n=10):* Mean age: 33.1 yr; Gender: males=7, females=3; Level of injury: C5-6=3, T8-9=7; Level of severity: AIS: A/B-C/D=3/3/4; Mean time since injury: 8.6 yr. **Intervention:** 20 min of underwater exercises at 71°F, 3x/wk for 10 wk in addition to conventional rehabilitation (passive range of motion (ROM) exercises, oral baclofen,	1. Both groups showed a significant decrease in AS (hydrotherapy p=0.01 and control p=0.02) with hydrotherapy having a larger reduction in spasticity but this difference was not significant. 2. Spasticity was significantly reduced with hydrotherapy (p<0.001) and with Control (p<0.05) as indicated by Penn Spasm Severity. Post-intervention hydrotherapy scores were reduced versus Controls (p<0.02).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	psychotherapy) versus conventional rehabilitation alone. **Outcome Measures:** Ashworth Scale (AS), Penn Spasm Frequency Severity (PSFS), Functional Indepednece Measure (FIM) scores and oral baclofen intake were recorded weekly and evaluated at the beginning and end of the intervention period.	3. Oral baclofen intake was significantly reduced for the hydrotherapy group but not for the control group ($p<0.002$). 4. Both groups demonstrated significant increases in FIM scores (hydrotherapy $p=0.0001$ and control $p=0.01$), with a larger increase for the hydrotherapy group ($p<0.001$).
Resistance Training		
Bye et al. 2017 Australia RCT PEDro=8 N=30	**Population**: SCI (n=30): Mean age=46yr (IQR=25-65); Gender: males=24, females=6; Level of injury: C1-4=10, C5-8=14, T1-S5=6; Median time since injury=2mo (IQR=1.4-3.1); AIS scale: A=8, B=1, C=11, D=10. **Intervention:** One of the following was selected as the target muscle group for each participant; Elbow flexors, elbow extensors, knee flexors, knee extensors. The target muscle on one side of each participants' body was randomly allocated to the experimental condition; the target muscle group on the other side of the body was allocated to the control condition. The experimental condition underwent a progressive resistance training program consisting of concentric and isometric target muscle contractions in addition to the usual standard of care. The control condition received the usual standard of care including gait and functional training for activities of daily living. The experimental limb was trained 3X/wk for 12 wk. Outcome measures were assessed at baseline and post-intervention. **Outcome Measures:** Maximal voluntary isometric strength (MIVS); spasticity; muscle fatigue; participant perception of strength; participant perception of function.	1. The between-group difference for MIVS had a 95% confidence interval which spanned the clinically meaningful intervention effect, indicating an uncertainty as to whether the intervention effect was clinically meaningful. 2. The between group difference in spasticity indicated no change due to intervention effect. 3. The between-group difference for fatigue had a 95% confidence interval which spanned the clinically meaningful intervention effect, indicating an uncertainty as to whether the experimental condition had a clinically meaningful change. 4. Between-group differences indicate a clinically meaningful increase in participants' perception of functional and strength improvement.
Combination Therapy		

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Martinez et al. 2018 USA RCT Crossover PEDro=5 $N_{Initial}$=21 N_{Final}=12	**Population**: SCI (n=12): Mean age=40.33±7.84yr; Gender: males=9, females=3; Level of injury: C=3, T=9; Mean time since injury=7.92±7.01; AIS scale: A=1, B=1, C=7, D=3. **Intervention:** In this randomized control trial crossover, participants received two 48-session interventions separated by a 6-wk washout period. 30min/session, 3-5x/wk. Interventions included treadmill exercise (TM) and multimodal exercise (MM). For TM, participants walked on a robotic-assisted treadmill at initial speeds of 1-1.5km/h. Speeds were graduated increased as tolerated to a maximum of 3.2 km/h. Additionally, the amount of assistance to reach a predefined gait pattern was gradually reduced as tolerated. MM consisted of simultaneous balance and upper extremity exercises. Outcome measures were assessed at baseline, post intervention, and 6-wk follow up. **Outcome Measures:** modified Ashowrth Scale (mAS); Spinal Cord Injury Spasticity Evaluation Tool (SCI-SET).	1. There was minimal SCI-SET change on both the individual and group level. 2. Four participants showed a decrease in mAS and 5 showed no change in mAS after TM. 3. Two participants showed an increase in mAS and 3 showed no change after MM.
Estes et al. 2017 USA RCT Crossover PEDro=4 $N_{Initial}$=18 N_{Final}=10	**Population**: SCI (n=10): Mean age=46.2±12.8yr; Gender: males=8, females=2; Level of injury: C=6, T=4; Mean time since injury=5.5±3.7yr; AIS scale: B=3, C=2, D=5. **Intervention:** This RCT crossover study consisted of four different physical therapeutic/electroceutic interventions and a sham control. Interventions were separated by at least 48 hr. Interventions included, 1) stretching targeting hip, knee, and ankle flexors and extensors, 2) cyclic passive movement (CPM) using a treadmill-mounted robotic gait orthosis for the lower limbs, 3) transcutaneous spinal cord stimulation (tcSCS) consisting of biphasic stimulation using anodes	1. Between-group comparisons against the sham group showed significantly greater increases in FSE for stretching, CPM and tcSCS immediately after the intervention ($p<0.05$). However, there was no significant between-group difference in FSE change when comparing tDCS and sham ($p>0.05$). 2. Only CPM and tcSCS had significantly greater increases in FSE when compared to sham at 45 min post-intervention ($p<0.05$). 3. There were no significant between-group differences in

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	placed on the back in the region of T11-T12 and the umbilicus, 4) transcranial direct current stimulation (tDCS) by placing an anode 1 cm anterior to the vertex, and a cathode over the inion, and 5) a sham control condition using electrodes. For the stretching, each stretch position was held for 60 seconds and muscle were stretched three times each. tcSCS, CPM, and the sham were administered for 30 min each. tDSC was administered for 20 minutes. Outcome measured were assessed at baseline, immediately after the intervention, and 45-min post-intervention. **Outcome Measures:** First swing excursion (FSE) angle from the pendulum test.	FSE change when comparing the intervention groups to each other at both follow-up assessments ($p>0.05$). 4. The sham condition showed a significant within-group decrease in FSE immediately after intervention and 45 min post-intervention ($p<0.05$). 5. There were no significant within-group changes in FSE for CPM, tcSCS, and tDCS at both follow-up assessments ($p>0.05$). 6. There was a significant within-group increase in FSE for stretching immediately following the intervention ($p<0.05$).
Gant et al. 2018 USA Pre-Post N=8	**Population**: SCI (n=8): Mean age=31.38±11.64yr; Gender: males=6, females=2; Level of injury: T=8; Time since injury=all >1yr; AIS scale: A=4, B=4. **Intervention:** All participants underwent three 4-wk multimodal training sessions separated by 1 wk each; 1) body-weight-supported treadmill training (BWSTT) was administered using a treadmill-based robotic orthosis 2x/wk. Treadmill speed was increased by 2.5%/wk with the most tolerable percentage of body-weight support provided. 2) Upper extremity circuit resistance training (CRT) was administered 3x/wk on non-consecutive days. 30-45 min/session. Participants performed 10 repetitions of each weightlifting maneuver followed by 2 min of arm cranking on a stationary machine. 3) Functional electrical stimulation (FES) cycling was performed on a cycle ergometer 3x/wk on non-consecutive days. 15 min/session. Stimulation consisted of computer-sequenced	1. Participants with high SL and TA F/M ratios at baseline showed significant declines in SL and TA F-wave to M-wave ratio (F/M) at the end of the study (rho=-.69, p=.047; rho=.952, $p<0.001$, respectively). 2. Participants with high SL F/M ratios at baseline also showed significant declines in the SCAT extensor score at the end of the study (rho=-.70, p=.047). 3. No other outcome measures differed significant when comparing baseline to the end of the study.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	electrical stimulation with a frequency of 35 Hz, current amplitude of 100-140 milliamperes, and a pulse width of 350 microseconds. Resistance (torque) was applied and increased at each successive session. Outcome measures were assessed at baseline before the initiation of the intervention, during the 1-wk period in between each intervention, and at the completion of the study. **Outcome Measures:** Spinal Cord Assessment Tool for Spastic reflexes (SCATS); modified Ashworth Scale (mAS); first swing excursion of pendulum test (FSE); EMG activity of soleus (SL), tibilais anterior (TA), rectus femoris (RF), and biceps femoris (BF).	
Mazzoleni et al. 2017 Italy Pre-Post N=7	**Population**: SCI (n=7): Mean age=45.28±3.09yr; Gender: males=5, females=2; Level of injury: T=7; Mean time since injury=NR; AIS scale: A=7. **Intervention:** Participants underwent a two-phase robot-assisted rehabilitation training program. The first phase consisted of functional electrical stimulation (FES) cycling. The quadriceps and femoral biceps of both legs were stimulated using a square biphasic alternated wave with a frequency of 50 Hz. Duration and cycle duty were set to 500 microseconds and 50%, respectively. Simulation amplitude range was 35-75 mA and 25-50 mA for the quadriceps and femoral biceps, respectively. The second phase consisted of overground robotic exoskeleton training consisting of assisted step initiation and active self-initiated modality interactions. Outcome measures were assessed at baseline, and after each phase. **Outcome Measures:** modified Ashworth Scale (mAS); Numerical Rating Scale on spasticity (NRS).	1. mAS was significantly lower after completing phase 1 and 2 compared to baseline ($p<0.05$ for both). 2. There was no significant change in NRS after completing FES cycling ($p>0.05$). However, after completing exoskeleton training, there was a significant decrease in NRS compared to baseline ($p<0.05$).

Discussion

Robot Assisted Exercise (involving voluntary or electrically assisted movement)

In Fang et al.'s (2015) crossover RCT (n=10) noted in the passive movement section previously, one of the conditions involved electrical stimulation-induced contractions for eight min, once/week over three weeks in addition to high speed cyclic passive exercise (50 cycles/min) or low speed cyclic passive exercise (20 cycles/min). Although the focus of that study was on the effects of robot passive-assisted exercise, a key finding related to ES-assisted muscle contractions was that H reflex amplitudes were reduced after passive exercise at both speeds but not after repeated ES-elicited contractions. This suggests reflex excitability is more affected by passive movement (i.e., stretching) than active muscle contraction. Also, electrical stimulation-induced contractions only had an effect in reducing total resistance during slow ($p<0.05$) but not fast cyclic stretching, whereas there was actually an ES-mediated increased resistance ($p<0.05$). Isometric torque decreased significantly after 8 minutes of electrical stimulation-induced contractions and the reduction persisted up to 20 minutes ($p<0.05$), thereby indicating fatigue.

Mirbagheri et al. (2002) previously reported on the use of a custom-made device producing sinusoidal ankle movements as well as mathematical modelling to assess variations in intrinsic (musculotendinous) and reflex contributions to spasticity calculated from measured ankle joint torque due to perturbations. This was employed as part of an RCT (n=46) reprted across two separate publications (Mirbagheri et al. 2015; 2013) examining the effects of robotic-assisted step training using Lokomat vs no treatment on ankle spasticity. The treatment group (n=23) received 1-hour sessions of robotic-assisted step training, three x/week for up to 45 minutes, for four weeks with measures completed prior to training and after 1, 2, and 4 weeks of robotic-assisted step training. The key finding was that reflex stiffness and intrinsic stiffness parameters of spasticity all showed significant decreases ($p<0.05$) whereas the control group did not show any change ($p>0.05$) for any of the parameters calaculated. Subjects were stratified into groups based on similar reflex or intrinsic parameter recovery patterns for both robotic-assisted step training and control groups. Three classes were identified based on greater baseline values for each of the reflex parameters and two classes were identified for the intrinsic parameters. Essentially, greater reductions in spasticity were seen in those with higher baseline levels of either reflex ($r^2=0.94$, $p<0.0001$) or intrinsic ($r^2=0.84$, $p=0.01$), although these changes were only apparent in the treatment group as there were no significant changes with the "no treatment" control condition.

In summary, there is some evidence that robot-assisted exercise (whether including voluntary or ES- assistance) appears to decrease all components of spasticity in the spinal cord injured individual: isometric torque, reflex and intrinsic stiffness. However, there is certainly more research required to identify more specific information associated with both the treatment and resulting spasticity parameters.

Exoskeleton Walking Device

Kressler et al, (2014) completed a case series study (n=3) of over-ground bionic ambulation training using an exoskeleton (Ekso). The study showed that there were no changes in Spinal

Cord Assessment Tool for Spastic Reflex (SCATS), Spinal reflex excitability, recordings of electromyographic activity (EMG), or electroencephalography measures.

Del-Ama et al. (2014) conducted a case series study (n=3) to determine the effects of electrical-muscle stimulation -induced hybrid gait training (interventions with a hybrid bilateral exoskeleton for 4 days). Study subjects demonstrated improvements in spasticity as marked by differences in the AS (-0.2±0.4) and Penn Spasm Frequency Scale (PSFS) (-0.4±0.5) after the intervention.

With a larger cohort of individuals (N=45), Juszczak et al. (2018) reported significantly reduced self-reported spasticity ($p<0.001$) after 8 weeks of graduated training over 3-4 sessions with the Indego Powered Exoskeleton. The importance of this finding is somewhat muted when it is noted that the self-reported spasticity assessment (i.e. 0-10 numerical rating) has not been psychometrically studied for SCI spasticity. Conversely, the MAS has been validated for use in assessment SCI spasticity and in this trial, the majority of participants (62.2%; n=28) did not register a change in spasticity with MAS. Of the remaining participants, reduced or increased spasticity, as measured by MAS, was detected in 26.7% (n=12) and 11.1% (n=5) after Indego training.

Functional Electrical Stimulation

Kapadia et al. (2014) completed an RCT (n=34) to assess FES walking and mobility, with spasticity (i.e., MAS, pendulum test) as primary outcomes. The intervention group (n=17) received FES on their quadriceps, hamstrings, dorsiflexors, and plantarflexors while performing ambulation exercises on a body weight supported treadmill. The control group (n=17) received conventional resistance and aerobic training. Both groups received 45-minute sessions, threex/week for 16 weeks with assessments at baseline, 16 weeks, 6 months, and 12 months post intervention. In general, there were no significant differences over time or between groups for the majority of the MAS and pendulum test. However, MAS scores significantly worsened over time (i.e., more spasticity) for both groups in the right quadriceps ($p=0.015$).

As part of a larger RCT, Manella et al. (2013) conducted an analysis (n=18) of high vs low clonus participants (i.e., high=at least four beats of clonus during drop test) in order to study the effect of various forms of locomotor training on ankle clonus and quadriceps muscle spasm. Study subjects were randomized to receive one of four body-weight supported locomotor training interventions, although sub-analyses were not conducted for each of these related to the spasticty measures. Participants underwent locomotor training for 1 hour per day, 5 days per week for 12 weeks. Only high clonus subjects showed significantly decreased extensor spasm duration (mean difference=-13.20 s, $p=0.05$), significantly increased overground walking speed (mean difference=0.06m/s, $p<0.01$) and non-significant decreases in clonus duration observed from the drop test (mean difference=-3.99s, $p=0.06$) and plantar flexion reflex threshold angle (mean difference=-5.82°, $p=0.09$). The low clonus group did not show any significant changes in any of theoutcome measures. The key finding was that walking speed improvements (no matter the modality of locomotor training) were strongly correlated with reductions in spasticity (i.e., reduced clonus and spasms).

Ralston et al. (2013) completed a crossover RCT (n=14) to study the effect of FES-assisted cycling. Study subjects were randomized to receive 2 weeks of either FES cycling for 30-45 minutes per day, 4 days per week combined with usual care vs only usual care, with a 1-week washout between the two conditions. FES was applied to the quadriceps, hamstrings and gluteals of each leg. Usual care consisted of standard inpatient physical and occupational therapies including treatment for poor strength, restricted joint mobility, limited fitness, reduced dexterity, pain and functional skills training. Urine output, as the primary measure, as well as lower limb swelling, spasticity (Ashworth) and individuals' perception of treatment effect (patient reported impact of spasticity measure- and Global impression of change scale-GICS) were measured. No measures achieved statistical significance, perhaps related to the relative brevity of the intervention. However, all means were improved in favour of an effect of FES-cycling. Urine output increased by 82 mL with FES cycling compared to the control group. Lower limb swelling (-0.1 cm), Ashworth scores (-1.9 points on a 32-point scale obtained by summing four muscle groups bilaterally), and individual reported impact of spasticity measure reports (-5 points) were all reduced with FES. All 12 study subjects reported improvements with FES cycling on the GICS with a median improvement of three points. During the study, two individuals reported adverse events: an increase in spasticity and one reported a bowel accident.

Kuhn et al. (2014) completed a pre-post FES cycling study (n=30) involving training sessions of 20 minutes, two times per week for 4 weeks. MAS scores had significant improvements ($p=0.002$) in hip abduction ($p=0.016$), knee flexion ($p=0.003$), knee extension ($p=0.001$), and dorsal extension ($p=0.001$). In contrast, no significant changes were seen on the MAS and four-point spasms scale in a small pre-post trial (n=5) of FES cycling conducted by Mazzoleni et al. (2013). This study involved training for 15-30 minutes per day, 3 days per week for 20 weeks with the pedaling time increasing as individuals progressed over time.

Sadowsky et al. (2013) reported an increase in muscle strength but not spasticity levels associated with a retrospective, controlled cohort trial (n=45) of lower extremity FES cycling. Participants were non-randomly grouped into intervention (n=25) and control (n=20) groups.

Reichenfelser et al. (2012) completed a prospective controlled trial (n=36) to study the effects of FES cycling over a period of 2 months. The treatment group was divided into Group A (n=13; non-spastic group, MAS score<1) and Group B (n=13; spastic group, MAS score>=1). The study subjects performed training sessions three times per week over an average timespan of 2 months. The control group (n=13; Group C, able=bodied individuals) performed the training session twice. Active power output (30 and 60 rpm), and spasticity (decrease within the cycling session as measured by passive resistance over the cycle) were assessed as part of a customized, commercial tri-cycle ergometer system. Group A treatment subjects showed the highest decrease in passive resistance overall (i.e., within a session and greater as time progressed) with Groups B treatment subjects and Group C control subjects showing lesser and comparable decreased passive resistance. However, the difference between these two groups increased at higher rpm and passive resistance decreased more in Group C control subjects across the various rpm. In addition, there was a monthly mean increase in power output of 4.4 W at 30 rpm and 18.2 W at 60 rpm.

Krause et al. (2008) used a randomized, crossover study design in which five individuals with complete AIS A SCI underwent 1) FES cycling and 2) passive movement by a motor-assisted cycling ergometer. For both of the interventions, the legs were moved for the same period of time at the same velocity and frequency. The study demonstrated that FES (i.e., active muscle contractions) was significantly more effective than passive movements at reducing spastic muscle tone in individuals with complete SCI, although even passive movement resulted in spasticity reductions. This was indicated by a greater reduction in the MAS for FES versus passive movement ($p<0.001$ versus $p<0.05$, respectively), also with the Pendulum Test ($p=0.01$). Further research may be useful in determining precise stimulation patterns to use for FES-cycling as Mela et al. (2001) have noted that specific stimulation frequency parameters may influence spastic reactions variably which suggests careful selection of stimulation parameters so as to optimize the delivery of FES as a clinical tool to reduce spasticity.

Mirbagheri et al. (2002) calculated reflex and intrinsic stiffness of the ankle, as described earlier, as a means of assessing spasticity prior to and following a FES-assisted walking training program. This program involved four individuals with longstanding AIS C or D SCI who underwent locomotor training for a minimum of 16 months. Both reflex and intrinsic stiffness were reduced following FES-assisted walking. Conversely, an individual with SCI, who was not using FES-assisted walking demonstrated no reduction in spasticity. Although the MAS was noted as an outcome measure in the methods, the authors failed to report the final results associated with this clinical measure.

In a similar trial of FES-assisted walking in people with longstanding SCI (Frankel C or D), Granat et al. (1993) also found reductions in spasticity as assessed by a pendulum drop test but did not show any change pre-and post-training when considering AS scores. Granat et al. (1993) performed the final spasticity assessment 24 hours after the final FES-assisted walking session; thereby ensuring the final outcomes would not be unduly influenced by the short-term effects of muscle stimulation.

Thoumie et al. (1995) examined the effects of a FES-assisted Reciprocating Gait Orthosis II on spasticity following a long-term program (i.e., three-13 months) of gait training. No group results (n=21) were reported for spasticity although it appeared that no systematic effects were obtained on a customized self-report version of the AS. Some subjects (n=7) reported decreases in spasticity in the short-term, while others reported increased spasticity (n=4).

Effects of Standing

Sadeghi et al. (2016) completed a prospective controlled trial (n=10) where study subjects underwent two different standing training interventions (dynamic and static). These interventions were given for 20 minutes and separated by 1 week. Outcome measures including the MAS, VAS, andEMG were completed immediately before standing training, at 5 minutes after, and at 1 hour after training. The study showed non-significant decreases in spasticity for both dynamic and static standing trials for individuals with SCI as measured by MAS, VAS and EMG.

Body Weight Supported Treadmill Training versus Tilt Table Standing

Adams et al. (2011) completed a small crossover RCT (n=7) to determine the effects of 12 sessions of body-weight supported treadmill training and tilt-table standing on clinically assessed and self-reported spasticity, MAS, soleus H/M ratio, SCATS, SCI-SET, and the PSFS. The study showed that extensor spasms decreased following tilt-table standing but not after body-weight supported treadmill training (electrical stimulation=0.68) and there was a greater reduction in passive resistance to movement (Ashworth; ES=0.69) and flexor spasms (electrical stimulation=0.57) after body-weight supported treadmill training compared to tilt-table standing . Following body-weight supported treadmill training, there was a greater reduction in the H/M ratio compared to tilt-table standing (electrical stimulation=0.50). Extensor spasms were reduced after tilt-table standing (electrical stimulation=0.95) with a greater reduction after tilt-table standing than body-weight supported treadmill training (electrical stimulation=0.79); however, flexor spasms were observed to be reduced to a greater extent after body-weight supported treadmill training as compared to tilt-table standing (electrical stimulation=0.79). There were no observed changes in the H/M ratio, SCI-SET or PSFS scores following either body-weight supported treadmill training or tilt-table standing.

Dynamic Standing

Boutilier et al. (2012) completed a pre-post study (n=8) on dynamic standing using the Segway device. Study subjects underwent a 4-week dynamic standing program using a Segway, three times a week, for 30-minute sessions. Outcomes were measured by the MAS and the SCI-SET. The study showed that in individual muscle MAS scores there was a decrease after the intervention in at least two out of three muscle groups for every subject. There was a statistically significant reduction in MAS immediately from pre-to post training ($p<0.001$) though there was no significant improvement over time. In spasticity evaluations using the SCI-SET, an improvement from -0.91±0.30 initial, to -0.63±0.24 midway, to -0.57±0.24 final scores were observed. These improved SCI-SET scores were not statistically significant. However, there was a statistically significant reduction in pain over time ($p<0.05$) for the three visits (initial 42.75±8.49, midway 40.88±10.10, final 32.88±7.17). There was no significant difference between initial and final visits for fatique, though mean fatigue scores did improve (mean=4.2±0.42 to 3.7±0.54).

Upper Limb

Cortes et al. (2013) completed a pre-post study (n=10) of wrist spasticity using a robot training intervention with a primary focus on enhancing motor performance and neurorecovery. Study subjects received a 6-week wrist-robot training intervention from the InMotion 3.0 Wrist robot, for 1 hour/day, 3 day/week, for a total of 18 training sessions. After 6 weeks of robotic training there was no significant changes in upper limb spasticity as assessed by the MAS in the right trained arm ($p=0.43$) or left untrained arm following training ($p=0.34$).

Hydrotherapy

Kesiktas et al. (2004) employed an experimental non-RCT design to test the effectiveness of a water-based exercise (i.e., hydrotherapy) program in reducing spasticity in a group of individuals (n=10) with complete and incomplete paraplegia and tetraplegia. Subjects were matched within

a treatment group (i.e., hydrotherapy + conventional rehabilitation) versus a control group (conventional rehabilitation only) on the basis of age, gender, time post-injury, injury level and severity, spasticity (Ashworth) and function (Functional Independence Measure FIM). This study produced consistent results across all spasticity-related measures with spasticity reductions evident following the 10-week hydrotherapy treatment program for both AS scores and the Penn Spasm Severity scores. The control group also showed significant spasticity reductions relative to baseline with these measures but not to the same degree. In addition to these measures, dosages of oral baclofen were significantly reduced for those receiving hydrotherapy versus conventional rehabilitation only (i.e., >50%) and the hydrotherapy treated group made much greater FIM gains than did the control group. These latter results may reflect the deleterious effect that high baclofen doses can have on motor and cognitive function and the benefits of reduced spasticity on motor function. Kesiktas et al. (2004) did not indicate how soon after the final intervention the measures were taken so there is no indication of how long the beneficial effect might have been maintained.

Resistance Training

Although unblinded study participants perceived that strength training of partially paralyzed muscles improved their strength and function, the clinically measured effect on spasticity (and strength) was inconclusive with respect to clinically meaningful changes as measured by the Ashworth (and maximal voluntary isometric strength). Importantly though, strength training did not have a deleterious effect on spasticity (or strength).

Combination Therapy

Combination therapies are intended to leverage simultaneous targeting of more than a single type of neural circuitry during rehabilitation training. Martinez et al. (2018; level 2 evidence), in a small level 2 crossover trial, were not able to show significant differences between multimodal training and robotic treadmill training for spasticity as assessed with the SCI-SET (and lower extremity strength and reflexes and ambulation and pain). The control intervention consisted of 48 sessions of robotic treadmill training at increasing speeds and decreasing body-weight support to reach a predefined gait pattern and was compared to the control intervention augmented with simultaneous balance and skilled upper extremity exercises (i.e. multimodal intervention). Participants were assigned to start with treadmill only or multimodal training and after a washout period of 6 weeks, continued with the comparison intervention. Two of 9 participants actually showed an increase in spasticity after multimodal training while 4 of 9 showed a decrease after the control intervention. Three and 5 showed no change, respectively. These less than clear results may have been the result of only 43% (9/21) or participants completing both arms of the trial.

Physical and electroceutic neuromodulatory methods are sought as an alternative to pharmacological control of spasticity due to the avoidance of deleterious side effects accompanying drug treatments. Estes et al. 2017 (level 2 RCT) systematically tested 4 non-pharmacological approaches against a sham-control to achieve spasticity reduction in the lower extremeties as quantified by the pendulum test. Stretching (hip/knee/ankle flexors/extensors), cyclic passive movement (through a treadmill-mounted robotic gait orthosis), transcutaneous spinal cord stimulation (using biphasis stimulation at T11/12 and umbilicus), and transcranial

direct current stimulation (with anode 1cm anterior to the vertex and cathode over inion) while the sham-control consisted of a brief ramp-up/-down of knee/ankle stimulation with the leg extended and participant in the reclined position. Each participant was randomized to receive a different order of the 4 interventions and sham (all single sessions only), after 48 hours washout between sessions. Continuous passive motion and transcutaneous spinal cord stimulation were shown to be viable non-pharmacological treatments for induction of prolonged periods (45 minutes) of spasticity reduction. For immediate and only short-term spasticity reduction, stretching was the most effective compared to sham. The sham-control condition confirmed that spasticity is problematic with increased immobility. Further investigations of dosing and timing would be necessary to maximize efficacy for these alternative anti-spasticity treatments.

Controlling for confounding variations in overall body condition is a factor to be considered when assessing efficacy of novel interventions such as pharmacological and cellular therapies. To understand the effects of various rehabilitation therapies without the addition of novel interventions, Gant et al. (2018; level 4 evidence)) utilized a 12-week training program for participants with chronic thoracic level motor-complete participants, to deliver body-weight-supported treatmill training for locomotion, circuit resistance training for upper body conditioning, FES for activation of sublesional muscles and wheelchair skills training for overall mobility. Without the addition of any novel intervention, upper extremity strength improved for all 8 participants and some also experienced improved function that was likely a result of the improved strength. However, no improvements led to a change in neurological function and changes to pain and spasticity were highly variable between participants. Obviously, a larger study is required to validate these findings in a generalizable way but the current small trial is an indication of the importance of balancing, standardizing and documenting rehabilitation therapies whether additional novel interventions are included when attributing functional recovery to the intervention under study. In this study, spasticity (assessed with SCATS) was not consistently influenced by this 12-week multi-modal training program.

Mazzoleri et al. (2017; level 4 evidence) investigated the effect of integrated gait training (20 sessions of functional electrical stimulation cycling followed by 20 sessions of overground robotic exoskeleton training) on spasticity (and patient-robot interaction). Spasticity was assessed with the MAS, numerical rating scale and PSFS. Spasticity was significantly reduced after the first phase of FES based training (MAS; $p<0.05$) with a further decrease after the second phase of robotic exoskeleton training (MAS and NRS; $p<0.05$ for both). The effects on spasticity also likely contributed to improved gait parameters after overground robot-assisted gait training (significant increase of standing time and number of steps). Although the anti-spasticity effect reported here conflicts with results of other combination therapy studies (Martinez et al. 2019, Estes et al. 2017, Gant et al. 2018), the particular combination and intensity of integrated gait training may be key to the differing results.

Conclusion

Robot-Assisted

There is level 1b evidence from two RCTs (Fang et al. 2015; Mirbagheri et al. 2015) robot-assisted exercise appears to decrease all components of spasticity (isometric torque, reflex and intrinsic stiffness).

Functional Electrical Stimulation

There is level 4 evidence that single bouts of FES-assisted cycling ergometry, with a single level 2 study also showing that similar passive cycling movements are effective in reducing spasticity over the short-term although FES is more effective than passive movement.

There is level 1 evidence from 1 study, with conflicting evidence across two level 4 evidence studies, that show FES cycling decreases spasticity over the long-term.

There is level 4 evidence from three studies that a program of FES-assisted walking acts to reduce ankle spasticity in the short-term (i.e., ≤ 24 hours), however, a level 2 study showed no reduction across several lower limb muscles when considering an overall sustained effect.

There is no evidence to describe the optimal length and time course of FES-assisted walking for reducing spasticity.

Effects of Standing

There is level 2 evidence (from one prospective controlled trial; Sadeghi et al. 2016) that dynamic and static standing training does not reduce spasticity.

Body Weight Support Treadmill Training versus Tilt Table Standing

There is level 2 evidence (from one RCT; Manella & Field-Fote 2013) that electrical stimulation treadmill training and LOKOMAT robotic-assisted training decreases ankle clonus.

There is level 4 evidence (from one pre-post study; Adams et al. 2011) that use of tilt-table standing decreases extensor spasms and body-weight support treadmill training results in a reduction in passive resistance to movement and flexor spasms.

Dynamic Standing

There was level 4 evidence (from one pre-post study; Boutilier et al. 2012) that showed use of a Segway device for dynamic standing results in a reduction of spasticity.

Exoskeleton

There is conflicting level 4 evidence (from two case series; Kressler et al. 2014; Del-Ama et al. 2014) that use of an exoskeleton walking device results in a reduction in spasticity.

Upper Limb

There is level 4 evidence (from one pre-post study; Cortes et al. 2013) that use of robotic training of the wrist does not improve upper limb spasticity.

Hydrotherapy

There is level 4 evidence (from one pre-post study; Kesiktas et al. 2004) that hydrotherapy is not more effective in producing a short-term reduction in spasticity than conventional rehabilitation alone.

Resistance Training

Resistance training is not deleterious but does not decrease spasticity as evidenced by one level 1b RCT (Bye et al. 2017).

Combination Therapy

There is level 2 evidence (from 2 RCTs; Martinez et al. 2018, Estes et al. 2017, further supported by 1 small level 4 pre-post study by Gant et al. 2018)) that combination therapies do not consistently reduce spasticity. This is slightly challenged by level 4 evidence (small pre-post, Mazzoleri et al. 2017) that FES cycling followed by robotic exoskeleton training may reduce spasticity.

Key Points

Active exercise interventions such as hydrotherapy, FES-assisted cycling and walking and robot-assisted exercise (including specific exercises combined) may produce short-term reductions in spasticity.

3.3 Interventions Based on Direct Muscle Electrical Stimulation

A variety of electrical stimulation methods have been employed to reduce spasticity including direct muscle stimulation, sometimes also termed patterned electrical stimulation or patterned neuromuscular stimulation, FES and TENS. In the present section, we will examine the effect of interventions based on direct muscle stimulation (or stimulation of the motor nerve over the muscle belly) (i.e., patterned electrical stimulation or patterned neuromuscular stimulation). The objective of direct muscle stimulation is to produce a muscle contraction and related therapies are focused on the beneficial effects of series of muscle contractions. Often this stimulation is cyclical in nature (patterned) so as to simulate natural physiologic conditions such as might be seen in walking or cycling. With FES, the stimulation parameters are set to produce a coordinated contraction of several muscles with the intent of producing purposeful movement. This approach is often used to assist or simulate active exercise paradigms and therefore, the articles addressing FES have been summarized in the previous section on active movement-based approaches. TENS, on the other hand, is focused on stimulating large, low threshold afferent nerves to alter motor-neuron excitability and thereby reduce spasticity. Stimulation intensities are maintained sub threshold for eliciting muscle contraction when stimulating mixed motor and sensory nerves so that only lower threshold sensory nerves are selectively stimulated.

For this reason, articles concerning TENS will be included in the next section that is directed towards interventions based on afferent stimulation.

Table 3. Studies of Direct Muscle Stimulation for Reducing Spasticity

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Sivaramakrishnan et al. 2018 India RCT Crossover PEDro=6 N=10	**Population**: SCI (n=10): Etiology: Trauma=4, Infective=2, Degenerative=2, Tumor=2; Mean age=39±12.98yr; Gender: males=9, females=1; Level of injury: C=6, T=4; Mean time since injury=8.8±9.09mo; AIS scale: A=2, B=0, C=6, D=1, E=1. **Intervention:** Participants were randomly allocated to receive either transcutaneous electrical nerve stimulation (TENS) or functional electrical stimulation (FES) first. Interventions were separated by a 24-hr washout period. TENS was administered with biphasic square wave impulses at 100 Hz and a pulse duration of 300 microseconds for 30 min. Stimulation intensity was 15 mA. FES was administered with biphasic rectangular pulses at a 35 Hz pulse rate and 300 microsecond pulse width for 30 min. Stimulation intensity was increased until a visible muscle contraction (motor threshold) was elicited. Outcome measures were assessed at baseline, post intervention, and at 1, 4, and 24-hr follow ups. **Outcome Measures:** Modified Ashworth Scale (MAS) scores for hip adductors, knee extensors, and plantar flexors; Spinal Cord Assessment Tool for Spastic Reflexes (SCATS).	1. There were no significant between-group differences in MAS and SCAT scores for hip adductors, knee extensors and plantar plexors post intervention, as well as at the 1, 4, and 24-hr follow ups ($p>0.05$ for all). 2. TENS and FES showed statistically significant within-group differences for mAS scores of hip adductors and knee extensors. mAS scores were significantly lower post intervention, and at 1 and 4-hr follow ups ($p<0.01$). However, there were no statistical differences in the 24-hr follow and baseline values. 3. There were no significant within-group differences in MAS scores for plantar flexors in both FES and TENS groups ($p>0.05$). 4. TENS SCAT scores were significantly lower post intervention and at the 1-hr follow up when compared to baseline ($p<0.05$). There was no statistically significant difference at the 4 and 24-hr follow ups when compared to baseline. 5. FES SCAT scores were significantly lower post intervention and at the 1 and 4-hr follow ups when compared to baseline ($p<0.01$). However, there was no statistically significant

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		difference between the 24-hr follow up and baseline.
Gomez-Soriano et al. 2018 Spain Pre-Post N=39	**Population**: SCI with spasticity (SCIS, n=14): Mean age=39.3±15.2yr; Gender: males=10, females=4; Level of injury: C=10, T=3, L=1; Mean time since injury=3.8±2.0mo; AIS scale: C=8, D=6. SCI without spasticity (SCI, n=14): Mean age=43.5±15.6yr; Gender: males=10, females=4; Level of injury: C=7, T=5, L=2; Mean time since injury=6.5±3.8mo; AIS scale: C=7, D=7. Non-injured (NI, n=11) **Intervention:** Plantar tibialis anterior (Pl-TA) cutaneous reflex (CR) and soleus (SOL) H-reflex were evoked with a controlled current simulator delivering 5 rectangular pulses (with 1 millisecond duration, with a 5-millisecond interval) at 1.2X the required stimulus to induce Pl-TA reflex during a controlled plantarflexion protocol. All participants participated in two randomized session including vibratory and transcutaneous nerve stimulation (TENS). 80 Hz vibratory conditioning was applied to the plantar surface of the foot. TENS consisted of a biphasic asymmetrical current of 100 Hz with a 100-microsecond pulse width using an anode and cathode placed on the dorsum and plantar surfaces of the foot, respectively. Both conditions were applied between the second and third metatarsal joints of the plantar foot for 30 seconds prior to reflex measurement and maintained throughout the testing protocol. Outcome measures were assessed at baseline and during the respective intervention (at rest, and duration ramp and hold phases of the plantarflexion protocol). **Outcome Measures:** Pl-TA CR; SOL H-Reflex.	1. There was a significant decrease in Pl-TA CR during the rest phase and hold phase during the vibrational intervention ($p<0.001$; $p<0.05$, respectively). However, there were no significant changes in SOL H reflex for all phases and Pl-TA CR during the ramp phase ($p>0.05$). 2. During TENS, Pl-TA CR showed a significant decrease during the hold phase ($p<0.05$). There were no significant differences for the remaining outcome measures ($p>0.05$).
van der Salm et al. 2006	**Population:** Age range: 21-42 yr; Gender: males=8, females=2; Level of injury: C3-	1. Only the agonist muscle stimulation differed

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Netherlands Prospective Controlled Trial N=10	T11; Level of severity: AIS A=9, AIS C=1; Time since injury range: 28-275 mo. **Intervention:** Electrical motor (agonist or antagonist) or afferent (S1 dermatomal) stimulation of the triceps surae or a placebo (application of electrodes but no current). 1–45 min session of each type of stimulation. Intensity at 3x motor threshold for motor stimulation and 80% of motor threshold for afferent stimulation. **Outcome Measures:** Modified Ashworth Scale (MAS), Clonus score, H reflex, and H/M ratios. Measurements were conducted just prior to, immediately after, 1 hr after and 2 hr after the intervention for each of the 4 conditions.	significantly (46% reduction) from the placebo as indicated by reduced MAS ($p<0.001$). 2. No significant carry-over effect (over 2 hr) although there was a trend of continued reductions for the MAS ($p=0.113$). 3. No significant intervention effect was shown for the clonus score or the H/M ratio. 4. The reflex-initiating angle showed a significant change for antagonist stimulation ($n=8$, $p=0.015$) but the carryover effect was not significant.
Seib et al. 1994 USA Prospective Controlled Trial N=10	**Population:** Age range: 19-73 yr; Gender: males=6, females=4; *SCI (n=5):* Time since injury range: 3-16 yr. *TBI (n=5)*: Time since injury range: 1-6 yr. **Intervention**: One, 20 min session of electrical stimulation over the tibialis anterior measured in ipsilateral (intervention) and contralateral (control) leg versus sham stimulation (control). **Outcome Measures:** Viscous and elastic ankle stiffness measured by frequency-dependent torque resistance immediately post-stimulation (n=10/9), and 24 hr post-stimulation (n=9/8), and immediate post-stimulation subjective spasticity assessment (n=9).	1. Spasticity was reduced in 9/10 participants ($p<0.05$) ($p<0.05$ for SCI subjects only) and this was sustained for 24 hr over all subjects ($p<0.01$) but not for SCI subjects only. 2. Spasticity was not reduced immediately or after 24 hr in the contralateral leg nor with sham stimulation. 3. Subjective spasticity assessment immediately post-stim only recorded notable reductions for SCI subjects for up to 6 hr post-simulation.
Carty et al. 2013 Ireland Pre-Post N=14	**Population:** Gender: males=11, females=3; Injury etiology: SCI=14 Level of severity: AIS A/B=14; Mean time since injury: 10.2 yr **Intervention:** Investigate alterations in body composition variables and spasticity following subtetanic neuromuscular electrical stimulation (NMES) training.	1. Within subjects, statistically significant decrease in SCATs ($p<0.001$), showing reduction in measured spasticity. 2. Within subjects, no significant difference in spasticity VAS scores at any of three test points.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Outcome Measures: Lean body mass (LBM), Other body composition variables, Spinal Cord Assessment Tool for Spastic Reflexes (SCATs), Visual analog scale (VAS), Verbal and written feedback for spasticity.	3. No significant differences between control, testing and pretraining measures. 4. Significant differences between pretraining and posttraining for lower-limb LBM, total mass and regional body fat; tendency toward reduction in total body fat but no statistical significance.
Tancredo et al. 2013 Brazil Pre-Post N=11	**Population:** Mean age: 34.5 yr; Gender: males=11, females=0; Level of severity: AIS A=9, AIS B=1, AIS D=1. **Intervention:** Individuals received Neuromuscular electrical stimulation (NMES) on the quadriceps muscles and fibular nerve for 20 min and 15 min respectively. Goniometer and accelerometer sensors for the pendulum test were placed on the right leg with measurements being repeated three times. Assessments were completed at baseline and post- intervention. **Outcome Measures:** Modified Ashworth Scale (MAS), Pendulum test, Subjective spasticity scale.	1. A decrease in spasticity from baseline to post- intervention according to the MAS scores was reported for all but three individuals who remained stable. 2. The pendulum test revealed a decrease in spasticity with a larger variation between the maximum and minimum peaks of motion from baseline to post- intervention. 3. When individuals were stratified based on those taking medication (baclofen and clonazepam) and those who were not, both groups still demonstrated improvements on the pendulum test. 4. Of the nine individuals who completed the subjective spasticity scale, eight reported lower ratings of spasticity after receiving NMES whilst one individual reported stable ratings.
Robinson et al. 1988a USA Pre-Post N=12	**Population:** Age range: 21-62 yr; Level of injury: paraplegia=6, tetraplegia=6; Level of severity: complete=6, incomplete=6. **Intervention:** 1, 20 min session of electrical stimulation of quadriceps with leg maintained at 60° flexion (isometric exercise). **Outcome Measures:** Normalized relaxation index obtained during	1. Decrease in spasticity was noted with pendulum test (average R2n increased in most cases) ($p<0.005$). 2. The greatest reduction in spasticity after stimulation was noted for individuals who were the most spastic before stimulation.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Pendulum test (R2n) collected prior and immediately after stimulation.	3. No carry over effect of stimulation in spasticity measured 24 hr later.
Robinson et al. 1988b USA Pre-Post $N_{Initial}$=31, N_{Final}=8 4wk tx N=21, 8wk tx N=8	**Population:** Level of injury: paraplegia=15, tetraplegia=16; Level of severty: complete, incomplete; Time since injury: <1yr=15, >1yr=16. **Intervention:** 4-8 wk quad reconditioning program of twice daily 20 min stimulation sessions of quadriceps, which were at least 4 hr apart, 6x/wk. Stimulus currents were set at 120-160 mA. **Outcome Measures:** R2n-index of spasticity (by means of pendulum drop test). Peak isometric quad torque in response to surface electrical stimulation. Biweekly tests of spasticity and torque at baseline, 4 and 8 wk (1-3 evaluations performed each time).	1. Most participants had increased spasticity after 4 wk of reconditioning but not after 8 wk. 2. Twice as many legs had R2n decreases (spasticity increases) as had increases or no change. 3. Baseline versus 4 wk left and right R2n yielded a significant within subject difference between baseline and 4 wk values (p=0.008).

Discussion

In an RCT (n=10), Sivaramakrishnan et al. (2018) compared the anti-spasticity effects of a single session of FES or TENS electrical stimulation. Changes in spasticity of the hip abductors, knee extensors and ankle plantar flexors were measured using the mAS and SCATS. Upon analysis of mAS scores, TENS and FES significantly reduced spasticity up to 4 hours in the hip abductors and knee extensors ($p<0.01$). Similarly, SCATS scores showed significant reductions in spasticity 1 hour following TENS ($p=0.01$) and 4 hours following FES ($p=0.01$). However, no significant differences were observed between groups at 24 hours. This suggests that both TENS and FES exert similar anti-spasticity effects, which may be effective as *temporary* therapeutic adjuncts.

Carty et al. (2013) conducted a pre-post study (n=14) to investigate alterations in body composition variables and spasticity following subtetanic neuromuscular electrical stimulation. Subtetanic contractions were elicited bilaterally in the proximal and distal quadriceps and hamstrings muscle groups using a hand-held neuromuscular electrical stimulation device. Measurements were taken before (2x) and after an 8-week neuromuscular electrical stimulation training program for hamstrings and quadriceps. There was a statistically significant within-subject decrease in SCATS ($p<0.001$), showing reduction in measured spasticity. There was no significant difference in spasticity VAS scores at any of three test points.

Tancredo et al. (2013) conducted a pre-post study (n=11) of the effect of neuromuscular electrical stimulation on spasticity as assessed bythe pendulum test and MAS at baseline and post-treatment. Neuromuscular electrical stimulation was applied within a single session to the

quadriceps muscles and fibular nerve for 20 minutes and 15 minutes, respectively. The study revealed a decrease in MAS scores from baseline to post-treatment in eight subjects while spasticity levels remained stable in three subjects. The pendulum test revealed an overall decrease in spasticity with a larger variation between the maximum and minimum peaks of motion from baseline to post-treatment. Even when subjects were analyzed based on those who did or did not take medication (baclofen and clonazepam), both sub-groups still demonstrated improvements on the pendulum test. Of the nine study subjects who completed the subjective spasticity scale, eight reported lower ratings of spasticity after receiving neuromuscular electrical stimulation and one reported stable rating.

Van der Salm et al. (2006), Seib et al. (1994) and Robinson et al. (1988a) tested the effects of a single session of muscle stimulation on spasticity. Each employed slightly different stimulation parameters and a variety of outcome measures. Of note, Van der Salm et al. (2006) and Seib et al. (1994) each employed prospective controlled trials of electrical stimulation and demonstrated immediate effects of reduced spasticity although these effects waned until mostly absent by the next day. In particular, van der Salm et al. (2006) examined three different stimulation methodologies versus a placebo condition and assessed ankle plantar flexor spasticity with the MAS, a clonus score and via EMG responses (i.e., H-reflex and H/M ratio). The various stimulation methods consisted of stimulation over the triceps surae (agonist), the tibialis anterior (antagonist) and the S1 dermatome versus a control placebo condition of electrode application but no current generation. Presumably, subjects were not aware of this because subjects had no sensation in the stimulated areas. Significant spasticity reductions were only obtained with agonist muscle stimulation for the MAS ($p<0.001$) and not the clonus or EMG responses. This was not sustained for 2 hours post-stimulation although there was still a trend for reduced MAS scores at this time ($p=0.113$). Spasticity was also reduced (but not statistically significantly) with antagonist muscle stimulation but not for dermatomal or sham (placebo) stimulation.

Interestingly, van der Salm et al. (2006) noted that if they had examined their data by employing t-tests to test for pre-post effects (i.e., univariate analysis) within a specific stimulation method, they also would have demonstrated a reduction in spasticity for antagonist muscle stimulation, thereby illustrating the potential of obtaining false positives in uncontrolled or poorly controlled studies. Robinson et al. (1988a) conducted a pre-post study design without control conditions and Seib et al. (1994) conducted a prospective controlled trial but then inappropriately employed univariate analysis. Regardless, the results of these studies corroborate the finding of an immediate post-stimulation effect (van der Salm et al. 2006). Seib et al. (1994) and Robinson et al. (1988a) employed stimulation of different muscles (tibialis anterior, i.e., ankle dorsiflexion and quadriceps, i.e., knee extension respectively) and each demonstrated short lasting reductions in spasticity. Similar to the findings of van der Salm et al. (2006), Seib et al. (1994) reported that the effect of reduced spasticity waned quickly but was still evident up to 6 hours post-stimulation (mean 4.4 hours) as indicated by subject self-report.

In the only study of the long-term effects of stimulation, Robinson et al. (1988b) employed a similar stimulation protocol for the quadriceps as noted above over a period of four–eight weeks with twice daily 20-minute sessions at least four hours apart, 6 days per week. Although 31 individuals initiated the study and 21 complete 4 weeks of the stimulation program, the study had severe subject retention issues with only eight individuals continuing participation for the

intended eight weeks. Study results showed that most subjects actually had increased spasticity at four weeks but for the subjects who remained in the study for eight weeks there was no significant difference. This null result begs further study of the long-term effects of muscle stimulation given the beneficial results obtained with short-term stimulation and in reports involving individuals with other etiologies (Chen et al. 2005; Ozer et al. 2006).

The other aspect of these studies worth noting is the variability in outcome measures. Within these papers there were measures that were clinical, neurophysiological, biomechanical, and subject self-report in nature. Researchers have noted that spasticity is a multi-faceted construct with individual components of spasticity weakly related to each other suggesting that while different tools may measure unique aspects of spasticity the overall construct is best measured with an appropriate battery of tests (Priebe et al. 1996).

Conclusions

There is level 1b evidence (from oneRCT; Sivaramakrishnan et al., 2018) that a single session of electrical stimulation with FES or TENS exerts similar anti-spasticity effects, suggesting both TENS and FES may be used as therapeutic adjuncts.

There is level 1b evidence (from oneRCT; Gomez-Soriano et al., 2018) that TENS and vibration therapy may reduce plantar flexion spasticity through inhibition of the plantar tibialis anterior cutaneous reflex, rather than the soleus H reflex.

There is level 2 evidence (from two prospective controlled trials and one pre-post study; Van der Salm et al. 2006; Seih et al. 1994; Robinson et al. 1988a) that a single treatment of surface muscle stimulation reduces local muscle spasticity with agonist stimulation more effective than stimulation to the antagonist.

There is conflicting evidence for how long the effects of a single treatment of electrical stimulation on muscle spasticity persist, although they appear to be relatively short lasting (i.e., ≤ 6 hours).

There is level 4 evidence (from one pre-post study; Robinson et al. 1988b) that a long-term program of muscle stimulation does not reduce muscle spasticity and may even increase local muscle spasticity.

There is conflicting level 4 evidence (from two pre-post studies; Cart et al. 2013; Tancredo et al. 2013) that use of neuromuscular electrical stimulation decreases spasticity.

Key Points

Electrical stimulation applied to individual muscles may produce a short-term decrease in spasticity; however, there is also some concern that long-term use of electrical stimulation may increase spasticity.

3.4 Interventions Based on Various Forms of Afferent Stimulation

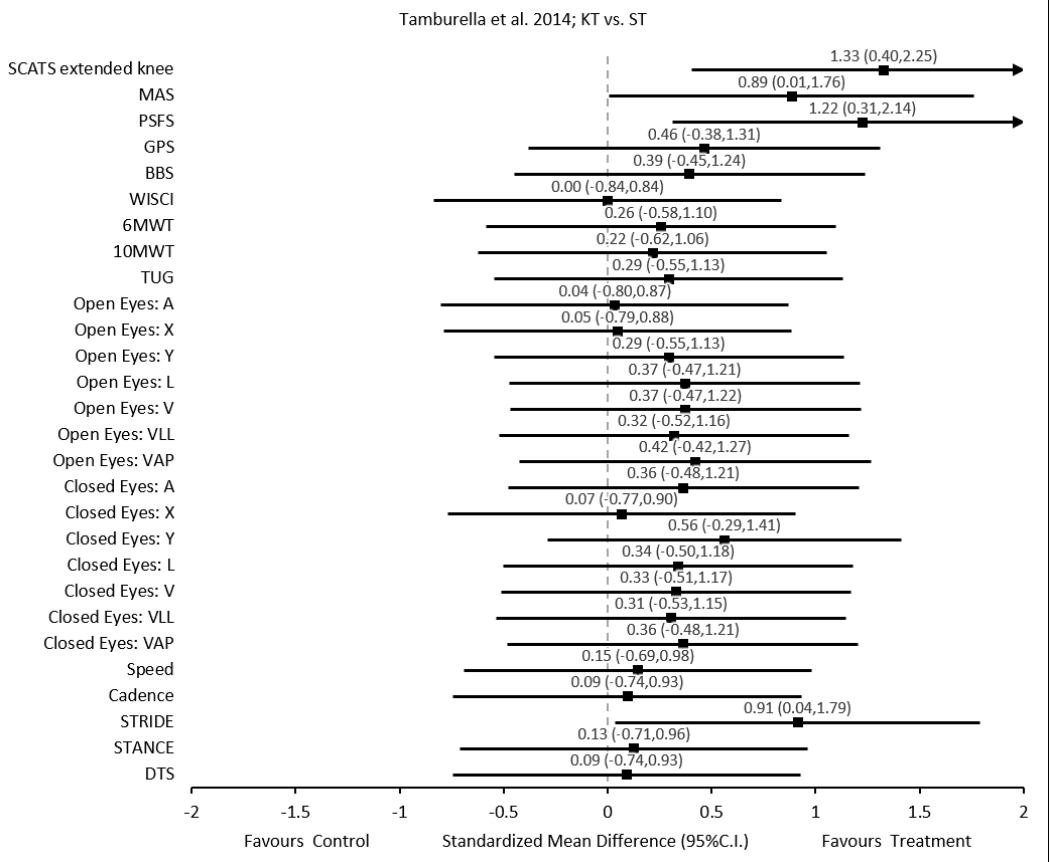
There are a variety of approaches that have been investigated which employ afferent (i.e., sensory) stimulation for the reduction of spasticity in people with SCI. As noted previously, electrical stimulation, TENS, is one of the preferred methods for providing afferent stimulation. This technique differs from the approaches noted in the previous sections that involve stimulation to the motor system, whether via muscles or motor nerves. TENS may involve the stimulation of large, low threshold afferent nerves (Goulet et al. 1996) or dermatomal stimulation which is directed towards cutaneous skin receptors supplying the skin in the dermatome of the muscle of interest (Bajd et al. 1985; van der Salm et al. 2006). These methods are aimed at altering motor-neuron excitability through sensory reflex arcs, thereby reducing spasticity. An alternate approach employing electrical stimulation involves rectal probe stimulation, developed originally to enable ejaculation in males and heretofore a technique employed only within fertility clinics (Halstead & Seager 1991).

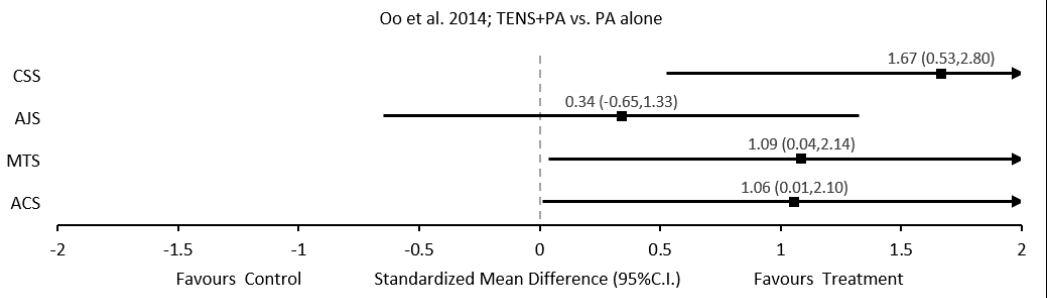
In addition, a variety of methods of mechanical or thermal stimuli to various afferent systems have also been studied. These include therapeutic massage over the spastic muscle (Goldberg et al. 1994), penile vibration (Laessoe et al. 2004; Alaca et al. 2005), the application of cold (i.e., cryotherapy) to reduce local muscle spasticity (Price et al. 1993), also irradiation of the skin overlying sensory nerves with a helium-neon laser purported to induce photochemical reactions which may trigger neural activity (Walker 1985). It should be noted that the article examining cryotherapy (i.e., Price et al. 1993) did not meet the review criteria of having 50% of subjects with SCI. The article was included in the review as individual results were presented for all subjects with SCI (N=7), enabling independent discernment of the effects on SCI (thereby meeting review criteria for studies having SCI N≥3).

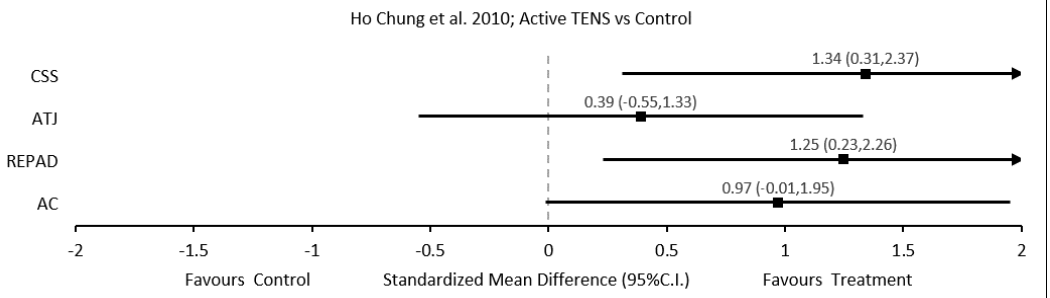
Table 4. Studies of Various Forms of Afferent Stimulation for Reducing Spasticity

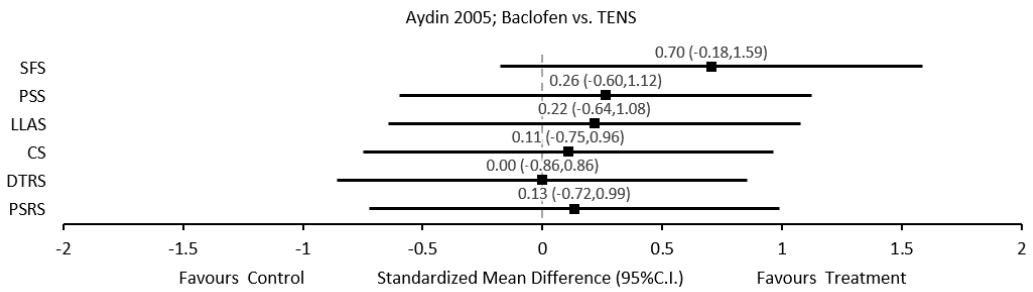
Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Taping		
Tamburella et al. 2014 Italy RCT Crossover PEDro=7 N=11	**Population:** Mean age: 52.0 yr; Gender: males=6, females=5; Injury etiology: traumatic=4, non-traumatic=7; Level of injury: cervical=5, thoracic=6; Level of severity: AIS D=11. **Intervention:** Individuals were randomly allocated to receive either KinesioTape (KT) or conventional silk tape (ST) for 48 hr. After a 7 days washout period, the individuals were crossed over and received	1. Patients who received KT demonstrated significant improvements from baseline to post- intervention in active ROM, passive ROM, extended knee SCATS, MAS, PSFS, BBS and 6MWT (all $p<0.001$), flexed knee SCATS ($p<0.005$), and GPS ($p<0.05$) compared to the ST condition. No significant differences were reported on the WISCI, 10MWT and TUG.

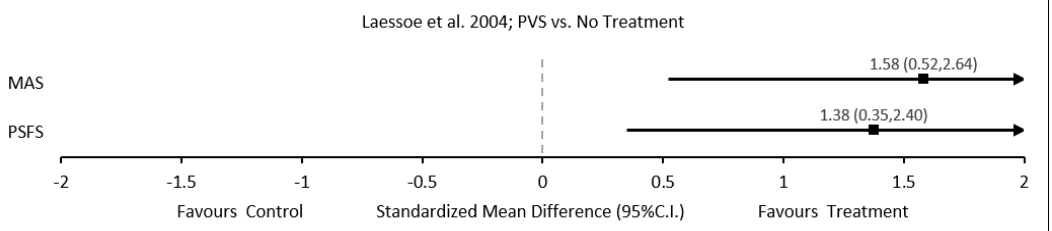
Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	another 48 hr of intervention. Tape was applied to the soleus and gastrocnemius muscles with the knee extended and ankle at 90° passive dorsiflexion. Assessments were conducted at baseline and at post- intervention. **Outcome Measures:** Modified Ashworth Scale (MAS), Penn modified Spasm Frequency Scale (PSFS), Spinal Cord Assessment Tool for Spastic Reflexes subscale for clonus assessment (SCATS), Global Pain Scale (GPS), Berg Balance Scale (BBS), Walking Index for Spinal Cord Injury (WISCI), 10-meter Walk Test (10WT), 6-minute Walking Test (6MWT), Timed Up and Go test (TUG), Range of motion (ROM), Centre of pressure (COP) parameters, Kinematic gait parameters.	2. COP parameters revealed significant improvements for the KT condition in regard to path length, mean duration and anteroposterior velocity with eyes open (all $p<0.05$) and path length, mean duration, laterolateral velocity and anteroposterior velocity with eyes closed (all $p<0.05$) from baseline to post-intervention compared to the ST condition. 3. Patients who received KT also reported significant improvements in all kinematic gait parameters compared to the ST condition including stride length, stance phase (both $p<0.001$), speed, cadence and double-time support phase (all $p<0.05$) from baseline to post- intervention.
	Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- and post-intervention data.	

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		
TENS		
Oo, 2014 Myanmar RCT PEDro=9 N=16	**Population:** *TENS group (n=8)*: Mean age: 33.4 yr; Gender: males=8, females=0; Level of injury: AIS A=3, AIS B=3, AIS C=1, AIS D=1; Mean time since injury: 3.3 mo. *Control group (n=8)*: Mean age: 40.5 yr; Gender: males=7, females=1; Level of injury: AIS A=3, AIS B=2, AIS C=1, AIS D=2; Mean time since injury: 3.1 mo. **Intervetion:** Study the immediate and short-term efficacy of adding transcutaneous electrical nerve stimulation (TENS) to standardized physical therapy on subacute spasticity. **Outcome Measures**: Composite spasticity score (sub-scores: ankle	1. After first session: statistical significance for reduction in clinical spasticity for TENS group (mean difference=1.75; 99%CI, 0.47-3.03; p=0.002) but not significant in control group (mean difference=0.63; 99%CI, -0.51-1.76; p=0.095). 2. After first session: significant between group difference in composite spasticity score (mean difference 1.63; 99% CI, 0.14-3.11; p=0.006). 3. After first session: within-group and between-group differences in sub-scores revealed no significant improvement.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	jerk, muscle tone, ankle clonus scores), Serial evaluations.	4. After final session: significant improvement for composite spasticity score in TENS group (2.75; 99% CI, 1.31-4.19; p<0.001) but not significant in control group (1.13; 99% CI, -0.55-2.80; p=0.051). 5. After final session: significant between group difference in composite spasticity score (2.13; 99% CI, 0.59-3.66; p=0.001). 6. After final session: sub-score analysis showed significant decreases for muscle tone score in TENS group (1.75; 99% CI, 0.16-3.34; p=0.006) and ankle clonus score (0.75; 99% CI, 0.18-1.32; p=0.003), no sub-scores in control group significantly reduced. 7. After final session: between-group differences, muscle tone score significant after 15 TENS sessions (1.50; 99% CI, 0.15-2.85; p=0.005).
	Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- and post-intervention data. 	
Chung & Cheng 2010 Hong Kong RCT PEDro=10 N=18	**Population:** Age range: 24-82 yr; Injury etiology: traumatic, non-traumatic SCI; Level of injury: C3-T12; Level of severity: AIS A-D; Time since injury range: 4-364 wk. **Intervention:** 60 min of active TENS (0.25 ms, 100 Hz, 15 mA) or 60 min of placebo non-electrically stimulated TENS over the common peroneal nerve.	1. Significant reductions were shown in the CSS by 29.5% (p=0.017), resistance to full-range passive ankle dorsiflexion by 31.0% (p=0.024) and ankle clonus by 29.6% (p=0.023) in the intervention group; these reductions were not observed in the placebo group. 2. Between-group differences on both CSS and resistance to full-range passive ankle dorsiflexion

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Outcome Measures: Composite Spasticity Score (CSS), Achilles tendon jerks.	were significant (p=0.027 and p=0.024, respectively).
	Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- and post-intervention data. 	
Aydin et al. 2005 Turkey RCT PEDro=6 N=41	**Population:** *SCI (n=21):* Injury etiology: trauma; Level of severity: complete, incomplete; Chronicity: chronic. *Health controls (n=20).* **Intervention**: Either oral baclofen (titrated up to 80 mg/day) for 8 wk or TENS for 15 min/day for 15 days. **Outcome Measures:** SFS, Painful Spasm Scale (PSS), Ashworth Scale (AS), Various clinical (clonus, deep tendon reflexes, Response to plantar stimulation) or electrophysiologic measures (H-reflex latency and amplitude, H/M ratio) of spasticity as well as measures of function (FIM and FDS. Measures were taken pre-and post-first intervention (15min after) and 15 min and 24 hr after the last TENS session.	1. For both intervention groups a significant improvement was noted immediately post intervention in the lower limb AS (p<0.011 baclofen group and p=0.020 TENS group), SFS (p<0.014 for both groups), deep tendon reflex score (p=0.025 for both groups) as well as in measures of disability (FIM-baclofen group p=0.005, TENS group p=0.003; FDS--baclofen group p=0.004, TENS group p=0.003. 2. In comparison with baseline, TENS showed a trend for a reduced AS immediately after the first intervention (p=0.059), a significant reduction immediately after the last intervention (p=0.006) and a significant but lesser reduction 24 hr after the last intervention (p=0.020). Similar findings were obtained for Deep Tendon Reflex scores. Plantar Stimulus Response scores were only significantly reduced immediately following the last intervention session (p=0.034) whereas clonus scores were only significantly reduced immediately

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		following the first intervention (p=0.046). 3. There was a significant reduction in H-reflex maximal amplitude (p=0.032) 24 hr after the final session. This reduction was even more apparent when tested only 15 min after the last intervention (p=0.026). There were only small (statistically non-significant) changes in other electrophysiologic variables with either baclofen or TENS.
	Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- and post-intervention data. 	
Goulet et al. 1996 Canada Pre-Post N=14	**Population:** Age range: 21-54 yr; Gender: males=13, females=1; Level of injury: C4-T12; Level of severity: AIS: A-D; Time since injury range: 2-194 mo. **Intervention**: TENS stimulation (i.e., low threshold afferent nerve stimulation) over the common peroneal nerve for 30 min. **Outcome Measures:** Modified Ashworth Scale (MAS), Clonus score, Achilles tendon reflex score (ATR), H-reflex amplitude, and H-reflex/M response ratio collected just prior to and after TENS. H-reflex and M responses were also collected during TENS.	1. Significant decreases were seen in clinical measures of spasticity as seen by reductions in MAS (p=0.04), ATR (p=0.01), and global spasticity scores (p=0.01). A trend was seen with reduced clonus scores (p=0.11). 2. No significant effects of TENS were seen with electrophysiological measures of spasticity as indicated by H-reflex amplitudes (p=0.89) and H/M ratio (p=0.50).
Bajd et al. 1985 Yugoslavia Pre-Post	**Population:** Age range: 11-52 yr; Level of injury: C5-T9; Level of severity: complete=4,	1. Group statistical analysis was not conducted. 2. In 3 individuals, spasticity decreased markedly as indicated

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
N=6	incomplete=2; Time since injury range: 5-48 mo. **Intervention:** TENS stimulation over L3, 4 dermatomes. Stimulation amplitude of up to 50 mA was used and applied continuously for 20 min. **Outcome Measures:** Pendulum test (relaxation index) performed just prior to and just after stimulation as well as 2 hr post-stimulation.	by increased relaxation index values immediately after the stimulation and returned to pre-stimulation values at 2 hr. The remaining 3 individuals showed no change.
Penile Vibratory Stimulation		
Laessoe et al. 2004 Denmark RCT PEDro=6 N=9	**Population:** Age range: 27-67 yr; Gender: males=9, females=0; Level of injury: C2-T8; Level of severity: AIS: A–D; Time since injury range: 4 mo-50 yr. **Intervention:** Penile Vibratory stimulation for 5 min or to ejaculation. **Outcome Measures:** Modified Ashworth Scale (MAS), Penn Spasm Frequency Scale (PSFS), 24 hr EMG recordings of quadriceps and tibialis anterior activity. All collected pre-stimulation and 24 hr post-stimulation. MAS was also collected immediately after stimulation.	1. There was a significant decrease in spasticity after penile stimulation as indicated by decreases MAS ($p<0.01$). This was not sustained at 24 hr. 2. There was a slight reduction in the PSFS 24 hr after penile stimulation but this was not significant. 3. There was a significant reduction in EMG activity in the initial 3 hr after vibration, as compared to before vibration ($p<0.05$). This was not seen in the no-vibration condition. 4. The largest reduction in EMG activity occurred in the 1st hr after vibration, after which the events gradually decreased until no significant effect was observed following the 3 hr after vibration.
	Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- and post-intervention data. 	
Alaca et al. 2005 Turkey Pre-Post	**Population:** Age range: 22-35 yr; Gender: males=10, females=0; Level	1. There was a significant decrease in spasticity after penile stimulation as indicated by decreases in the

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
N=10	of injury: C8-L1; Level of severity: AIS A; Time since injury range: 1.1-9 yr. **Intervention:** Penile Vibratory stimulation for 6, 3 min periods (separated by 1 min) or to ejaculation. **Outcome Measures:** Ashworth Scale (AS), Spasm Frequency Scale (SFS) and nominal scales of painful spasms, plantar stimulation response, deep tendon reflexes, clonus and effect on function. All collected pre-stimulation and 3, 6, 24 hr and 48 hr post-stimulation.	AS ($p<0.001$). This was significantly lower than baseline at hr 3 ($p=0.001$) and 6 ($p=0.03$) with a trend lower at 24 hr ($p=0.08$). 2. There were slight (non-significant) reductions in the SFS and clonus scores at hr 3. 3. There were no changes in painful spasms, plantar stimulation responses, deep tendon reflexes and effect on function scale scores with penile vibration.
Helium-Neon Laser Irradiation		
Walker 1985 USA RCT PEDro=4 N=41	**Population:** Level of injury: T12-L2; Time since injury: >2 yr. **Intervention:** Helium-neon laser irradiation to peripheral nerve sites (radial, median, saphenous nerves) for 20 or 40 sec to each site versus a variety of control conditions including sham irradiation (same probe but not emitting laser), irradiation to skin not innervated by peripheral nerves and electrical stimulation for 45 min or 1 hr over innervated and non-innervated areas. (n=5-7 in various experimental groups). **Outcome Measures:** Clonus count after brisk dorsiflexion of the foot by a blinded registered PT before intervention and at 30 min intervals up to 2 hr after irradiation.	1. No statistical comparisons reported. 2. 40 sec of laser irradiation and 1 hr of electrical stimulation similarly produce complete suppression of clonus lasting 30 and 60 min after cessation of stimulation. 3. 20 sec of laser irradiation and 45 min of electrical stimulation similarly only produce partial suppression of clonus. 4. Distal nerve irradiation or electrical stimulation still produced clonus suppression but not when stimulation was applied to skin not overlying a peripheral nerve.
Electrical Nerve Stimulation		
Possover et al. 2010 Switzerland Case Reports N=3	**Population:** Gender: males=2, females=1; Level of injury: T5=1, T7/8=1, T10=1. **Intervention:** Continuous 20 Hz electrical stimulation to the sciatic, pudendal nerves and to the sacral nerve roots S3 and S4.	1. A frequency of 20 Hz permitted complete control of the spasticity of the lower extremities and of reflex incontinence. 2. Electrical stimulation of the femoral nerves enabled the T5 paraplegic lower-limb cycling and the two other individuals standing and alternative locomotion.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Outcome Measures: Spasticity of lower extremities, motion of the legs.	
van der Salm et al. 2006 Netherlands Pre-Post N=10	**Population:** Age range: 21-42 yr; Gender: males=8, females=2; Level of injury: C3-T11; Level of severity: AIS A=9, AIS C=1; Time since injury range: 28-275 mo. **Intervention:** Electrical motor (agonist or antagonist) or afferent (S1 dermatomal) stimulation of the triceps surae or a placebo (application of electrodes but no current). 1–45 min session of each type of stimulation. Intensity at 3x motor threshold for motor stimulation and 80% of motor threshold for afferent stimulation. **Outcome Measures:** Modified Ashworth Scale (MAS), clonus score, H reflex, and H/M ratios. Measurements were conducted just prior to, immediately after, 1 hr after and 2 hr after the intervention for each of the 4 conditions.	1. No significant difference was seen with S1 dermatomal stimulation. Only the agonist muscle stimulation differed significantly (46% reduction) from the placebo as indicated by reduced MAS ($p<0.001$) 2. No significant carry-over effect (over 2hr) although there was a trend of continued reductions for the MAS ($p=0.113$). 3. No significant intervention effect was shown for the clonus score or the H/M ratio. 4. The reflex-initiating angle showed a significant change for antagonist stimulation (n=8, $p=0.015$) but the carryover effect was not significant.
Halstead et al. 1993 USA Pre-Post N=9	**Population:** Age range: 21-41 yr; Gender: males=6, females=3; Level of injury: paraplegia=3, tetraplegia=6; Level of severity: Frankel grade: A=4, B=5; Time since injury range: 0.5-15 yr. **Intervention:** At least 6 sessions of Rectal Probe Electrical Stimulation (RPES) 6 times spaced 1-4 wk apart. Each session consisted of 7 or 15 stimulations of ~1 sec duration and lasted 5-10 min. Three subjects underwent a placebo with probe insertion but no stimulation. **Outcome Measures:** Ashworth scale (AS), Spasm Frequency Scale (SFS), Deep Tendon Reflexes, Ankle Clonus, Subject self-report (5-point scale) on interference of spasticity on selected self-care activities. All were collected just prior to	1. Spasticity was reduced as indicated by reduced AS assessed within 1hr post-stimulation ($p<0.01$). 2. Spasticity relief as indicated by self-report was for 7.8/9.5 hr (quad/para mean values). 3. No significant correlation of RPES effect on spasticity was seen with age, duration of injury, level of injury or completeness. 4. In general, spasticity was reduced as indicated by the pendulum test in the 4 subjects assessed. 5. SSEPs were abolished in the 2 subjects tested following stimulation. 6. Probe size, number of stimuli, voltage and current did not reveal

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	stimulation, within 1 hr after and 2-4 hr after. Subject self-reports were collected every 2 hr up to 24 hr after stimulation. Pendulum tests were collected on 4 subjects and somatosensory evoked potentials (SSEPs) on 2 subjects' pre-and post.	any significant correlation with the amount of relief provided.
Vibration		
Estes et al. 2018 USA RCT Crossover PEDro=4 $N_{Initial}$=35 N_{Final}=29	**Population**: SCI (n=34): Mean age=46.29±12.48yr; Gender: males=28, females=6; Level of injury: C=29, T=5, C=9, D=25; Mean time since injury=6.80±7.87yr; AIS scale: C=9, D=25. **Intervention:** This RCT crossover study consisted of four whole-body vibration (WBV) intervention sessions at varying frequencies and durations and a sham control session. All sessions were separated by a minimum of 1 wk. WBV consisted of participants standing on a vibrational platform with knees flexed approximately 30 degrees from full extension for 45-second bouts. Participants had 1-minute seated rest in-between bouts. Sessions consisted of one of the following; high frequency (50 Hz vibration) with short duration (four 45-second bouts) (HFSD), low frequency (30 Hz vibration) with short duration(LFSD), high frequency with long duration (eight 45-second bouts) (HFLD), low frequency with long duration (LFLD), or sham (electrical stimulation while standing with eight 45-second bouts). Spasticity was assessed using the outcome listed below. The outcome measure was assessed at baseline, immediately after the intervention, and 15 min and 45 min post-intervention.	1. There were no significant between-group differences in baseline FSE (p>0.05). 2. There were no significant between-group differences when comparing the four WBV groups to the sham at all time points (p>0.05). 3. There was a significant within-group increase in FSE for the sham group when comparing baseline to the immediate post-intervention follow-up (p=0.023). However, none of the WBV groups showed a significant within-group change at any of the follow-up time points (p>0.05). 4. Participants were also stratified into low and high spasticity. There were no significant between-group differences when comparing the four WBV groups to the sham group at all time points (p>0.05). 5. For the high spasticity group, there were significant within-group increases in FSE for the sham and HFSD groups immediately after the intervention (p=0.013; p=0.048, respectively). Moreover, there were significant within-group increases in HFSD and HFLD at 15 min post-intervention (p=0.027; p=0.014). There were no significant within-group differences at the 45 min assessment (p>0.05).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Outcome Measures: First swing excursion (FSE) angle from the pendulum test.	6. For the low spasticity group, there were no significant within-group changes immediately post-intervention ($p>0.05$). in contrast, there was a significant within-group increase in FSE for HFSD and HFLD at the 15-min and 45-min assessments ($p<0.05$ for all).
In et al. 2018 Korea RCT PEDro=7 $N_{Initial}$=32 N_{Final}=28	**Population**: Whole-body vibration (WBV, n=14): Mean age=46.1±9.8yr; Gender: males=9, females=5; Level of injury: C=14; Mean time since injury=13.7±3.2mo; AIS scale: NR. Control (CG, n=14): Mean age=49.9±9.3yr; Gender: males=10, females=4; Level of injury: C=14; Mean time since injury=14.3±4.9mo; AIS scale: NR. **Intervention:** Participants were randomly assigned to either whole-body vibration (WBV) or a control group. The WBV training consisted of participants holding a semi-squat position while standing on a moveable platform that oscillated with a frequency of 30 Hz and a vertical displacement of 2-4 mm. WBV training sessions lasted 16 min/session, 2x/d, 5x/wk for 8 wk. The control group followed the same protocol, however, this group only received ultra-low frequency vibration. Both groups also received conventional physical therapy consisting of range of motion exercises, mat exercises, and gait training 30 min/d during the same period of the respective intervention. Outcome measures were assessed at baseline and post intervention. **Outcome Measures:** ankle plantar-flexor spasticity assessed using manual muscle tester (MMT).	1. There was a significant time X group interaction for both right and left ankles ($p<0.001$ for both). 2. WBV was more effective at reducing spasticity in both ankles compared to the control group ($p<0.001$). 3. Both groups showed significant within-group decreases in spasticity in both ankles ($p<0.05$).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Murillo et al. 2011 Spain Pre-Post N=28	**Population:** *Intervention group (n=19)*: Mean age: 36.0 yr; Gender: males=16, females=3; Injury etiology: trauma=1, myelitis=2; Level of injury: cervical=1, thoracic=6; Level of severity: AIS A=9, AIS C=9, AIS D=1; Mean time since injury: 5.6 mo. *Healthy Controls (n=9):* Mean age: 33.8 yr. **Intervention:** Vibration at a frequency of 50 Hz during 10 min over the rectus femoris (RF) muscle was delivered in all participants. **Outcome Measures:** Modified Ashworth Scale (MAS), Range of Motion (ROM), Frequency of clonus, Duration of clonus, Soleus T wave amplitude, Hmax/Mmax ratio. Assessments were conducted at baseline and during vibration.	1. Significant intervention improvements in individuals with SCI: • Decrease in MAS at knee joint ($p<0.001$) • Increase in ROM for knee extension ($p=0.001$) • Reduction in duration and frequency of clonus (both $p\leq0.006$). 2. Vibration induced a significant reduction in Hmax/Mmax ratio in the control group ($p=0.005$) and in the individuals with SCI ($p=0.001$). The change was not significantly different between the two groups. 3. Vibration induced a significant inhibition of Twave amplitude in both individuals with SCI ($p=0.002$), and control subjects ($p=0.007$). 4. The Hmax and the Mmax were significantly smaller in the complete SCI than in the incomplete SCI ($p=0.03$, $p=0.04$). 5. The Hmax/Mmax ratio was significantly greater in the individuals with complete SCI than in the individuals with incomplete SCI ($p=0.02$).
Ness & Field-Fote 2009 USA Observational N=16	**Population:** Mean age: 46.9 yr; Gender: males=14, females=2; Injury etiology: SCI=14; Level of injury: C3-C6=10, T4-T8=6; Time since injury: >1yr. **Intervention:** Whole-body vibration (4, 45 sec bouts of 50 Hz stimulation) 3 days/wk for 4 wk. **Outcome Measures:** Gravity-provoked stretch (swing excursion).	1. Whole body vibration was associated with significant increase in first swing excursion (reduction in quadriceps spasticity) from the initial to final session ($p=0.005$) and persisted for at least 8 days. 2. There was no significant difference between the initial first swing excursion values of subjects who did and those who did not use antispastic agents ($p=0.198$).
Massage		
Goldberg et al. 1994 Canada	**Population:** *Study 2 (n=10):* Age range: 21-33 yr; Gender: males=9, females=1; Level of injury: C4-T10;	1. Significant decrease in H-reflex amplitude during massage as compared to before and after

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Pre-Post N=17	Severity of injury: complete, incomplete; Time since injury range: 3-11 mo. *Study 1 (n=7):* Healthy controls. **Intervention:** One-handed petrissage (massage) applied to the belly of the triceps surae muscle group for 3 min. **Outcome Measures:** H-reflex peak amplitude, H-reflex latency (Study 2, SCI only), M-responses collected during massage plus 3 and 6 min prior and 3 and 6 min after massage (10 responses of each averaged).	(p=0.008). The response 3min after massage is somewhat reduced but not to the same extent as during the massage. 2. No difference between M-response amplitudes (p=0.13) or H-Reflex latencies (p=0.22) before, during or after massage. 3. Study 1: Verified that H-reflex amplitude decre ases seen in controls in supine position were also able to be obtained in prone position which was preferred position for SCI subjects.
Cryotherapy		
Price et al. 1993 USA Pre-Post N=25	**Population:** Injury etiology: stroke=9, head injury=9, SCI=7. **Intervention:** Cryotherapy (water and ice placed on calf for 20 min). **Outcome Measures:** Elastic and viscous components of ankle stiffness represented by mathematical modelling of torque versus position in response to 5° sinusoidal ankle displacements at frequencies from 3 to 12 Hz. This resulted in measures of total path length associated mainly with passive spasticity of the ankle and elastic path length associated with viscous stiffness. Data was collected prior to, during and 1hr after cryotherapy.	1. Clinically significant reductions in spasticity as indicated by a reduction in total path length of 11 Nm/rad or greater were seen in 5 of 7 subjects with SCI during cryotherapy and 5 of 7 one hr after. 2. Reduction in spasticity as indicated by total (p=0.009) and elastic (p=0.006) path length resulted from cryotherapy compared to the baseline measures. 3. Significant differences between the baseline measure and 1hr after intervention were noted in spasticity as indicated by elastic path length (p=0.0198) but only a trend was noted for total path length (p=0.058).
Extracorporal Shock Wave Therapy		
Altindag & Gursoy 2014 Turkey Pre-Post N=9	**Population:** Mean age: 25.6 yr; Gender: males=5, females=4; Injury etiology: hemiplegia =3, cerebral palsy=2, SCI=4. **Intervention:** Individuals received physiotherapy and extracorporeal shock wave therapy (ESWT; sound waves). ESWT was applied every	1. There was a significant decrease in muscle tone 2 wk after ESWT intervention compared with the baseline measurement (p=0.001).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	other day during the 1st wk of physio (3 total). Outcomes were measured 2 wk after ESWT **Outcome Measures:** Modified Ashworth Scale (MAS).	
Galvanic Vestibular Simulation		
Cobeljic et al. 2018 Denmark Pre-Post N=7	**Population**: SCI (n=7): Mean age=NR; Gender: males=NR, females=NR; Level of injury: Mean time since injury=NR; AIS scale: A=7. **Intervention:** Participants underwent Galvanic vestibular stimulation (GVS) was administered by placing an anode and cathode over the right and left mastoid process, respectively. Participants received 10 monophasic pulses ranging from 1 to 10 mA over 15 seconds. A sham stimulation was administered after the initial GVS. Outcome measures were assessed prior to stimulation, immediately after, and 5min and 30 min after stimulation. Spasticity was assessed with the outcome measures listed below. **Outcome Measures:** Spasticity: Modified Ashworth Scale (MAS); Pendulum test (PT).	1. mAS and PT were reduced in 2 out of 7 participants, however there were no statistically significant changes overall in both MAS and PT ($p>0.05$).

Table 5. Systematic Review of Various Forms of Afferent Stimulation for Reducing Spasticity

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Sadeghi & Sawatzky 2014 Canada Review of published articles between 1887-2013 AMSTAR=8 N=10	**Method:** Comprehensive literature search of articles on the application of either whole-body vibration (WBV) or focal vibration (FV). Articles were restricted to three or more participants >17 yr of age, with chronic SCI, and who had spasticity for >4 mo after their injury. **Databases:** MEDLINE, EMBASE, CINAHL, PsycINFO. **Level of evidence:** Evidence was categorized according to the Centre for Evidence Based Medicine levels of evidence. *Level 2B*: 1 paper, *Level 2C*: 1 paper, *Level 3B*: 6 papers, *Level 4:* 2 papers. **Questions/measures/hypothesis:** 1. Examine the effectiveness of WBV and FV on managing spasticity in individuals with SCI.	1. There is limited support for using WBV and FV to manage spasticity with SCI. 2. A short-term reduction in spasticity is seen after FV within 50-100 Hz and 2.5-3 mm amplitude. 3. A 6 to 8 day decrease in spasticity was observed after 1 mo of WBV at 50 Hz and 2-4 mm amplitude.

Discussion

It should be noted that several of the modalities described in this section have not been employed in regular clinical practice and may be deemed as more investigational in nature. For example, helium-neon laser irradiation has only been employed in one investigation and has not been considered as a viable therapeutic approach. Similarly, penile and rectal stimulation, first noted as delivering potential side benefits within fertility clinic investigations, may not be acceptable forms of therapy to individuals from either a safety or a psychological perspective. Other therapies might simply be impractical to implement. For example, hippotherapy requires access to a suitable equine facility with appropriately trained individuals.

Taping

Tamburella et al. (2014) completed a crossover RCT (n=11) to study the effects of Kinesio Tape versus silk tape on spasticity. Study subjects were randomly allocated to receive either Kinesio Tape or conventional silk tape (ST) for 48 hours. After a 7-day washout period, the study subjects were crossed over and received 48 hours of the alternate treatment. Tape was applied to the soleus and gastrocnemius muscles with the knee extended and ankle at 90^{o} passive dorsiflexion. Baseline and post-treatment spasticity assessments included MAS, PSFS, Spinal Cord Assessment Tool for Spastic Reflexes and the subscale for clonus assessment (SCATS). Study subjects who received Kinesio Tape demonstrated significant improvements from baseline

to post-treatment in active and passive ROM, extended knee SCATS, MAS, PSFS (all $p<0.001$) and flexed knee SCATS ($p<0.005$), compared to the ST condition.

Transcutaneous Electrical Nerve Stimulation (TENS)

Oo et al. (2014) completed a prospective randomized controlled single-blinded clinical trial (n=16) of active 3-week course (five sessions/week) of TENS and standard physical therapy (n=8) vs standard therapy alone (n=8) to study the immediate and short-term efficacy of TENS in subacute spinal spasticity. Composite spasticity scores of ankle jerk, muscle tone, and ankle clonus scores were completed at baseline and immediately after the first and last interventions for both groups by a physiatrist familiar with the testing procedures. After the first session, statistical significance for reduction in the composite spasticity score was seen in the TENS group only (mean difference=1.75; 99%CI, 0.47-3.03; p=0.002) which was also apparent in a significant between group difference (mean difference 1.63; 99% CI, 0.14-3.11; p=0.006). After the final session, a significant improvement for the composite spasticity score was seen in the TENS group only (2.75; 99% CI, 1.31-4.19; $p<0.001$) along with a related significant between-group difference in the composite spasticity score (2.13; 99% CI, 0.59-3.66; p=0.001). The study demonstrated that the combination of TENS with standard physical therapy was beneficial in the synergistic reduction of clinical spasticity in both the immediate and short-term basis in the subacute phase of SCI rehabilitation.

Aydin et al. (2005) employed an RCT design to compare oral baclofen (N=10) to TENS (N=11) to the bilateral tibial nerves (i.e., innervating gastrocnemius muscle) in reducing lower limb spasticity. 15-minute sessions of TENS were applied to the tibial nerve over 15 days demonstrating significantly reduced spasticity as indicated by reductions in the following measures assessed immediately after the last treatment session: AS, PSFS, deep tendon reflex score, FIM and Functional Disability Scores and H-reflex amplitude. In addition, there were also some lasting effects over the next 24 hours as repeat testing the next day indicated continued spasticity reductions although to a lesser degree. It should also be noted that significant reductions were obtained on some measures (but not all) following a single session. However, the long-term effects were more profound after the 15 sessions than those obtained following a single session.

Other researchers have examined the effects of TENS following a single session (Bajd et al. 1985; Goulet et al. 1996; Chung & Cheng 2010; van der Salm et al. 2006). Goulet et al. (1996) employed a single 30-minute bout of TENS over the common peroneal nerve in an attempt to reduce plantar flexor spasticity in 14 individuals with SCI. This study showed significant decreases in scores for the MAS and the Achilles tendon reflex but no significant changes were seen for H-reflex amplitude. A trend for decreased clonus scores was observed but this was not statistically significant. Chung and Cheng (2010) also examined the effect of 60-minute TENS sessions over the common peroneal nerve. The authors reported a significant reduction on the Composite Spasticity score (p=0.017), and a reduction in resistance to full range passive ankle dorsiflexion (p=0.024), and ankle clonus (p=0.023). In these two studies, TENS appears to be effective in reducing spinal spasticity following a single session.

In contrast, van der Salm et al. (2006) and Bajd et al. (1985) each examined dermatomal TENS as opposed to direct nerve stimulation with conflicting results. Bajd et al. (1985), in a small pre-

post trial (n=6) reported reduced spasticity in three subjects as indicated by increased relaxation indexes associated with the pendulum test. However, no mean data or group statistical analysis was provided. Van der Salm et al. (2006) conducted a more thorough analysis of the effect of a single 45-minute session of TENS to the L1 dermatome in 10 individuals with longstanding SCI (mostly AIS A) and obtained no short-term effects, although as noted in the previous section obtained benefits with motor stimulation. A critical element within these investigations of single-session effects is the precise time of assessment, relative to treatment, a detail not always precisely reported in the various studies, although van der Salm et al. (2006) assessed individuals as close as possible to treatment cessation.

Penile Vibratory Stimulation

Penile vibration has also been investigated as a method of providing sensory stimulation to reduce spasticity (Laessoe et al. 2004; Alaca et al. 2005). In particular, Laessoe et al. (2004) employed an unblinded, crossover RCT design (N=9) in which male participants either received penile vibration or no treatment followed by the opposite condition with a minimum washout period of 1 week. The MAS and PSFS were conducted in addition to an EMG assessment in which ongoing muscle activity was recorded over a 24-hour period. Penile vibration was shown to be effective in reducing spasticity as indicated by reductions in MAS scores ($p<0.01$) and a slight trend for reduced PSFS scores ($p=0.26$). These were not maintained over 24 hours. The EMG analysis showed that reduced muscle activity was most apparent in the first hour post-stimulation, and had returned to baseline by 3 hours suggesting the effect lasted no more than 3 hours. The authors attempted to include female subjects involving clitoral vibratory stimulation but were only able to recruit two subjects willing to submit to the procedure. Both women reported similar reductions in spasticity although evaluation of the effectiveness of the stimulation was more difficult (i.e., no confirmatory ejaculation). Results from Alaca et al. (2005) confirmed the overall study findings as penile vibratory stimulation in 10 males resulted in significant reductions in AS scores as assessed 3 hours after stimulation ($p=0.001$) and maintained at 6 hours ($p=0.03$) with a trend for reduced values still apparent at 24 hours ($p=0.08$). The longer carry over effect in this study may have been due to a prolonged stimulus period as Alaca et al. (2005) employed six, 3-minute periods of stimulation (separated by 1-minute) whereas Laessoe et al. (2004) used a single 5-minute period.

Helium-neon Laser Stimulation

Walker (1985) employed a helium-neon laser to irradiate the skin overlying sensory nerves and demonstrated a similar beneficial effect of suppressing clonus as seen with electrical stimulation of sensory nerves. This investigator employed an RCT design with a variety of small group control conditions (N=5 to N=7), but failed to report several important experimental details (i.e., method of concealment, method of analysis and statistical comparisons). This approach has not been investigated since this brief 1985 report.

Rectal Electrostimulation

Halstead et al. (1993) have evaluated another form of electrical stimulation, rectal electrostimulation, when they observed individuals undergoing this procedure, for the purpose of sperm retrieval, reporting improved spasticity. These investigators conducted a prospective

pre-post trial examining the effects of a minimum of six sessions of rectal probe electrostimulation on various clinical measures of spasticity including the AS, PSFS, deep tendon reflexes and ankle clonus. Although they achieved good to excellent effects in more than half of the individuals examined including significant reductions in the AS ($p<0.01$) and with the effects outlasting the intervention by a mean of 8.2 hours according to individual self-report further therapeutic development of this approach has not continued.

Vibration

Murillo et al. (2011) conducted a pre-post study (n=28) to determine if a decrease in muscle spasticity could be demonstrated with muscle vibration in study subjects with SCI. Muscle vibration at a frequency of 50 Hz during 10 minutes over the rectus femoris muscle was applied. The study showed significant treatment improvements in SCI study subjects with a decrease in MAS at the knee joint ($p<0.001$), an increase in ROM for knee extension ($p=0.001$) and a reduction in duration and frequency of clonus (both $p\leq0.006$). Muscle vibration induced a significant reduction in Hmax/Mmax ratio in the control group ($p=0.005$) and in the individuals with SCI ($p=0.001$). The change was not significantly different between the two groups. Muscle vibration also induced a significant inhibition of Twave amplitude in both individuals with SCI ($p=0.002$), and control subjects ($p=0.007$). The Hmax and the Mmax were significantly smaller in the complete SCI than in the incomplete SCI ($p=0.03$, $p=0.04$) populations, and the Hmax/Mmax ratio was significantly greater in the individuals with complete SCI than in the individuals with incomplete SCI ($p=0.02$). The study showed that prolonged vibration on proximal extremity muscles decreased limb spasticity in study subjects in both complete and incomplete SCI.

Ness and Field-Fote (2009) examined the effect of whole-body vibration at 50 Hz on individuals with SCI for 4 weeks. Sessions occurred three times per week with four bouts of vibration occurring each day for 45 seconds each. A significant reduction in quadriceps spasticity was reported, as determined by first swing excursion, and persisted for at least 8 days.

In a small group of individuals with chronic motor incomplete SCI (N=29; Estes et al. 2018, level 2 RCT), whole body vibration, across single sessions of 4 different frequency/duration parameters (with 1 week washout between sessions), did not result in quadriceps spasticity reduction as measured with the pendulum test (at baseline and immediately/15min/45min post-intevention) when compared to the sham-control group, but stretch reflex excitability was significantly dampened after high frequency/long duration whole body vibration in those participants with more severe spasticity. The whole-body vibration intervention consisted of 4 or 8, 45s bouts of 30 or 50 Hz vibration while sham-control treatment consisted of 8, 45s bouts of electrical stimulation. All bouts were interspersed with 1 minute of rest. Spasticity reduction was in part attributed to repeated sitting and standing across treatment bouts as some effect was also seen in sham- treated participants.

The effect of whole-body vibration training on ankle spasticity reduction did appear to be significant based on the work of In et al. (2018; N=28; level 1b evidence). This group of participants with incomplete cervical SCI were randomly assigned to whole body vibration or placebo training. Whole body vibration included 16 minutes of 30Hz vibration, twice daily for 5 days each week over 8 weeks. Placebo training followed the same parameters with ultra low frequency vibration. Spasticity (passive resistive force) of the ankle plantar-flexors was

measured with a hand-held dynamometer. The control group also showed a significant reduction in spasticity which was attributed to the standard physical therapy (range of motion, mat exercise and gait training). The added effect above this control effect was seen in the active intervention group and attributed to whole body vibration.

Therapeutic Massage

Afferent stimulation may also be produced via mechanical means. Goldberg et al. (1994) have employed therapeutic massage over the triceps surae muscle and assessed H-reflex amplitude to demonstrate that ∝-motor neuron excitability is reduced significantly during a short 3-minute period of massage and somewhat reduced 3 minutes after but not 6 minutes after. Reductions in ∝-motor neuron excitability are indicative of decreased spasticity.

Cryotherapy

The short-term effect of cryotherapy was investigated by Price et al. (1993) who used a biomechanical approach similar to that described earlier (i.e., Seib et al.1994) to monitor ankle viscoelastic stiffness through measurements of resistance torque to repetitive sinusoidal ankle movements. Although the majority of subjects were individuals with stroke or head injury, five of seven people with SCI showed a significant reduction in spasticity both immediately following cryotherapy and also at 1 hour after the cold stimulus was removed.

Sadeghi and Sawatzky (2014) completed a systematic review on the application of either whole body vibration or focal vibration for reducing spasticity. Articles were restricted to those published between 1987 and 2013 and having three or more participants >17 years of age, with chronic SCI, and who had spasticity for >4 months after their injury. Evidence was categorized according to the Centre for Evidence Based Medicine levels of evidence. *Level 2B*: one paper, *Level 2C*: one paper, *Level 3B*: six papers, *Level 4:* two papers (n=10). The authors found that there is limited support for using whole body vibration and focal vibration to manage spasticity secondary to SCI. A short-term reduction in spasticity is seen after focal vibration (frequency of 50-100Hz and amplitude of 2.5-3mm) and a 6 to 8 day decrease in spasticity was observed after 1 month of whole-body vibration at 50 Hz and 2-4 mm amplitude. Studies done by Murillo et al. (2011) and Ness and Field-Fote (2009) were also included in this literature review which did demonstrate a decrease in spasticity after use of vibration.

Galvanic Vestibular Stimulation

Galvanic vestibular stimulation involves painlessly and electrically activating the nerve in the ear that maintains balance. Galvanic vestibular stimulation applied to a small group of participants (N=7, Cobelijic et al. 2018, level 4 evidence) with complete SCI did not significantly reduce lower extremity spasticity as measured by the MAS and the pendulum test, when compared to participants given a sham galvanic vestibular stimulation. That 2 participants experienced some anti-spasticity effects suggests that galvanic vestibular stimulation may be able to influence residual vestibulospinal influences over spasticity but that a better clinical and neurophysiological understanding of responders vs nonresponders is needed to optimize galvanic vestibular stimulation stimulation parameters.

Conclusions

Taping

There is level 1b evidence (from one RCT; Tamburella et al. 2014) that kinesio tape has short-term effects of decreasing spasticity and improving balance and gait in individuals with chronic SCI.

TENS

There is level 1a evidence (from three RCTs; Oo 2014; Chung & Cheng 2010; Aydin et al. 2005) that an ongoing program of TENS acts to reduce spasticity as demonstrated by various clinical and electrophysiological measures.

There is level 1b evidence (from a single RCT; Aydin et al. 2005) that reductions in spasticity with ongoing programs of TENS may persist for up to 24 hours.

There is level 1a evidence (from two RCTs; Oo 2014; Aydin et al. 2005) that a single treatment of TENS acts to reduce spasticity but to a lesser degree than that seen with ongoing programs of TENS.

Penile Vibratory Stimulation

There is level 1b evidence (from one RCT and one pre-post study; Laessoe et al. 2004; Alace et al. 2005) a single RCT supported by a single pre-post study that a single bout of penile vibration acts to reduce spasticity lasting for at least 3 hours and possibly up to 6 hours.

Helium-Neon Irradiation

There is level 2 evidence (from one RCT; Walker 1985) that helium-neon irradiation of sensory nerves may suppress ankle clonus for up to 60 minutes following 40 seconds of stimulation.

Electrical Nerve Stimulation

There is level 4 evidence (from one pre-post study; Halstead et al. 1993) that several sessions of rectal probe stimulation reduces lower limb muscle spasticity for up to 8 hours.

There is level 4 evidence (from one pre-post study; Van der Salm et al. 2006) that electrical stimulation of the triceps surae does not significantly reduce spasticity.

Vibration

There is level 1b (In et al. 2018, N=28 RCT) evidence that reflects reduced plantar-flexor spasticity resulting after whole body vibration (16 minutes, twice daily, 5 times per week over 8 weeks).

There is level 2 (Estes et al. 2018, N-29 RCT) evidence supporting that single whole-body vibration sessions (4 or 8, 45 second bouts of 30 or 50Hz vibration) does not result in reduced quadriceps spasticity.

There is level 4 evidence (from one pre-post study; Murillo et al. 2011) that vibration over the rectus femoris muscle results in reduced knee spasticity and increased knee range of motion.

There is level 5 evidence (from one observational study; Ness & Field-Fote 2009) that (whole body vibration; 4, 45 second bouts of 50Hz vibration, 3 times per week over 4 weeks) results in reduced quadriceps spasticity over the short term.

Massage

There is level 4 evidence (from one pre-post study; Goldberg et al. 1994) that short periods of massage (e.g., 3 minutes) of the triceps surae results in reduced H-reflexes with the effect lasting no longer than a few minutes.

Cryotherapy

There is level 4 evidence (from one pre-post study; Price et al. 1993) that cryotherapy may reduce muscle spasticity for up to 1 hour after removal of the cold stimulus.

Extracorporal Shock Wave Therapy

There is level 4 evidence (from one pre-post study; Altindag & Gursoy 2014) that three sessions of extracorporal shock wave therapy may reduce muscle tone over the short term.

Galvanic Vestibular Stimulation

There is level 4 evidence (from one pre-post study; Cobelijic et al. 2018) that better clinical and neurophysiological understanding is needed for galvanic vestibular stimulation responders vs nonresponders to potentially optimize galvanic vestibular stimulation stimulation parameters for responders.

Key Points

Ongoing TENS nerve stimulation programs result in short-term reductions in spasticity which may last for up to 24 hours.

Use of TENS and standard physical therapy showed a reduction in clinical spasticity in the subacute phase of rehabilitation.

Penile vibration and rectal probe stimulation may be effective at reducing lower limb muscle spasticity for several hours.

Other forms of afferent stimulation including taping, massage, cryotherapy, helium-neon irradiation, whole-body vibration, and galvanic vestibular stimulation may result in immediate spasticity reduction but require more research to understand effects and intervention parameters.

3.5 Interventions Based on Direct Spinal Cord Stimulation

Initial investigations of spinal cord stimulation were conducted in the early 1970s and were directed at individuals with multiple sclerosis (Cook & Weinstein 1973). Later studies have examined the effect of this approach in people with SCI to enhance bladder or bowel function

and for the relief of pain and spasticity (Richardson & McLone 1978; Illis et al. 1983; Dimitrijevic et al. 1986a; Barolat et al. 1988). Typically, these studies employ a surgically implanted electrode under either general or local anaesthesia placed over the dorsal columns of the spinal cord that supplies ongoing electrical stimulation. Pinter et al. (2000) noted a declining interest with this approach in the 1990s because of technical concerns and "the realization that spinal cord stimulation was less effective in individuals with severe spasms of the lower limbs" (Dimitrijevic et al. 1986b; Barolat et al. 1995).

Table 6. Studies of Spinal Cord or Transcranial Stimulation for Reducing Spasticity

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Hofstoetter et al. 2014 Austria Pre-Post N=3	**Population:** Mean age: 32.7 yr; Gender: males=2, females=1; Injury etiology: motor-incomplete SCI=3. **Intervention:** Examine the effects of transcutaneous spinal cord stimulation (tSCS) on lower-limb spasticity. **Outcome Measures:** Wartenberg pendulum test (WPT), Neurological recordings of surface electromyography (EMG), Non-functional co-activation during volitional movement, Timed 10 metre walk test (10MWT).	1. Average Index of spasticity from pendulum test changed from 0.8±0.4 to 0.9±0.3, improvement in subject with lowest pre-stim index, and no changes other two subjects. 2. All subjects decreased EMG activities during WPT. 3. All subjects showed decreased exaggerated reflex responsiveness after tSCS, most effect on passive lower-limb movement (pre- to post-tSCS EMG ratio: 0.2:0.1). 4. Gait speed for two subjects increased by 39%. 5. Subject reports: lightness feeling in limbs, increased sensation, especially of foot sole during ground contact. 6. Anti-spastic effects felt for 2-6hr post tSCS.
Pinter et al. 2000 Austria Pre-Post N=8	**Population:** Age range: 18-34 yr; Gender: males=4, females=4; Level of injury: C5-T6; Level of severity: AIS: A–C; Time since injury range: 19–94 mo. **Intervention:** Epidural spinal cord stimulation over the upper lumbar cord. Final internal placement for surgical implantation determined following an 8 wk trial period during which the stimulator was external. **Outcome Measures:** Ashworth scale (AS), Clinical Rating Scale,	1. Spasticity was reduced as indicated by reduced Ashworth scale scores (p=0.0117). 2. Pendulum test in 4 of 8 subjects showed reduced spasticity when stimulator was on for at least 1hr versus off for >12 hr. 3. 6 subjects showed marked reductions and 2 subjects showed moderate reductions with the clinical rating scale. It was not described what this entailed. 4. EMG responses to stretch in the presence of stimulation were significantly reduced for all muscles

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Pendulum test, EMG activity in response to passive stretch.	combined of the left (p=0.0040) and the right (p=0.0035). 5. Antispastic medication discontinued in all but 1 individual when continuous stimulation started. This individual had baclofen dose reduced and tizanidine discontinued.
Barolat et al. 1995 USA Pre-Post N=48	**Population:** Age range: 17-66yr; Gender: males=43, females=5; Level of injury: cervical=32, thoracic=16; Severity of injury: complete=25, incomplete=23; Time since injury range: 6–545 mo. **Intervention:** Spinal cord stimulation following surgical implantation of the Medtronic Resume® electrode in the dorsal epidural space. Stimulus parameters determined in a training period 1-2 days after implantation typically resulted in a therapeutic window of stimulation between the motor and sensory threshold. **Outcome Measures:** Average number of spasms, intensity of spasms and frequency of spasms. Severity score including both the intensity and frequency of the spasms. All were collected just prior and 3, 6, 12 and 24 mo after implantation.	1. Of 48 initial subjects, 40 provided data at 3 mo, 33 at 6 mo, 31 at 1 yr and 18 at 2 yr. The remainder were discontinued due to lack of efficacy or lost to follow up. 2. Average # of spasms/hr improved=19.9 initially, 11.3 at 3mo, 9.2 at 6 mo, 8.8 at 1 yr and 12.9 at 2 yr. 3. A significantly greater proportion of subjects indicated reduced severity scores over time with significant differences at 6mo (p=0.0424), 1yr (p=0.0001) and 2 yr (p=0.0012) relative to baseline. 4. Spasm intensity showed improvement over time with the proportion of individuals experiencing severe spasms being 83% initially, 33% at 3 mo, 45% at 6 mo, 32% at 1 yr and 28% at 2 yr. 5. Subjective rating of spasm relief also decreased with 68% of individuals experiencing good or excellent relief at 3 mo, 69% at 6 mo, 70% at 1 yr and 79% at 2 yr.
Dekopov et al. 2015 Russia Case Series N=71	**Population:** Mean age: 35.7 yr; Gender: males=40, females=31; Injury etiology: cerebral palsy=52, spinal trauma=13, multiple sclerosis=2, spinal cord tumour=2, spinal stroke=1, pyogenic epiduritis=1; Level of Injury: paraparesis=41, tetraparesis=11. **Intervention:** Assess the effectiveness of spinal cord stimulation (SCS) in different	1. Decrease in muscle tone in all cases for groups with spinal spasticity (3.71±0.61 to 2.26±0.56, p>0.001). 2. Therapy was discontinued in 8(11%) cases due to improvement (Cerebral palsy=7 cases, spinal injury=1 case). 3. In spinal injury spasticity group, Arens Scale showed significance for functional improvement (2.68±1.2 to 3.31±1.6; p=0.004). 4. 1 case in spinal injury group had SCS system removed after 6mo due to

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	groups of individuals with spasticity of different origin. **Outcome Measures:** Ashworth Scale (AS), Range of passive and active motion; Group 1: Gross Motor Function Measure (GMFM-88); Group 2: Arens Scale.	worsening spasticity and function, fixed contractures before operation.
Midha & Schmitt, 1998 USA Case Series N=29	**Population:** Age range: 29-63 yr; Level of injury: C4-T10; Level of severity: complete, incomplete; Time since injury range: 6 mo-30 yr. **Intervention:** Retrospective analysis of those having undergone implantation of an epidural stimulator between 1986 and 1988. **Outcome Measures:** Telephone follow-up (asked to quantify symptom relief on a scale from 0-10, 10=total symptom relief) and how long they had had the symptom relief since the time of the implantation.	1. At the time of the retrospective study, 1 of 17 individuals reported that the epidural stimulator was producing symptomatic relief. 2. The average length of time that all units produced symptomatic relief was 6mo (range 0-96mo). 3. Fourteen units were removed within 3.4 yr (5 days-7 yr); 9 implantations failed from the day of implantation. 4. Total cost of initial implantation (not including follow-up) is $23,600 per unit.

Discussion

Hofstoetter et al. (2014) conducted a pre-post study (n=3) on subjects with motor-incomplete SCI who could walk ≥10 metres to examine the effects of transcutaneous spinal cord stimulation (tSCS) on lower-limb spasticity. Two interconnecting stimulating skin electrodes were placed paraspinally at the T11-12 veterbral levels. Biphasic 2-millisecond width pulses were delivered at 50 Hz for 30 minutes at intensities producing paraesthesias but no motor responses in the lower limbs. The Wartenberg pendulum test and neurological recordings of surface- EMG were used to assess the effect of exaggerated reflex excitability, non-functional co-activation during volitional movement, and for clinical function assessment the timed 10-m walk test was used. The study demonstrated that the average Index of spasticity from pendulum test changed from 0.8±0.4 to 0.9±0.3 with improvement in the subject with the lowest pre-stimulation index, and no changes in the other two subjects. All subjects showed decreased EMG activities during the Wartenberg pendulum test and on exaggerated reflex responsiveness after tSCS, with the most effect seen on passive lower-limb movement (pre-to post-tSCS EMG ratio: 0.2±0.1). Gait speed for two subjects increased by 39% and all subjects reported a lightness of feeling in the limbs, increased sensation especially of the sole of the foot during ground contact and anti-spastic

effects of two-6 hour post tSCS. The study suggests that tSCS may be used for spasticity control without negatively affecting residual control in iSCI.

Pinter et al. (2000) showed improvements following implantation of an epidural spinal cord stimulator with a variety of clinical measures including significant decreases in AS scores ($p=0.0117$), the pendulum test and muscle activity as indicated by reduced summed EMG activity collected during passive movements in both the left ($p=0.0040$) and the right ($p=0.0035$) lower limb. In addition, it was possible to discontinue anti-spastic medication in seven of eight subjects and reduce the dose in the remaining subject. These positive findings were achieved in a rather small population (N=8) and additional studies from independent groups are required to further demonstrate the feasibility and efficacy of this approach. In particular, the long-term effectiveness of spinal cord stimulation is uncertain, as this study did not specify the specific time points when measures were collected. However, they did state that spinal cord stimulation had been conducted for a mean of 14.4 months (Pinter et al. 2000). These authors asserted that better results were obtained with their approach as they were more careful in optimising location and other methodological aspects and outcomes could be further enhanced by improved stimulator design.

Barolat et al. (1995) also reported beneficial reductions in spasticity with epidural spinal cord stimulation as assessed by subjective scales of spasm frequency and intensity. Spasm intensity and spasm frequency were reduced significantly over the follow-up period of 2 years and a significantly greater proportion of subjects indicated reduced spasticity severity scores over time with significant differences at 6 months ($p=0.0424$), 1 year ($p=0.0001$) and 2 years ($p=0.0012$) relative to baseline. It should be noted that the positive nature of the long-term findings are somewhat muted as subjects were increasingly dropped from the analysis over time when they were lost to follow-up or discontinued due to lack of efficacy. Of 48 initial subjects, 40 provided data at 3 months, 33 at 6 months, 31 at 1 year and 18 at 2 years.

In contrast to these findings, Midha and Schmitt (1998) conducted a telephone or in-person follow-up of individuals having epidural stimulators implanted between 1986 and 1988 to determine their long-term status (N=17). In only one of these individuals was the stimulator continuing to provide symptomatic relief although most felt it was initially effective with an average time of effectiveness of 6 months. The rate of stimulator failures was high with several removals and re-implantations of devices. At the time of follow-up only 10 individuals reported having an implanted stimulator.

Conclusion

There is level 4 evidence (from three pre-post studies and one case series; Hofstoetter et al. 2014; Pinter et al. 2000; Barolat et al. 1995; Dekopov et al. 2015) that ongoing spinal cord stimulation may provide some relief from otherwise intractable spasticity.

There is level 4 evidence (from one pre-post study and one case series; Hofstoetter et al. 2014; Midha & Schmitt 1998) that the beneficial effects of spinal cord stimulation may subside for most initial users over a short period of time. This, combined with the potential for equipment failure and adverse events, suggests that spinal cord stimulation may not be a feasible approach for ongoing management of spasticity.

Key Points

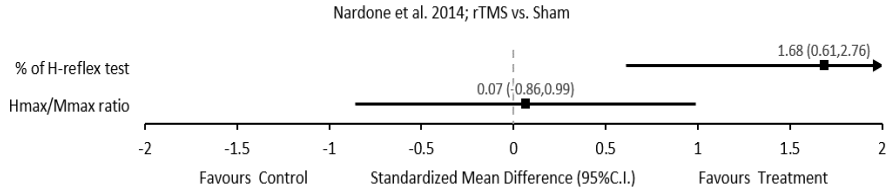
Spinal cord stimulation may provide spasticity relief over a few months but long-term effectiveness and feasibility is less certain.

3.6 Repetitive Transcranial Magnetic Stimulation

After a lesion, functional reorganization of the remaining circuits at the cortical and subcortical levels can contribute to the recovery of function. Repetitive transcranial magnetic stimulation (rTMS) s a non-invasive technique that has been shown to modulate cortical excitability and induce changes over the descending corticospinal output (Kumru et al. 2010). This cortical modulation may be useful in promoting active recovery of motor function to obtain functional benefit from gait rehabilitation. Previous studies have shown rTMS to be beneficial in reduced spasticity among individual with multiple sclerosis, cerebral palsy, and spastic quadriplegia (Wassermann & Lisanby 2001).

Table 7. Studies of rTMS for Reducing Spasticity

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Nardone et al. 2014 Austria RCT Crossover PEDro=7 N=9	**Population: Individuals** *(n=9)*: Mean Age: 45.7 yr; Gender: males=8, females=1; Injury etiology: fracture=7, disc prolapse=2; Level of injury: cervical=5, thoracic=4; Level of severity: AIS C=4, AIS D=5. *Controls (n=8)*: Mean Age: 44.4 yr; Gender: males=7, females=1. **Intervention:** Individuals were randomly allocated to receive either real rTMS (n=4) or a sham rTMS (n=5). Intervention was conducted daily over 5 days with real rTMS individuals receiving 2 sec-long bursts at 20 Hz with interstimulus interval of 28 sec, for a total of 1600 pulses over 20 min at an intensity of 90% of the resting motor threshold. After a 4 wk washout period, individuals were crossed over, although only four of the five sham rTMS individuals received real rTMS. Assessments were conducted at	1. Spasticity was significantly reduced after real rTMS intervention, as measured by both MAS (p=0.0013) and SCAT (p=0.0008). 2. MAS and SCAT values significantly decreased after the first intervention session (MAS: p=0.0001; SCAT: p=0.0001). 3. MAS and SCAT scores at 1 wk follow-up were still significantly lower than baseline scores (MAS: p=0.0006; SCAT: p=0.0002). 4. H-max/M-max ratio did not change significantly over the four assessments (p=0.17) amongst individuals (controls not assessed for H-max/M-max). 5. Reciprocal inhibition according to H-reflex responses was significantly modified in individuals during real rTMS intervention (p=0.00004) compared to healthy controls.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	baseline, after first session, after final session and at 1 wk follow-up. **Outcome Measures:** Modified Ashworth Scale (MAS), Spinal Cord Injury Assessment Tool for Spasticity (SCAT), Monosynaptic test reflex responses (H-reflex), Maximal H-reflex response (H-max), Maximum soleus motor action potential (M-max).	6. The conditioned H-reflex response significantly decreased after first intervention session and from first to last intervention session (both p<0.0001). 7. Conditioned H-reflex responses at 1 wk follow-up were still significantly lower than baselines scores (p<0.0001).
	Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- and post-intervention data. 	
Benito et al. 2012 Spain RCT PEDro=7 N=17	**Population:** Mean age: 37.3 yr; Gender: males=13, females=4; Injury etiology: traumatic=9, non-traumatic=8; Level of injury: cervical=7, thoracic=10; Level of severity: AIS D=17. **Intervention:** Individuals were randomly allocated to receive either real rTMS (n=7) or a sham rTMS (n=10). Three individuals who received sham rTMS were crossed-over to receive real rTMS 3 wk after completing the sham protocol. Real rTMS individuals received 2 sec bursts at 20 Hz (40 pulses/burst) with intervals of 28 sec, for a total of 1800 pulses over 20 min. The intensity of stimulation was set at 90% of the resting motor threshold. Assessments were conducted at baseline, after the last intervention session, and at 2 wk follow-up. **Outcome Measures:** Modified Ashworth Scale (MAS), Lower Extremities Motor Score (LEMS), Walking Index for SCI II Scale (WISCI II), Gait velocity, Step length and	1. Real rTMS individuals experienced significantly less spasticity according to MAS scores at the end of the last intervention session compared to baseline (p=0.027) but sham rTMS group did not (p=0.066). 2. Real rTMS individuals demonstrated significant improvements in LEMS scores at the end of the last intervention session compared to baseline (p=0.005) but sham rTMS group did not (p=0.258). 3. No significant changes were observed within each group for WISCI II scores (p=0.68 and p=0.109 for real and sham rTMS respectively). 4. Gait velocity, cadence, step length, and TUG significantly improved amongst real rTMS individuals at the end of the last intervention session in comparison to baseline (p=0.005, p=0.009, p=0.013, and p=0.017 respectively).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	cadence assessment during the Ten-meter Walking Test, Timed Up and Go test (TUG).	5. Sham rTMS individuals only improved in step length and TUG after the last intervention session compared to baseline (p=0.018 and p=0.043 respectively).
Kumru et al. 2010 Spain Case Control N=21	**Population:** Mean age: 36.2 yr; Injury etiology: traumatic and non-traumatic SCI; Level of injury: C4-T2, AIS C/D; Mean time since injury: 7.3 mo. **Intervention:** Cases (n=14)–5 days of excitability of the primary motor cortex with high frequency repetitive transcranial magnetic stimulation (rTMS) to the leg motor area (20 trains of 40 pulses at 20 Hz; intensity of 90% of resting motor threshold for the biceps brachii muscle); Controls (n=7)–Sham procedure. **Outcome Measures:** Modified Ashworth Scale (MAS), Visual Analog Scale (VAS), Spinal Cord Injury Spasticity Evaluation Tool (SCI-SET).	1. 8/14 individuals receiving the intervention spontaneously reported improved sleep quality and longer uninterrupted sleep. 2. Mean stimulation intensity used was 41.9±6.0% of maximal stimulator output. 3. Spasticity was significantly reduced at the end of the first and the last intervention sessions from both lower extremities when compared with the baseline condition as measured by the MAS ($p<0.006$) and Visual Analog Scale ($p<0.002$); these effects were maintained 1 wk post intervention. 4. According to SCI-SET, spasticity was reduced significantly after 5 days of intervention (p=0.003), and this improvement remained 1 wk post intervention.

Table 8. Systematic Reviews of Repetitive Transcranial Magnetic Stimulation for Reducing Spasticity

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Nardone et al. 2015 Austria Review of published articles between 1966-2014 AMSTAR=4 N=49	**Method:** Comprehensive literature search with no language restrictions. Missing or incomplete data was obtained after direct contact with the authors of selected articles. **Databases:** MEDLINE, EMBASE. **Level of evidence:** No restrictions on research design were implemented. Only articles	1. Two studies revealed significant improvements in spasticity, focusing the intervention on leg motor areas of the brain was found to improve walking speed and spasticity of lower limbs. 2. Pain relief and significant analgesic effects were found to be obtained after rTMS intervention.

	reporting data on studies using Transcranial Magnetic Stimulation (TMS) and Repetitive TMS (rTMS) on individuals with SCI were included. Questions/measures/hypothesis: 1. Examine the effectiveness of TMS/rTMS as a clinical tool after SCI. 2. Examine the use of TMS/rTMS techniques to observe and map neural mechanisms and cortical exctiability post-SCI.	3. The use of sub-threshold TMS can also be used to study the mechanisms of reorganisation processes by inhibiting outgoing electromyography readings. 4. TMS can enable mapping of motor cortical output by accurately assessing the number of cortical sites eliciting evoked potentials for a target muscle. 5. Further studies are required to assess the safety and efficacy of TMS/rTMS with one study suggesting that high levels are required to obtain motor cortical excitability which can induce discomfort and pain in the patient.

Discussion

Nardone et al. (2014) completed a double blinded, sham controlled crossover RCT to evaluate the disynaptic reciprocal primary inhibition (i.e., mediated via pathway of muscle spindle 1a afferent to motoneurones of the antagonist muscle) of the soleus motoneurons in SCI study subjects. Study subjects were randomly allocated to receive either real rTMS (n=4) or a sham rTMS (n=5). Treatment was conducted daily over 5 days with real rTMS individuals receiving two second duration bursts at 20 Hz with an interstimulus interval of 28 seconds for a total of 1600 pulses over 20 minuntes at an intensity of 90% of the resting motor threshold. After a 4-week washout period, study subjects were crossed over, although only four of the five sham rTMS individuals received real rTMS. Assessments were conducted at baseline and at initial, final, and 1-week follow-up visits using the MAS, SCATS, monosynaptic test reflex responses (H-reflex), maximal H-reflex response, and maximal soleus motor action. Study results showed that spasticity was significantly reduced after real rTMS intervention, as measured by both MAS ($p=0.0013$) and SCATS ($p=0.0008$). MAS and SCATS values significantly decreased after the first treatment session (MAS: $p<0.0001$; SCAT: $p<0.0001$). MAS and SCAT scores at 1-week follow-up were still significantly lower than baseline scores (MAS: $p=0.0006$; SCAT: $p=0.0002$). maximal H-reflex response/M-max ratio did not change significantly over the four assessments ($p=0.17$) among study subjects (controls not assessed for maximal H-reflex response/M-max). Reciprocal inhibition, according to H-reflex responses, was significantly modified in study subjects during real rTMS intervention ($p=0.00004$) compared to healthy controls. The conditioned H-reflex response significantly decreased after the first treatment session and from first to last treatment sessions (both $p<0.0001$). Conditioned H-reflex responses at 1-week follow-up were still significantly lower than baselines scores ($p<0.0001$). The results of this study support and extend previous findings demonstrating the effects of rTMS on spasticity in individuals with SCI.

Similarly, Benito et al. (2012) completed a double-blind sham controlled RCT (rTMS n=7, sham n=10) to study the effects of rTMS on spasticity in SCI. Three individuals who received sham rTMS were crossed-over to receive real rTMS 3 weeks after completing the sham protocol. Real

rTMS individuals received two second bursts at 20 Hz (40 pulses/burst) with intervals of 28 seconds, for a total of 1800 pulses over 20 minuntes. The intensity of stimulation was set at 90% of the resting motor threshold. The study demonstrated that real rTMS resulted in significantly less spasticity according to MAS scores at the end of the last treatment session compared to baseline ($p=0.027$), but sham rTMS did not ($p=0.066$).

Kumru et al. (2010) examined the efficacy of rTMS on 15 individuals with incomplete SCI. rTMS was applied in two-second bursts at 20 Hz (40 pulses/burst) to the primary motor cortex over 5 days. Spasticity was significantly reduced at the end of the first and the last treatment sessions from both lower extremities when compared with the baseline condition as measured by the MAS ($p<0.006$). Additionally, unsolicited disclosures of improved sleep quality were reported by individuals. These results remained 1-week post-treatment.

Nardone et al. (2015) completed a systematic review of published articles between 1966 and 2014 (n=49) using the MEDLINE, EMBASE Databases with no language and research design restrictions. Only articles reporting data on studies using Transcranial Magnetic Stimulation (TMS) and repetitive TMS (rTMS) on individuals with SCI were included. Nardone et al. (2015) sought to examine the effectiveness of TMS/rTMS as a clinical tool after SCI and examine the use of TMS/rTMS techniques to observe and map neural mechanisms and cortical excitability post-SCI. Two studies revealed significant improvements in spasticity; in particular, focusing treatment on leg motor areas of the brain was found to improve walking speed and spasticity of lower limbs. Additionally, pain relief was also reported post rTMS treatment.

Sub-threshold TMS can also be used to study the mechanisms of reorganisation processes by inhibiting outgoing EMG readings. As well, TMS can enable mapping of motor cortical output by accurately assessing the number of cortical sites eliciting evoked potentials for a target muscle. Nardone et al. (2015) recommended that further studies are required to assess the safety and efficacy of TMS/rTMS as one study suggested that high levels of stimulation are required to obtain motor cortical excitability which can then induce discomfort and pain in the patient.

Conclusion

There is level 1a evidence (from two RCTs and one case control; Nardone et al. 2014; Benito et al. 2012; Kumru et al. 2010) that rTMS decreases spasticity and improves walking speed.

Key Points

Repetitive transcranial magnetic stimulation may provide spasticity relief and improve walking speed over the short-term but long-term effectiveness is unknown.

3.7 Transcranial Theta-Burst Stimulation

TMS has already been described in section 3.6. Transcranial theta-burst stimulation differs from TMS in that the stimulation includes patterned (vs non-patterned in rTMS bursts of shorter

duration pulses. Conceptually, intermittent theta-burst stimulation (iTBS)et al. may produce a more robust strengthening of synaptic activity in residual neural pathways (Martin 2016; Huang et al. 2005).

Table 9. Studies of Transcranial Theta-Burst Stimulation for Reducing Spasticity

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Gharooni et al. 2018 UK RCT Crossover PEDro=6 $N_{Initial}$=11 N_{Final}=10	**Population**: SCI (n=10): Mean age=46.8±11.9yr; Gender: males=8, females=2; Level of injury: C=10; Mean time since injury=0.95±1.18; AIS scale: B=1, C=4, D=5. **Intervention:** Participants were randomized to receive either intermittent transcranial theta-burst stimulation (iTBS) or sham first. A 90 mm circular coil placed on the Cz position of the skull delivered iTBS. Three stimuli at 50 Hz were repeated at 200 millisecond intervals for 2 seconds. An inter-train interval of 8 seconds was repeated 20 times for a total of 600 pulses in 200 seconds. Stimulator output intensity was determined as 80% of the resting membrane threshold as observed by a muscle twitch in the upper limbs during resting state. Sham iTBS consisted of the same protocol with the exception that the coil was turn 90 degrees about its vertical midline axis to ensure no brain stimulation. A 2-wk washout period was used in between crossover. Each condition consisted of 10 sessions over 2 wk. Outcome measures were assessed at baseline and 2 wk post intervention. **Outcome Measures:** Combined upper-limb Modified Ashworth Scale of bilateral elbow and wrist extension and flexion (MAS); Leeds Arm Spasticity Impact Scale (LASIS); Visual Analogue Scale for spasticity (VAS-S).	1. While there was an observed reduction in MAS, it does not appear to be large enough to improve participants' perception of spasticity or improvement in function as measured by LASIS and VAS-S. 2. Intervention effects (adjusted for baseline) include; mAS=-2.67 (CI: -5.17 to -0.17), LASIS=0.16 (CI: -0.18 to 0.48), VAS-S=-1.99 (CI: -21.00 to 17.01).
Nardone et al. 2017 Austria RCT Crossover PEDro=7 N=10	**Population**: SCI (n=10): Mean age=42.8±11.9yr; Gender: males=7, females=3; Level of injury: C=6, T=4; Mean time since injury=8.3±4.5yr; AIS scale: C=4, D=6. **Intervention:** Participants were randomly allocated to receive either intermittent theta burst stimulation (iTBS) or sham iTBS first. Interventions were separated by a wash out period of at least 2 mo. iTBS was delivered over the scalp site corresponding to the motor cortex area of the dominant leg at an intensity	1. Results indicate a significant treatment X time interaction effect for mAS and SCAT ($p<0.001$ for both). 2. There was also a significant time effect for mAS and SCAT in the iTBS group ($p<0.001$ for

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	of 80% active motor threshold. Ten bursts (composed of 3 stimuli at 50 Hz) were repeated with a theta frequency of 5 Hz every 10 seconds for a total of 600 stimuli/200 seconds. The same protocol was utilized for the sham iTBS, except that the coil was rotated by 90 degrees so that no current was induced in the brain. Both interventions were administered daily for 10 days each. Outcome measures were assessed at baseline, post intervention, and at 1-wk and 4-wk follow ups. **Outcome Measures:** Spinal Cord Assessment Tool for Spasticity (SCAT); modified Ashworth Scale (mAS).	both). More specifically, there was a decrease in mAS and SCAT followed by a return to baseline. 3. There were no significant time effects for the sham iTBS group for both mAS and SCAT ($p>0.05$).

Discussion

Intermittent theta-burst stimulation is a new intervention being applied to people with incomplete cervical SCI to potentially improve upper limb spasticity, pain and sensorimotor function. Gharooni et al. (2018; RCT) administered a total of 600 pulses in 200 seconds 3 stimuli at 50Hz, repeated at 200 ms intervals for 2 seconds and interspersed by 8 seconds between pulse trains). Sham intermittent theta-burst stimulation was the same except with the stimulation coil rotated 90° from the participants midline axis to ensure no brain stimulation. Sessions of intermittent theta-burst stimulation (or sham intermittent theta-burst stimulation) were delivered 10 times over 2 weeks with a 2-week washout period before crossover to the alternative intervention. Three spasticity outcome assessments (MAS), Leeds Arm Spasticity Impact Scale and a VAS-spasticitywere applied to bilateral elbow and wrist extension and flexion. Results were reported to support a non-significant reduction in MAS compared to sham intermittent theta-burst stimulation and that were not of a magnitude that could be perceived by participants as improved function (via VAS-spasticity and Leeds Arm Spasticity Impact Scale).

Nardone et al. (2017), using SCATS and MAS and a stimulation protocol as described above (Gharooni et al. 2018) with the exception that the washout period was 2 months (versus 2 weeks), found a significant reduction of upper extremity spasticity ($p<0.001$ for both SCAT and MAS) that returned to baseline within 1 week.

Conclusion

There is level 1b evidence (from 1 RCT: Nardone et al. 2017) that intermittent theta-burst stimulation reduces upper extremity spasticity for up to 1 week.

Key Points

Treatment with intermittent theta-burst stimulation is likely to reduce upper extremity spasticity for up to 1 week.

4 Neuro-Surgical Interventions for Spasticity

Surgical approaches have been considered as a treatment option for those individuals with severe spasticity which has been refractory to more conservative approaches and for which no useful or potential function exists below the level of the lesion (Livshits et al. 2002). Individuals often shy away from this treatment option because of the irreversibility of the procedures. There are few well-controlled neuro-surgical interventional studies that have examined the influence of this approach on spasticity as their main purpose. The primary, and most commonly investigated technique is that of longitudinal myelotomy and this approach has also been applied to pain management and spasticity reduction in other etiologies, although spasticity in individuals with SCI is the most common application (Laitinen & Singounas 1971; Yamada et al. 1976; Fogel et al. 1985; Putty & Shapiro 1991). Other surgical techniques include laminectomy, cordectomy, and adhesolysis (Falci et al. 2009; Ewelt et al. 2010). Gautschi et al. (2009) reported significant improvements in health-related quality of life, in individuals undergoing cordotomy for syringomyelia. Spasticity was mentioned as a symptom of syringomyelia. Areas like mobility and daily activities improved; which could be in part due to reduced spasticity, despite spasticity not being specifically measured as an outcome in this study.

Table 10. Neurosurgical Interventions for Reducing Spasticity

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Livshits et al. 2002 Israel RCT PEDro=5 $N_{Initial}$=40, N_{Final}=32	**Population:** *Pourpre group:* Mean age: 27.6 yr; Gender: males=15, females=5; Level of injury: paraplegia=20; Level of severity: complete, incomplete; Mean time with spasticity: 2.8yr; *Bischof II group:* Mean age: 27.1 yr; Gender: males=14, females=6; Level of injury: paraplegia=20; Level of severity: complete, incomplete; Mean time with spasticity: 2.8 yr. **Intervention:** Longitudinal T-myelotomy by Pourpre versus Bischof II technique.	1. Authors states that "good" versus "bad" results with respect to spasticity were obtained with the Pourpre technique in 90% of subjects at 6 mo, 75% at 5 yr and 64.7% at 10 yr. The Bischof II technique was less effective in that "good" effects were seen in 65% of subjects at 6 mo, 45% at 5 yr and 40% at 10 yr. The author did not specify what constituted a "good" versus a "bad" effect other than to say it was a return of spasticity. 2. AS scores and PSF scale scores were significantly reduced

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Outcome Measures: Short form of McGill pain questionnaire (SFM), Present Pain Intensity (PPI), Visual analog score for pain (VAS), Ashworth scale (AS), Penn Spasm Frequency (PSF) scale. All collected prior to surgery and 6 mo, 5 yr and 10 yr post-surgery.	relative to pre-surgery values (p values unreported). 3. People undergoing the Pourpre technique had significantly reduced AS scores and PSF scores than those undergoing the Bischof II technique (p values unreported). 4. Pain measures were relieved in all cases although there were successively increasing SFM, PPI and VAS scores at 6 mo versus 5 yr versus 10 yr ($p<0.0001$ for all). 5. Pain was relieved better (i.e., lower scores for all measures at all follow-up times) for the Pourpre technique versus Bischof II technique.
Ewelt et al. 2010 Switzerland Case Series N=15	**Population:** Mean age: 50.4 yr; Gender: males=13, females=2; Injury etiology: traumatic syringomyelia and tethered cord=13, spinal ependymoma and surgical cord injury =2; Level of injury: paraplegia, T3-T9. **Intervention:** Laminectomy, adhesiolysis, cordectomy. **Outcome Measures:** 3-point scale for spasticity.	1. 2 individuals improved in their spasticity. 2. 9 individuals stabilized in spasticity symptoms. 3. 4 individuals reported further spastic deterioration of their lower limbs.
Falci et al. 2009 USA Case Series N=362	**Population:** Mean age: 40.5 yr; Level of injury: C6=163, C6-T1=83, T1=116; Injury severity: AIS A=231, AIS B=36, AIS C=42, AIS D=51, AIS E=2. **Intervention:** Surgery to arrest progressive myelopathy. **Outcome Measures:** Self-reported change in spasticity.	1. 59% reported improvement of spasticity. 2. 27% reported no change in spasticity. 3. 13% reported worsening of spasticity.
Putty & Shapiro 1991 USA Case series $N_{Initial}$=23, N_{Final}=20	**Population:** Injury etiology: SCI=11, MS=7, other=2; Age range: 22-69 yr; Gender: males=12 females=8; Level of injury: C5-T9; Level of severity: complete, incomplete; Time since injury range: 2–23 yr. **Intervention:** Posterior T-myelotomy. **Outcome Measures:** Subjective clinical impression.	1. No statistical results were reported; 9 of 10 individuals with SCI had relief from spasms (1 died, unrelated to surgery).

Discussion

Livshits et al. (2002) conducted a study comparing two approaches of dorsal longitudinal T-myelotomy technique (i.e., Pourpre versus Bischof II) on the effectiveness of reducing pain and spasticity in people with SCI (N=40) with a follow-up period of up to 10 years. For the purpose of this review we have assessed this article as a low-quality RCT (i.e., level 2 evidence, PEDro<6). The authors presented the article as a prospective trial with the two surgical techniques that were "randomly" applied as "it was unknown which of the operations would prove to be more effective" (Livshits et al. 2002). Unfortunately, the method of randomisation was not clearly stated and the explicit designation as a prospective trial was not noted. Regardless, it was demonstrated that good to excellent results were obtained with either of these surgical techniques with AS scores and PSFS scores significantly reduced relative to pre-surgery values (p values unreported). More individuals had positive results with the Pourpre technique versus the Bischof II technique in that 64.7% of subjects had maintained benefits at 10 years with the former as compared to 40% with the latter. These results are laudable considering these individuals were originally refractory to more conservative treatment.

Putty and Shapiro (1991) in a retrospective review of 20 subjects (n=11 with SCI) employed a modified posterior T-myelotomy technique to reduce spasticity and improve nursing care. Although group results were not reported and no standardized measures of spasticity were employed, these authors concluded that this intervention achieved relief from spasms in almost all individuals while the impact on nursing care and individual comfort was less specified.

Two level 4 studies examined the effect of varying surgical techniques on individuals of varying etiologies (Falci et al. 2009; Ewelt et al. 2010). Although some individuals reported improvement of spasticity, no statistically significant improvements could be determined. There is insufficient evidence to suggest one technique over another for any SCI etiology.

Conclusion

There is level 2 evidence (from one RCT and one case series; Livshits et al. 2002; Putty & Shapiro 1991) that dorsal longitudinal T-myelotomy may result in reduced spasticity in those individuals initially refractory to more conservative approaches. These reductions may not always be maintained over the course of several years.

There is level 2 evidence (from one RCT; Livshits et al. 2002) that Pourpre's technique for dorsal longitudinal T-myelotomy is more effective in maintaining reduced levels of spasticity than the Bischof II technique.

Key Points

Dorsal longitudinal T-myelotomy may result in reduced spasticity.

4.1 Cell Therapy for Spasticity

Recovery of function through neuroregeneration is the intent of cell therapy for SCI with its many secondary health manisfestations including problematic spasticity. Various forms of stem cells have been clinically applied to SCI such as embryonic stem cell derived oligodendrocyte progenitor cells (NCT02302157), neural stem cells (NCT 01321333, 02163876, 01725880, 03069404), and mesenchymal stem cells derived from umbilical cord blood, adipose or bone marrow; protocols can be reviewed at www.ClinicalTrials.gov.

To date, safety and feasibility of stem cell administration in human SCI have been reported (Levi et al. 2018a and b; Vaquero et al. 2018). Preliminary efficacy, including for spasticity, has also been reported (Levi et al. 2018 and Vaquero et al. 2018).

Table 11. Cell Therapy Interventions for Reducing Spasticity

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Vaquero et al. 2018 Spain Pre-Post $N_{Initial}$=11 N_{Final}=9	**Population**: SCI (n=11): Mean age=44.91±10.17yr; Gender: males=7, females=4; Level of injury: C=4, T=4, TL=3; Mean time since injury=13.65±14.79yr; AIS scale: A=3, B=4, C=3, D=1. **Intervention:** All participants received autologous mesenchymal stromal cell (MSC) therapy consisting of 3 intrathecal administrations of 100 x 10^6 MSCs. Administrations consisted of subarachnoid administration by lumbar puncture Outcomes were measured at baseline, and at 4, 7, and 10 mo follow ups. **Outcome Measures:** Ashworth Scale (AS); Penn Scale (PS).	1. While there was a decrease in AS and PS post intervention, statistical significance was not achieved for any of the follow up time points (p>0.05 for all).

Discussion

Human neural stem cells were surgically implanted in trial participants with chronic (4-24 months post-injury) cervical SCI and assessed for neurological improvement focusing on the Upper Extremity Motor Score of the International Standards for Neurological Classification of SCI and Graded Redefined Assessment of Strength, Sensation and Prehension measures for upper extremity function. (Levi et al. 2018; RCT). Of the secondary measures in this RCT, the MAS revealed a non-significant decrease in spasticity over 6 months of observation in the treated group.

Similarly, the primary outcome of a pre-post trial for intrathecal administration of autologous mesenchymal stromal cells in chronic (13.65+/-14.79 years post-injury) SCI was the International

Standards for Neurological Classification of SCI for sensory and motor improvements and spasticity was assessed secondarily using the Ashworth and Penn scales (Vaquero et al. 2018). No statistical difference was seen in spasticity, pre and post stem cell administration. However, variable improvement was documented during the trial without persistence of effect to the end of follow-up.

Conclusion

Level 1b evidence (Levi et al. 2018; RCT, N=10) has not demonstrated that transplantation of human neural stem cells results in persistent spasticity reduction in participants with chronic cervical SCI.

Level 4 evidence (Vaquero et al. 2018; Pre/post, N=11) reveals that initial improvements in spasticity are not persistent as a result of intrathecal administration of autologous mesenchymal stem cells in SCI.

Key Points

Human neural stem cell transplantation in chronic SCI does not reduce spasticity secondary to SCI.

Intrathecal injection of autologous mesenchymal stem cells in people with chronic SCI is unlikely to result in persistent spasticity reduction.

5 Pharmacological Treatment for Spasticity

5.1 Oral Medications

Baclofen, a derivative of gamma aminobutyric acid, is widely used as the first line of pharmacological treatment for spasticity in people with SCI[1] (Kirshblum 1999; Taricco et al. 2006). Baclofen, also identified as Lioresal®, CIBA Ba-34647 and β-(parachlorophenyl) gamma aminobutyric acid, crosses the blood-brain barrier more readily than gamma aminobutyric acid itself and is believed to reduce spasticity by enhancing inhibitory influences on the spinal stretch reflex by increasing presynaptic inhibition (Kirshblum 1999).

In typical practice, baclofen requires a careful dose titration period with a usual maximal recommended dose of 20 mg four times each day (Burchiel & Hsu 2001) which is also the dosage employed in the majority of studies involving people with SCI (Aydin et al. 2005; Nance 1994). Veerakumar et al. (2015), in an analysis of a single provider's individual database over 25 years, reported a significant but marginal increase in baclofen dosage over the 25-year span and individuals with gunshot related SCI receiving earlier baclofen initiation than individuals with

SCI related to motor vehicle accident. Baclofen may be especially effective in reducing flexor spasms (Shahani & Young 1974; Duncan et al. 1976; Gracies et al. 1997) although these effects may also act to impair specific functional tasks such as walking or standing (Kirshblum 1999; Burchiel & Hsu 2001). The mechanism for impairment in functional tasks may require further exploration as Chu et al. (2014) did not record substantial decreases in voluntary EMG activity despite baclofen's effectiveness in reduced stretch reflexes. A variety of adverse events may limit the use of baclofen including lowering of seizure threshold, sedatory effects (i.e., drowsiness), insomnia, dizziness, weakness, ataxia, anxiety and mental confusion (Hinderer 1990; Gracies et al. 1997; Kirshblum 1999; Burchiel & Hsu 2001). A significant side effect of antispasmodics, with baclofen being the most commonly used, is the potential for reduced torque during routine activities and for activity-dependent interventions such as locomotor treadmill training (Roy & Edgerton 2012; Harkema et al. 2012). Baclofen also increases cough threshold in cervical spinal cord subjects (Dicpinigaitis 2000). Sudden discontinuation or withdrawal of baclofen can result in seizures, confusion, hallucinations and rebound muscle overactivity with fever (Gracies et al. 1997). For the most part, tolerance with sustained use of baclofen is possible (Knutsson et al. 1974), but is not a major issue (Roussan et al. 1985; Gracies et al. 1997; Kirshblum 1999).

Benzodiazepines (i.e. diazepam/valium, clonazepam) are used for multiple problems encountered post-SCI such as anxiety, musculoskeletal pain and spasticity. Although Valium has been prescribed, since the 1960s (Neill et al. 1964, Kerr et al. 1966, Wilson & McKehnie 1966), for being superior to placebo in treatment of SCI related spasticity, benzodiazepines are not approved by the Food and Drug Administration for spasticity. However, they are sometimes prescribed for short-term treatment of spasticity (e.g. nocturnal spasticity). This class of drug acts by inhibiting afferent pathways to relax skeletal muscle or inhibiting gamma-aminobutyric acid pre- and post-synpatically to depress the central nervous system. Given that excessive central nervous system depression was often cited as an unwanted side effect, diazepam is not as commonly prescribed as a first line treatment for spasticity as it once was before newer more effective classes of medications became available (e.g. baclofen). Other common side effects of benzodiazepines are ataxia, dyscoordination, fatigue, weakness, hypotension, sedation, depression, memory impairment and risk of addiction. Despite the known sedative effect of valium, it was shown to be superior to Amytal (barbiturate used as sedative or hypnotic) and placebo in reducing SCI related spasticity (Corbett et al. 1972).

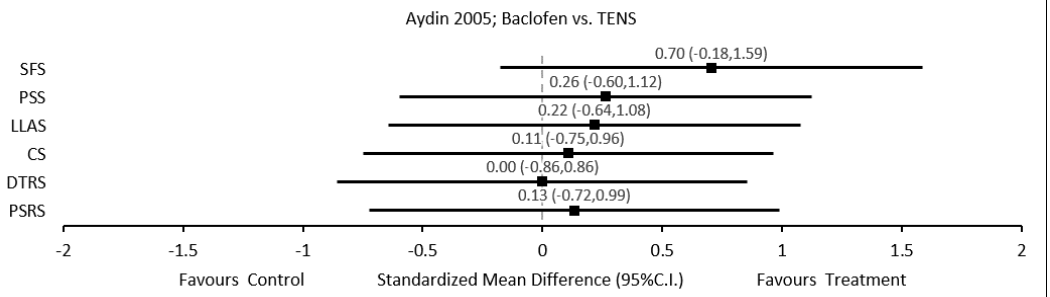
Table 12. Oral Medications for Reducing Spasticity

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Baclofen		
Yan et al. 2018 China RCT	**Population**: Baclofen (BA, n=112): Mean age=36.55±3.42yr; Gender: males=40, females=72; Level of injury: NR; Mean time since injury=211.45±25.47d; AIS scale: NR.	1. Compared to baseline, BA and BTI had significantly improved mAS scores at the 2-wk follow up (p=0.003; p=0.02,

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
PEDro=6 N=336	Botulinumtoxin A (BTI, n=112): Mean age=36.95±7.12yr; Gender: males=36, females=68; Level of injury: NR; Mean time since injury=207.45±20.49d; AIS scale: NR. Placebo (control group or CG, n=112): Mean age=35.47±2.21yr; Gender: males=30, females=82; Level of injury: NR; Mean time since injury=205.98±16.45d; AIS scale: NR. **Intervention:** Participants were randomized to receive one of three interventions, 1) Baclofen (BA), 2) botulin umtoxin A (BTI), and 3) placebo (CG). The BA group received 5, 10, 15, and 20mg of baclofen 3x/d in the 1st, 2nd, 3rd, and 4th wk, respectively. The BTI group received a local intramuscular injection of 500 U of botulin umtoxin A under EMG guidance. All groups including the placebo group received physical therapies including locomotor training and intensive task-specific training for 6 wk. Outcome measures were assessed at 2, 4, and 6 wk from the initiation of the intervention. **Outcome Measures:** Muscle tone was assessed for the thumb, wrist, and fingers using the modified Ashworth score (mAS). Other outcomes included the Disability Assessment Scale (DAS), mMRC, and Barthel Index.	respectively). CG showed no significant improvement at 2 wk. 2. At 4 wk, CG, BA, and BTI showed significant improvements in mAS compared to baseline ($p<0.001$ for all). 3. At wk 6 BA had no significant improvement in mAS when compared to baseline ($p>0.05$). However, BTI had significantly improved mAS scores compared to baseline ($p=0.02$). 4. Both BA and BTI resulted in improvements in Barthel Index.
Luo et al. 2017 China RCT PEDro=6 N=150	**Population**: Baclofen (BAC, n=75): Mean age=36.6±1.7yr; Gender: males=20, females=55; Level of injury=NR; Mean time since injury=NR; AIS scale=NR; Mean dosage=24.33±12.5 mg/d. Tolperisone (TOL, n=75): Mean age=35.5±1.5yr; Gender: males=27, females=48; Level of injury=NR; Mean time since injury=NR; AIS scale=NR; Mean dosage=378.2±102.1 U.	1. There were no significant between-group differences in mAS at baseline. BAC had significantly lower mAS scores compared to TOL at wk 2 and 4 ($p=0.003$; $p=0.02$, respectively), but by wk 6 there was no significant difference between the two groups ($p>0.05$). 2. Both groups showed significant within-group improvements in

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Intervention: Participants were randomly assigned to one of two groups; baclofen (BAC) or tolperisone (TOL). The BAC group received baclofen. Dosage was initiated at 5-10 mg 2-3x/d and was gradually increased by 5-10 mg/wk up to 80 mg/d. The TOL group received tolpersone. Dosage was initiated at 150-450 mg/d and increased to 600 mg/d. Both groups received treatment for 6 wk. Outcome measures were assessed at baseline and at wk 2, 4, and 6. **Outcome Measures:** Modified Ashworth Scale (MAS), Barthel Index, Coefficient of efficacy.	mAS over the 6 wk ($p<0.05$ for both). BAC showed a significant improvement in mAS at wk 2 and then remained consistent. TOL showed a significant improvement at wk 2 and 6 3. MRC improvement in both groups by wk 6. Barthel index improved in both groups by wk 6, but faster and to a greater extent in the TOL group. The BAC group had more side effects.
Chu et al. 2014 USA RCT Crossover PEDro=7 N=10	**Population:** Mean age: 48.9 yr; Gender: males=10, females=0; Level of severity: AIS C=4, AIS D=6; Mean time since injury: 138.7 mo. **Intervention:** Individuals were randomly allocated to the order in which they received oral administration of baclofen (30 mg), tizanidine (4 mg), and placebo (10 mg). Assessments were done at baseline and 90 to 120min after the administration of each drug. **Outcome Measures:** Ankle stretch reflex torque, Isokinetic knee extension torque, Isometric knee extension torque.	1. There was a significant decrease in stretch reflex torque after tizanidine ($p=0.034$) but not baclofen ($p=0.116$) compared to placebo. 2. Peak knee flexion torque during extension decreased significantly after baclofen ($p<0.001$) but not after tizanidine ($p=0.20$) when compared to placebo. 3. Peak knee extension torque during flexion decreased significantly after baclofen ($p=0.014$) and tizanidine ($p<0.001$) compared to placebo. 4. No significant changes in isokinetic knee torque were shown for either drug compared to placebo ($p=0.179$). 5. Knee flexion torque significantly increased after tizanidine compared to placebo ($p=0.033$). 6. Compared to placebo, there was a significant increase in isometric knee extension torque for both baclofen ($p<0.001$) and tizanidine ($p=0.001$). 7. Changes in peak torque for baclofen ($p=0.066$) and tizanidine

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		(p=0.99) did not differ significantly from placebo.
Nance et al. 2011 USA RCT Crossover PEDro=7 N=37	**Population:** Age range: 35-43 yr; Gender: males=25, females=15; Injury etiology: traumatic SCI=34, non-traumatic=3 SCI; Level of injury: AIS A=15, other=22. **Intervention:** Individuals received a sequence of extended-release arbaclofen placarbil tablets 10, 20 or 30 mg or a placebo every 12hr for 26 days for each sequence. **Outcome Measures:** Ashworth Scale (AS), Patient-rated Severity of Spasticity Scale.	1. Arbaclofen placarbil significantly improved AS scores compared to placebo over the dosing interval; least-squares mean reduction versus placebo was 0.60 for 20 mg (p=0.0059) and 0.88 for 30 mg (p=0.0007). 2. The difference was significant for the pre-morning dose time point, 12 hr after the prior evening dose, indicating that efficacy was maintained throughout the dosing interval. 3. Treatment differences for arbaclofen placarbil 10 mg versus placebo were not significant. 4. Severity of spasticity ratings were significantly reduced for the combined 20/30mg group versus placebo (p=0.018). 5. No statistically significant differences between arbaclofen placarbil and placebo were observed for muscle strength.
Aydin et al. 2005 Turkey RCT PEDro=6 N=41	**Population:** *SCI (n=21):* Level of severity: complete, incomplete; Injury etiology: trauma=41; Chronicity=chronic. *Healthy controls (n=20).* **Intervention**: Either oral baclofen (titrated up to 80 mg/day) for 8 wk or TENS for 15 min/day for 15 days. **Outcome Measures**: Spasm Frequency Scale (SFS), Painful Spasm Scale, Ashworth Scale (AS), Various clinical (clonus, deep tendon reflexes, response to plantar stimulation) or electrophysiologic measures (H-reflex latency and amplitude, H/M ratio) of spasticity as well as measures of function (FIM and FDS).	1. For both intervention groups a significant improvement was noted post treatment in the lower limb Ashworth score (p=0.011 baclofen group and p=0.020 TENS group), SFS (p<0.014 for both groups), deep tendon reflex score (p<0.025 for both groups) as well as in measures of disability (FIM-baclofen group p=0.005, TENS group p=0.003; FDS--baclofen group p=0.004, TENS group p=0.003. 2. There were only small (statistically non-significant) changes in electrophysiologic variables with either baclofen or TENS, other than a significant reduction in H-reflex maximal amplitude (p=0.032) 24 hr after

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		the final session of TENS. This reduction was even more apparent when tested only 15 min after the last treatment (p=0.026).
	Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- and post-intervention data. 	
Hinderer et al. 1990 USA RCT PEDro=9 N=5	**Population:** Gender: males=5, females=0; Level of severity: complete, incomplete; Cause of injury: trauma; Chronicity: chronic. **Intervention:** Baseline placebo period of varying length (2.5-4.5 wk), followed by a 2 wk dose titration period of baclofen at half target dose (40 mg/day), followed by 2.5-4.5 wk of 80 mg/day. **Outcome Measures:** Viscous and elastic stiffness as assessed by measuring viscous and elastic torque responses to a sinusoidal ankle perturbation of 5° at 3 to 12 Hz. Testing occurred 2x/wk for 9 wk.	1. No systematic effect of baclofen was noted. Of 300 total comparisons made, only 1 comparison reached significance, with an increased viscous stiffness apparent at a frequency of 4 cycles/sec when comparing placebo with initiation of baclofen at 40mg per day (p<0.05). 2. Visual inspection of the results for individual subjects showed no evidence for a therapeutic response of baclofen that might not have been demonstrated by group statistical analysis.
Duncan et al. 1976 USA RCT PEDro=8 N=22	**Population**: SCI (n=11), MS (n=11), 3 dropouts (etiology unknown). **Intervention**: Either oral baclofen (titrated up to 100 mg/day) for 4 wk or identical looking placebo. **Outcome Measures**: Self-report of # of spasms, nocturnal awakenings (daily) and global impression of treatment (at end of each intervention period). Clinician also provided global impression (at end of intervention period) and assessed resistance to movement and rated change on 5-point scale (weekly).	1. Number of spasms was significantly reduced with baclofen versus placebo (p<0.01) as was number of nocturnal awakenings (p<0.01). 2. 11 of 22 subjects demonstrated less resistance to passive movement by at least 2 grades on the initial 5-point scale with baclofen versus 1/22 with placebo and this was significant (p<0.01). 3. No improvement in gait was seen in any of those who could

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Also rated clonus, impressions of pain, use of limbs and transfer activity (weekly).	walk (n=8) nor were any improvements seen in tendon jerks, strength or voluntary movement. 4. In 9 cases (41%) both individuals and clinicians felt continued use of baclofen was warranted. 5. 15 subjects identified mild side effects while on baclofen (4 on placebo). All were deemed insignificant.
Burke et al.1971 Australia RCT PEDro=7 N=6	**Population:** Injury etiology: traumatic SCI=6; Level of injury: tetraplegic=6; Level of severity: complete, incomplete; Chronicity: chronic. **Intervention:** Placebo or active drug (CIBA 34,647-Ba) was titrated to a maximum of 60mg daily over a period of 2 wk in a crossover, double-blind design. **Outcome Measures:** Surface slope of EMG (quadriceps) versus velocity relationship associated with passive flexion of the knee.	1. No group statistical results were provided. 2. All 6 subjects had a reduced EMG/velocity ratio for any given speed tested with baclofen versus placebo (e.g., decreased to 37.5% (range 0%-67%) at a velocity of 200°/sec). 3. All subjects displayed clinical effects with baclofen such as reduced stretch reflex responses.
Dicpinigaitis et al. 2000 USA Prospective Controlled Trial N=24	**Population:** *Intervention group* (n=12): Mean age: 39.2 yr; Level of injury: C=12. *Control group* (n=12): Mean age: 43.2y r; Level of injury: C=12. **Intervention:** Both groups underwent Capsaicin cough challenge testing. The intervention group consisted of individuals receiving baclofen for the relief of muscle spasm while the control group did not. **Outcome Measures:** Cough thresholds.	1. Individuals in the intervention group had significantly higher cough thresholds than the control group in two or more coughs (p=0.009) or 5 or more coughs (p=0.024).
Veerakumar et al. 2015 USA Cohort N=115	**Population:** Mean age: 29.0 yr; Gender: males=97, females=18; Injury etiology: traumatic SCI=115; Level of injury: cervical=52, thoracic=59, lumbar=2, unknown=2. **Intervention:** Chart review. **Outcome Measures:** Oral baclofen use and dosage.	1. 53% (n=61) received oral baclofen. 2. No significant differences in terms of cause (p=0.17) or level of injury (p=0.65) between those who were and were not prescribed oral baclofen. 3. Patients given oral baclofen were significantly younger at time of injury than those not prescribed the medication (p=0.03).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		4. Other antispasmodics prescribed included diazepam and tizanidine. Individuals receiving baclofen alone had significantly higher dosages of baclofen then individuals on multiple antispasmodics ($p<0.05$). 5. Increases in yearly baclofen dosage, from time of injury, were seen for the whole sample (1.26 mg/yr, $p=0.01$), motor vehicle accidents (4.99 mg/yr, $p=0.0001$), thoracic-spine injuries (1.97 mg/yr, $p=0.238$), gunshot wounds (0.99 mg/yr, $p=0.032$), and individuals prescribed baclofen as the sole antispastic medication (1.29 mg/yr, $p=0.005$). 6. No factors were found to be significantly associated with the baclofen dosage slope.
Nance 1994 Canada Pre-Post N=25	**Population**: Gender: males=25, females=0; Injury etiology: SCI=25; Level of injury: paraplegia, tetraplegia; Level of severity: complete, incomplete. **Intervention:** 1 wk up-titration, 1 wk target dose (0.05 mg bid clonidine; 4 mg qid cyproheptadine; 20 mg qid baclofen), 1 wk down-titration. **Outcome Measures:** Ashworth Scale (AS), Pendulum test, VII.	1. A significant reduction in spasticity was seen with baclofen in all 3 outcome measures-as with the other 2 drugs tested ($p<0.0001$). 2. Generally, baclofen results were among the most improved as compared to the other 2 drugs although this was only significant for the pendulum test ($p=0.06$) and VII ($p<0.0007$–along with cyproheptadine).
Benzodiazapines		
Corbett et al. 1972 England RCT Crossover PEDro=7 $N_{Initial}$=22 N_{Final}=9	**Population**: Traumatic SCI(n=22): Mean age=NR; Gender: males=20, females=2; Level of injury: NR; Lesion type: complete=14, incomplete=8; Time since injury=>4 mo; AIS scale: NR. **Intervention:** This RCT crossover consisted of three conditions; 1) Valium 5 mg, 2) Amytal 30 mg, and 3) Placebo. The washout period consisted of 3 days. Participants received one tablet on the first day,	1. Valium was significantly more effective at reducing spasticity compared to both amytal and placebo when assessed by the senior doctor (n=19, $p<0.02$). 2. When assessed by the junior doctor, valium was significantly more effective at reducing spasticity compared to amytal (n=9, $p<0.05$). 3. Valium was significantly more effective at reducing spasticity compared to placebo when

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	one b.d. on the second day, and one t.d.s. for the remaining 3 days. The trial lasted 6 wk for each participant. Outcome measures were assessed by a senior doctor, two physiotherapists (one who treated the individual and who did not), a junior doctor, and the patient. Measures were taken on a daily basis with the exception of the senior doctor and treating physiotherapist who made measures once or twice per wk. **Outcome Measures:** Spasticity: subject assessment (worse, no effect, better, much better).	assessed by the treating physiotherapist (n=11, $p<0.05$). 4. There were no significant differences between the three drugs when assessed by the non-treating physiotherapist and individual (n=11, $p>0.05$).
Neill et al. 1964 UK Crossover $N_{Initial}$=21 N_{Final}=20	**Population**: SCI (n=21): Mean age=41.19±13.86yr; Gender: males=16, females=5; Etiology: SCI=14, Other=7; Level of injury: C=11, T=4; Lesion type: complete=10, incomplete=5; Time since injury=NR; AIS scale: NR. **Intervention:** Participants received two bottles of 250 tablets. Each bottle was given for 2 wk and consisted of either 2 mg diazepam or placebo. All participants received one bottle with diazepam and one with placebo. The starting dose consisted of two tablets every 6 hours. Dosage was increased to 3 tablets every 6hr after 1 week. Outcome measures were assessed prior to the intervention, as well as twice weekly. Assessments were completed by a senior and junior doctor, a physiotherapist, and the patient. **Outcome Measures:** Spasticity: assessed by passive movement of limbs [better (+1), worse (-1), or same (0) as initial condition].	1. 13/20 participants self-reported an improvement with diazepam, however, no improvement on placebo. 2. 5/20 participants self-reported no improvement in spasticity on either diazepam or placebo. 3. 2/20 participants self-reported the best benefit from the placebo. 4. 8, 3, and 9 participants had preference for diazepam, placebo, and neither pill, respectively. 5. According to the observers' assessments, 13/20 participants showed a significant improvement in spasticity when on diazepam (difference of 5 or more cumulatively). One individual showed significant improvement on placebo.

Discussion

Oral baclofen

Despite the general acceptance and clinical experience of using oral baclofen to reduce spasticity in people with SCI, at least two systematic reviews have noted a relative paucity of high-quality studies (i.e., RCTs) demonstrating specific or comparative efficacy (Chou et al. 2004; Taricco et al. 2006). Taricco et al. (2006) conducted a Cochrane Review of all pharmacological interventions for spasticity following SCI. Only one study examining the effect of oral baclofen (Burke et al. 1971) met the review inclusion criteria (i.e., RCT with at least 50% of participants with SCI published up to July 2004). The reviewers deemed this study to have been relatively poor quality with small sample size (n=6) so did not provide a positive assessment of the efficacy of oral baclofen.

Since the 2006 Cochrane Review, two additional RCTs (Aydin et al. 2005, n=21; Chu et al. 2014, n=10) published demonstrating effective reduction in spasticity with oral baclofen as measured using the AS, PSFS, deep tendon reflex score, FIM and Functional Disability Scores, and EMG measures. An earlier RCT (Duncan et al. 1976) demonstrated reduced spasticity as measured by the AS and PSFS. Further support for the efficacy of oral baclofen was provided by a pre-post study by Nance (1994) in which baclofen was compared to clonidine and cyproheptadine in 25 subjects with SCI. In general, all three agents were shown to be effective in relieving spasticity with baclofen among the most effective for each of the measures. Chu et al. (2014; N=10) compared baclofen and tizanidine and reported that baclofen was preferentially effective for flexors and tizanidine for extensors. This finding suggests that tailoring of antispastic drug therapy to spasticity characteristics of specific individuals may be possible.

Yan et al. (2018) directly compared baclofen to botulinumtoxin A and reported trial participants' modified Ashworth scores (MAS) reflected significant anti-spasmodic performance of both baclofen and botulinumtoxin A at 2 weeks ($p=0.003$ and $p=0.02$, respectively) compared to baseline. At 4 weeks, the control group's MAS score was also significantly decreased ($p<0.001$ for all 3 treatments). However, at 6 weeks post treatment, only the botulinumtoxin A group had significantly reduced spasticity ($p>0.05$) compared to baseline. These results confirm the known immediate efficacy of baclofen that could also be susceptible to resistence development. On the other hand, this trial demonstrates the persistence of botulinumtoxin A neurotransmitter release inhibition. Interestingly, only the baclofen group was significantly improved functionally as assessed by the Disability Assessment Scale (DAS; $p=0.05$). However, the DAS was specifically developed for use in stroke, not SCI. Both baclofen and botulinumtoxin A administration produced side effects such as asthenia and sleepiness, and bronchitis and elevated blood pressure, respectively.

Luo et al. (2017) compared baclofen to tolperisone (a centrally acting muscle relaxant) for the treatment of spasticity secondary to SCI. As with the comparison to botulinumtoxin A, after initial significant efficacy, MAS continued to significantly decline by 6 weeks with the comparator (tolperisone). Thomas et al. 2010 attributes long-term use of baclofen with reduced muscle activity and maximal tetanic forces. Accordingly, Luo et al. (2017) surmise that long-term use of baclofen weakens the whole muscle that in turn introduces fatigue.

Arbaclofen placarbil is a prodrug of R-baclofen in an extended-release oral formulation that is well absorbed throughout the gastrointestinal tract (Lal et al. 2009). Efficacy and safety of arbaclofen placarbil was studied (Nance et al. 2011) and results indicated that 20/30mg of arbaclofen placarbil every 12 hours for 26 days, significantly improved Ashworth scores and reduced severity of spasticity ratings compared to the placebo group. However, there was no significant difference in muscle strength between the arbaclofen placarbil and placebo group. Chu et al. (2014) also reported that neither baclofen or tizanidine had a negative impact on strength and postulated that individual reported weakness secondary to drug administration by be due to decreased motivation secondary to drowsiness.

In contrast to these studies, a counter-therapeutic response to baclofen was found by Hinderer (1990). In this RCT (n=5) the effect of baclofen on spasticity was studied by examining the viscous stiffness (resistance torque) following a 5° sinusoidal ankle perturbation at 3-12 Hz. No difference was noted between baclofen and placebo on this measure. No other outcome measures were assessed. Chu et al. (2014) noted that baclofen had a stronger inhibitory effect on knee flexors. These studies illustrate one of the limitations in establishing the efficacy for any spasticity-relieving agent–the heterogeneity of reported outcomes and outcome measures used across studies (Chou et al. 2004; Taricco et al. 2006). Spasticity is multi-dimensional with a variety of clinical manifestations and much day-to-day and diurnal variation within an individual. A battery of measures is needed to obtain valid and reliable measurement of spasticity within a given trial (Priebe et al. 1996). The range of studies outlined in the present review demonstrates various physiological, clinical and functional measures, yet there is minimal consistency of outcome measure selection across trials.

Interesting findings from a retrospective analysis of a single provider's 25-year individual database (Veerakumar et al. 2015, n=115) revealed that baclofen use varied with etiology of the SCI, time since injury and concomitant antispasmodic use. These findings provide further evidence that baclofen use requires careful dose titration and monitoring based on the unique spasticity profile of individual individuals.

Benzodiazepines

Although Valium proved to be superior to Amytal and placebo for controlling SCI related spasticity, only 2/22 participants did not require other treatment methods (e.g. physiotherapy, hydrotherapy) to fully control their spasticity (Corbett et al. 1972, RCT). Neill et al. (1964) confirmed anti-spasmodic efficacy (compared to placebo) on 13/20 people with SCI and the prominence of drowsiness as the most frequent side effect. However, Neill et al. concluded that the greatest benefit was recorded in participants with traumatic cervical SCI. This latter claim should be interpreted with caution given the small cohort of participants (N=20). Diazepam's effectiveness for treatment of spasticity in people with SCI was further supported with an observational survey of 35 participants where 30 reported good to excellent relief. Only 3 participants complained of drowsiness but did not require discontinuation or diminution of the dosage.

Conclusions

There is Level 1a evidence that oral baclofen improves muscle spasticity secondary to SCI. This conclusion is based on the results from eight RCTs (Yan et al. 2018, Luo et al. 2017, Chu et al. 2014; Nance et al. 2011; Aydin et al. 2005; Duncan et al. 1976; Burke et al. 1971, Jones et al. 1970) although is minimally muted by a single negative finding from one small RCT (Hinderer et al. 1990) with an overall lack of homogeneity in outcome measures and study participants. Additional evidence from a prospective controlled trial (Dicpinigaitis et al. 2000), a cohort (Veerakumar et al. 2015) and pre-post study (Nance 1994) also provide support for the use of oral baclofen in reducing spasticity.

There is Level 1b evidence (Yan et al. 2018, N=336, Luo et al. 2017, N=150) supporting the immediate effect of baclofen for the treatment of spasticity but that at 6 weeks post treatment, baclofen is inferior to botulinumtoxin A and tolperisone.

There is level 1b evidence (Corbett et al. 1972, RCT, N=9) supported by 2 other trials (level 2 evidence (Level 2, Neill et al. 1964, Cohort, N=20) confirming that valium (diazepam) is effective in decreasing spasticity secondary to SCI.

Key Points

Oral baclofen reduces muscle spasticity in people with SCI.

Oral baclofen is inferior to botulinumtoxin A injection and oral tolperisone by 6 weeks of spasticity treatment in people with SCI.

Diazepam is effective for the treatment of spasticity secondary to SCI.

5.2 Intrathecal Baclofen for Reducing Spasticity

Programmable pumps can be surgically implanted for the treatment of spasticity in SCI. The most commonly delivered drug is intrathecal baclofen. Many of the studies looking at intrathecal baclofen use for spasticity combine multiple causes of spasticity (SCI, multiple sclerosis and cerebral palsy) which makes the results difficult to interpret for SCI specifically. Several of the studies in this section include studies where fewer than 50% of the individuals have SCI. While these individual studies may not meet the formal SCIRE criteria, their importance for inclusion emerged by representing a larger number of individuals with spinal cord injuries when grouped together.

Outcome measures for intrathecal baclofen include direct spasticity measures such as the Ashworth and MAS and PSFS, and indirect measures such as functional outcome measures, complication rates and quality of life as well as cost-benefit analyses.

While oral baclofen can be useful in the treatment of spasticity, the use of high doses can lead to adverse effects, most commonly over sedation. Delivering baclofen directly into the cerebral spinal fluid allows a higher concentration of baclofen administration to the spinal cord with

fewer systemic side effects. Intrathecal baclofen is most effective in treating lower extremity spasticity and less so for upper extremity spasticity. However, the location of the intrathecal catheter tip can be adjusted at the time of surgical implantation depending on the clinical presentation with higher tip locations (cephalad at T6, compared to T10-L2) being used in individuals with higher injuries (Burns & Meythaler 2001). The pump can be programmed to provide a steady dose of intrathecal baclofen throughout the day or programmed to include boluses at certain times of the day. Intrathecal baclofen is usually only considered after 1 year post-SCI.

Potential complications from intrathecal baclofen treatment include overdose, withdrawal and surgical complications. Disruption or malfunction of the catheter-pump system is a common cause of withdrawal and can result in an acute life-threatening baclofen withdrawal syndrome. The signs and symptoms of acute intrathecal baclofen withdrawal include increased spasticity, itching, fever, altered mental status, rhaobdomyolysis, seizures, reversible cardiomyopathy, and death.

Table 13. Intrathecal Baclofen for Reducing Spasticity

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Ordia et al. 1996 USA Phase 1–RCT Phase 2-Pre-Post PEDro=6 N=66	**Population:** MS, SCI (n=27), Other causes of spinal spasticity. **Intervention:** Phase 1-Patients were randomized to receive normal saline or test dose intrathecal baclofen. Phase 2-Intrathecal baclofen pump implantation. Some individuals (n=10) were studied for costs study comparing 1 yr pre-and post pump implantation. **Outcome Measures:** Ashworth scores (AS), Spasm Frequency Scale (SFS), Drug tolerance, Treatment complications, Cost-benefit analysis.	1. Test dose: All 66 individuals responded positively to test bolus dose and none of the 9 randomized individuals responded to placebo. 2. Long-term: A decrease in AS and improvement in decreased from 4.3 pre-operatively to 1.4 ($p<0.0005$) at last follow-up, SFS improved from 3.6 to 0.5 ($p<0.0005$) at last follow-up. 3. An average reduction in 2.7 hospitalization days per individual was found for a cost savings of $2500 per day institutional costs (or $6700 per patient) with the cost of the treatment paid back in <2.5 yr.
Nance et al. 1995 Canada Phase 1–RCT Phase 2–Pre-Post PEDro=9 N=7	**Population:** Injury etiology: SCI=5, MS=2; Level of injury: C5-T8; Level of severity: Frankel grade: A-B. **Intervention:** Phase 1-A daily bolus of placebo or baclofen (12.5 to 100 mcg titrated dose). Phase 2-Intrathecal baclofen pump implantation.	1. Test dose: Intrathecal baclofen 50 mcg decreased the average AS. 2. Long-term: A decrease in AS mean=1.8 ($p<0.005$) and SFS mean=0.8 ($p<0.005$) and an improved leg swing in pendulum test. No change in bladder or respiratory function. Improvements in ADLs noted.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Outcome Measures: Ashworth Scale (AS), Spasm Frequency Scale (SFS), Pendulum test, Hospital Cost Analysis, Bladder and respiratory function, Adverse events.	3. n=6 were included in the cost analysis. Overall savings of $153,120 were calculated based on a reduction in hospital related spasticity treatment following pump implantation. 4. Follow-up ranged from 24 to 41 mo.
Coffey et al. 1993 USA Phase 1–RCT Phase 2-Pre-Post PEDro=8 N=75	**Population:** Injury etiology: SCI=59, MS/Other spinal pathology=16. **Intervention:** Phase 1-Randomized trial test injection baclofen versus placebo with up-titration from 50 mcg to 100 mcg. Phase 2-Intrathecal baclofen pump implantation. **Outcome Measures:** Ashworth Scale (AS), Spasm Frequency Scale (SFS).	1. Test dose: 88 individuals (94.6%) responded to the test dose with a decrease in AS and SFS. No individuals responded to placebo. 2. Long-term: For the SCI group, the AS and sfs decreased post-pump. 3. Patients were followed for 5-41 mo (mean 19 mo).
Kravitz et al. 1992 USA RCT Crossover PEDro=7 N=6	**Population**: Spastic Individuals (n=6): Mean age=38.33±5.34yr; Gender: males=4, females=2; Etiology: SCI=4, Multiple Sclerosis=2; Level of injury: C=3, T=1; Time since injury=NR; AIS scale: NR. **Intervention:** This RCT crossover consisted of two conditions with no washout period; 1) baclofen, and 2) saline (placebo). A subcutaneous baclofen pump system was implanted into the lumbar subarachnoid space of all participants. Participants received infusion over two nights. Saline or baclofen was infused on alternating nights. Subjects were monitored over two consecutive nights using a polysomnography. Electromyography (EMG) recordings of the tibialis anterior, hamstrings, quadriceps and triceps surae were conducted.	1. There was a significant interaction effect between treatment and time of EMG activity (i.e., before arousal, without arousal, and after arousal) (p=0.037). 2. The main effects of the treatment and time were not significant (p=0.06; p=0.22, respectively). 3. Pairwise comparisons revealed a significant reduction in EMG activity when on baclofen after arousal (p=0.019). However, there was no significant between-group difference without arousal or before arousal (p>0.05).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Outcome Measures: EMG Activity Index (EMG events/hr).	
Hugenholtz et al. 1992 Canada RCT Crossover PEDro=6 N=6	**Population:** Injury etiology: MS=2, SCI=4. **Intervention:** Crossover trial of intrathecal baclofen or saline over the course of 11 days followed by a 30-day trial of daily intrathecal baclofen bolus injections. **Outcome Measures:** Effects of spasticity on life questionnaire, Modified Ashworth Scale (MAS), Spasm Frequency Score (SFS), Reflex score, Passive range of motion (ROM), Muscle strength testing, A timed dressing evaluation, the Smith Hand Function evaluation, Urodynamic studies, Neurophysiologic studies.	Crossover phase 1. Baclofen had a significant effect on lower limb tone and reflexes, trunk and leg spasms, questionnaire scores and passive ROM in upper and lower limb joints ($p<0.05$). 2. A clinically significant placebo effect was observed for reduced tone, spasms and reflexes in 1 subject. 30-day bolus phase: 3. Subjects sustained the clinically significant effects of baclofen on tone, spasms and lower limb passive ROM. However, the magnitude of the effect decreased after 30 days. The effects on passive ROM in upper limb joints and lower limb reflexes were lost after 30 days ($p<0.05$). 4. Scores in the Smith Hand Function Evaluation & Dressing Test Evaluation did not change. Urodynamic results (bladder volume) improved in 2 subjects.
Loubser et al. 1991 USA Phase 1 – RCT Phase 2 – Pre-Post N=9	**Population:** Gender: males=9, females=0; Injury etiology: traumatic SCI=9; Level of injury: C2-T12. **Intervention:** Test dose: 5-day infusion of varying doses of baclofen and a single 12 hr placebo infusion over a 5-day period to determine optimum intrathecal baclofen dosage. Long-term: Intrathecal baclofen pump implantation. **Outcome Measures:** Ashworth scale (AS), Neurological reflex scale, Evaluation of functional abilities, Evaluation of personal independence, Global Assessment Scale (GAS).	1. Test dose: A decrease was seen in optimal reflex score ($t=7.69$, $p<0.001$) and the AS with baclofen grade ($t=6.05$, $p<0.001$), between placebo and optimal reflex score a change was noted ($t=3.68$, $p=0.01$) and Ashworth grade ($t=6.0$, $p<0.001$) and between placebo and control Ashworth grade ($t=2.95$, $p=0.02$). At optimum intrathecal baclofen dosage, 8/9 individuals benefited in functional evaluations. 2. Long-term: Only 7 subjects participated. The AS and mean reflex score decreased from 3.79±0.69 to 2.00±0.96 ($t=12.9$, $p=0.001$). The mean reflex score decreased from 3.85±0.62 to 2.18±0.43 ($t=6.76$, $p=0.001$). 3. Follow-up ranged from 3-22 mo.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Penn et al. 1989 USA Phase 1–RCT Phase 2-Pre-Post PEDro=9 N=20	**Population:** Injury etiology: MS=10, SCI=10; Level of injury: C5-T9. **Intervention:** Phase 1-A 3-day infusion of saline or intrathecal baclofen (100 mcg/mm) via programmable pump. Phase 2–An open label long-term observation of intrathecal baclofen. **Outcome Measures:** Ashworth scale (AS), Spasm Frequency Scale (SFS), Laboratory analysis of motor control (EMG), Individual impression.	1. Test dose: In both the SCI and MS groups, the period of baclofen administration could be identified from the saline administration period by the improvement in AS and SFS (<0.01). Overall (all subjects combined), the AS decreased from 4.0±1.0 to 1.2±0.4 (p=0.0001) and the SFS decreased from 3.3±1.2 to 0.4±0.8 (p=0.0005). 2. Long-term: For all individuals combined, the AS and SFS decreased. 3. Follow-up ranged from 10-33 mo (average 19).
Stetkarova et al. 2015 Czech Republic Post-Test N=39	**Population:** Age range: 21-56 yr; Gender: males=24, females=15; Injury etiology: chronic SCI=24, multiple sclerosis=15. **Intervention:** Intrathecal baclofen pump implantation. **Outcome Measures:** Complications of intrathecal baclofen pumps including frequency and severity of intrathecal baclofen withdrawal syndrome, Modified Ashworth Scale (MAS).	1. A total of 54 pumps were implanted in 39 individuals 24/54 pumps had complications and 14 (26%) of these complications were due to catheter problems. Other causes of complications included pump explantation (2 individuals), infection (4 individuals), CSF leakage (2 individuals), seroma (1 patient), skin dehiscence (1 patient). 2. Eight individuals developed baclofen withdrawal syndrome on a total daily dose of ITB in the range of 90-420 µg/day (average of 189 µg/day). Seven of these individuals had withdrawal syndrome due to catheter complications. 3. All but one individual with baclofen withdrawal symptoms developed increased MAS scores up to 3-4.
Calabro et al. 2014 Italy Pre-Post N=20	**Population:** Mean age: 34.9 yr; Gender: males=20, females=0; Injury etiology: traumatic SCI=10, spinal cord vascular lesion=3, degenerative diseases=6, syringomyelia =1; Mean time since injury: 6.1 yr. **Intervention: Individuals** were administered intrathecal baclofen in the subarachnoid space up to level T8. Outcomes	1. There was a significant decrease in IIEF median scores from before implantation to after implantation. 2. There was a correlation between lower IIEF scores and higher intrathecal baclofen doses. 3. MAS, SFS, VAS and HDRS improved significantly 2 mo after implantation (p<0.0001).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	were assessed before pump implantation and 2mo after. **Outcome Measures:** International index of erectile function (IIEF) to measure sexual function before and after pump implantation, Modified Ashworth Scale (MAS), Spasm frequency scale (SFS), Visual analog scale (VAS), Hamilton depression rating scale (HDRS), Diagnostic impotence questionnaire (DIQ).	
Heetla et al. 2010 Netherlands Pre-Post N=4	**Population:** Age range: 20-49 yr; Injury etiology: SCI, MS, CP; Level of injury: T6-T10. **Intervention:** Pulsatile bolus infusion of intrathecal baclofen on a daily dose. **Outcome Measures:** Modified Ashworth Scale (MAS).	1. Switching from continuous to pulsatile bolus infusion resulted in a decrease of the daily intrathecal baclofen dose. 2. The clinical effect could be kept stable, without introducing adverse events.
Korenkov et al. 2002 Germany Pre-Post N=12	**Population:** Gender: males=12, females=0; Injury etiology: SCI=12. **Intervention:** Intrathecal baclofen pump implantation. **Outcome Measures:** Ashworth Scale (AS), Spasm Frequency Score (SFS).	1. Significant post-operative reduction of muscle tone and SFS ($p<0.05$). AS decreased from 4.2 to 2.2 in the lower limbs and from 2.2 to 1.0 in the UE. 2. Decrease in AS. 3. Self-care, nursing care, PT, transfers, sitting tolerance, muscle pain and sleeplessness were all reported as improved but no measures were reported.
Denys et al. 1998 France Pre-Post N=9	**Population:** Gender: males=9, females=0; Injury etiology: MS=4, SCI=5; Level of injury: C4-T11=9; Level of severity: AIS A-C. **Intervention:** Intrathecal baclofen pump implantation. **Outcome Measures:** Genitosexual function self-report questionnaire.	1. No decrease in libido. 2. The ability of subjects to achieve reflexogenic (9/9) or psychogenic erections (3/9) was maintained but 8/9 subjects reported impaired erection after intrathecal baclofen. 3. 5/9 subjects reported decreased penile rigidity with 3/9 unable to achieve intercourse after intrathecal baclofen. 4. 6/9 subjects reported decreased erection duration. 2/9 reported increased erection duration.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		5. 3/3 subjects with ejaculatory function pre-pump reported loss of ejaculatory function (2/3) or more difficult ejaculation (1/3) post-pump. 6. At follow-up, impaired erection was reported by nine individuals, and rigidity reduction was reported in 5 individuals. 7. In five individuals, maximum erection duration was decreased. 4/5 reported duration of less than 5 min. Two individuals reported an increase in maximum erection duration when using baclofen. 8. Three individuals could reach ejaculation without stimulation. Two individuals lost the ability to ejaculate during treatment; however, it returned when treatment was discontinued. 9. Mean follow-up was 44mo.
Azouvi et al. 1996 France Pre-Post N=18	**Population:** Injury etiology: MS=6, SCI=12; Level of injury: C5-T11; Level of severity: Frankel A-D. **Intervention:** Intrathecal baclofen pump implantation. **Outcome Measures:** Ashworth Scale (AS), Spasm Frequency Score (SFS), Functional Independence Measure (FIM).	1. Improvement in AS, SFS and at 6 mo, AS was improved Z=-3.79 ($p<0.001$), SFS was improved Z=-3.78 ($p<0.001$). With FIM, the most dramatic improvements were seen in the 12 individuals with thoracic or low cervical lesions (FIM evolved from 50.9±9.7 to 76.3±14.5, Z=-3.06, $p<0.01$). The following items gained ≥2 FIM scores: bathing, dressing lower body, and the 3 items related to transfers. 2. Follow-up ranged from 9-72 mo (average 37.4)
Abel & Smith 1994 USA Pre-Post N=23	**Population:** Injury etiology: MS=6, SCI=17; Level of injury: C4-T12; Level of severity: AIS: A-D. **Intervention:** Intrathecal baclofen pump implantation. **Outcome Measures:** Ashworth Scale (AS) and Spasm Frequency Score (SFS).	1. Test dose: Decrease in AS and SFS. 2. Long-term: Decrease in AS 3. Follow-up ranged from 2-34 mo with average 16mo.
Ochs et al. 1989 Germany Pre-Post	**Population:** Injury etiology: MS=18, SCI=10.	1. Improvement in AS and SFS. Intrathecal baclofen influenced electrophysiological data.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
N=28	**Intervention:** Intrathecal baclofen pump implantation. **Outcome Measures**: Ashworth Scale (AS) and Spasm Frequency Scale (SFS), Electrophysiological data.	2. Follow-up up to 2 yr.
Parke et al. 1989 USA Pre-Post N=8	**Population:** Injury etiology: MS=4, SCI=4. **Intervention:** Intrathecal baclofen pump implantation. **Outcome Measures:** Ashworth Scale (AS), Muscle strength and modified PECS scale.	1. No statistical results were reported although all subjects showed an improvement in AS. Muscle strength did not change. Improvements were also noted in the PECS scores. 2. Follow-up was at least 6 mo.
Kawano et al. 2018 Japan Case Series N=34	**Population**: Spasticity of Spinal Origin (n=34): Etiology: SCI=29, Hereditary Spastic Paraplegia=3, Multiple Sclerosis=1, HTLV-1 associated myelopathy=1; Mean age=NR; Gender=NR; Level of injury=NR; Mean time since injury=NR; AIS scale=NR. **Intervention: Individuals** with spasticity of spinal origin were treated with surgical implantation of baclofen pump. Changes in spasticity and baclofen dose were recorded. Outcome measures were assessed before and after surgical implantation, as well as at follow up (M=6 yr, 11 mo). **Outcome Measures:** Ashworth score	1. Baclofen dose remained consistent over a long period of time for the majority of individuals. Few individuals had large fluctuations in dose. 2. There were significant decreases in Ashworth score after surgery and at follow up compared to before surgery.
Heetla et al. 2009 Netherlands Case Series N=37	**Population:** Gender: males=19, females=18; Injury etiology: traumatic SCI=10, MS=14, miscellaneous=13. **Intervention:** Prior history of use with intrathecal baclofen therapy, alter infusion mode. **Outcome Measures:** Ashworth Scale (AS), Dose titration, Co-medication, Drug-related side effects.	1. Baclofen dose increased in the first 18 mo after implantation ($p<0.05$), and then stabilized around a mean dose of 350 mcg per day. 2. Eight individuals (22%) developed tolerance, defined as a dose increase of >100 mcg per yr. 3. Altering the infusion mode from simple to complex continuous (n=6) had no effect on the development of tolerance.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		4. Pulsatile bolus infusion (n=1) and a drug holiday (n=2) were both effective in reducing the daily baclofen dose. 5. Pump-related complications occurred once per 10.5 yr of intrathecal baclofen treatment. 6. Drug-related side effects (mild) had an annual risk of 13.8%.
Boviatsis et al. 2005 Greece Case Series $N_{Initial}$=22, N_{Final}=21	**Population:** Injury etiology: MS=15, SCI=7; Level of injury: C4-T11=22. **Intervention:** Intrathecal Baclofen pump implantation. Subjects were implanted with an infusion pump delivering a continuous flow at a fixed rate of bolus intrathecal baclofen. **Outcome Measures:** Barthel Index (BI), Ashworth Scale (AS), Penn Spasm Frequency Scale (PSFS), Self-assessment pain scale.	1. The SCI group demonstrated a lower AS (4.57 to 2.57, p=0.0134) and a decrease in PSFS (3.71 to 1.28, p=0.00006) post pump insertion. 2. All individuals reported improved function after surgery with an increase in BI increased as a result of the treatment in the SCI group (from 17.1 before to 50.7 after treatment, p=0.0073). Dressing and transfers were 2 activities that improved significantly (p=0.0465 and p=0.0016, respectively). The degree of improvement was different according to level of lesion. 3. The self-assessment pain scale revealed a limited improvement in pain (p=0.0941). 4. Follow-up ranged from 9-55 mo (median 35 mo).
Plassat et al. 2004 France Case Series $N_{Initial}$=41, N_{Final}=37	**Population:** Injury etiology: SCI=17, MS and cerebral spasticity=24. **Intervention:** intrathecal baclofen pump placement. **Outcome Measures:** Visual analog scale (VAS), Satisfaction score Locomotion, Pain, Sleep, Ashworth Scale (AS).	1. At final assessment average VAS satisfaction with the pump was 7.4. 2. Ambulation status was unchanged in 85%. Improvements were noted in pain and sleep and AS decreased. 3. Follow-up average 4 yr.
Zahavi et al. 2004 Netherlands Case Series $N_{Initial}$=38, N_{Final}=21	**Population:** Injury etiology: SCI=6, MS and other spinal spasticity=22. **Intervention:** Intrathecal baclofen pump implantation. **Outcome Measures:** Ashworth Scale (AS), Spasm Frequency	1. Improvement in AS from baseline 2.82 to final assessment 0.91 ($p<0.05$) and SFS from baseline 1.79 to final assessment 0.67 ($p<0.05$). 2. Worsening in EDSS, AI and ISS (all $p<0.05$) compared with baseline (in progressive and non-progressive

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Score (SFS), Extended Disability Status Score (EDSS), Ambulation Index (AI), Injury Severity Score (ISS), Sickness Impact Profile (SIP), Hopkins symptom check list.	groups of individual disabilities). Worsening in level of disability (EDSS and ISS $p<0.05$) and the psychosocial aspect of the perceived health status scale (SIP) ($p<0.05$) were seen when compared from baseline and at 26 wk. 3. Follow-up ranged from 66 to 108 mo with a mean of 84.9 mo.
Avellino & Loeser 2000 USA Case series N=62	**Population:** Mean age: 38.6 yr; Gender: males=35, females=27; Injury etiology: SCI=38, MS=17, other spinal=7, traumatic brain injury=5, cerebral palsy=4; Level of injury: C=20, T=8. **Intervention:** Retrospective chart review was conducted on individuals implanted with intrathecal baclofen treatment for spasticity were retrospectively reviewed. **Outcome Measures:** Ashworth Score (AS), Spasm Frequency Score (SFS), Dosage, Complications.	1. Significant improvement at follow up (average 33.6 mo) was seen in the final AS and the SFS for individuals with SCI ($p<0.001$). 2. Individuals with SCI were administered an average dosage of about 500 mcgday. 3. 36% of individuals with SCI presented with complications. 4. Catheter failure was the most common complication.
Penn et al. 1992 USA Case Series N=66	**Population:** Injury etiology: MS=34, SCI=32. **Intervention:** Intrathecal baclofen pump implantation. **Outcome Measures:** Ashworth Scale (AS) and Spasm Frequency Scale (SFS).	1. Test dose: 64/66 individuals responded to a test dose of intrathecal baclofen with a decrease in either AS or SFS. 2. Long-term: 84% treated adequately for spasticity. 3. Follow-up average 30 mo (up to 81 mo).
Broseta et al. 1990 Spain Case Series N=19	**Population:** Injury etiology: MS, cerebral spasticity, SCI=5; Level of injury: T3-L1. **Intervention:** Implantation of programmable pump. **Outcome Measures:** Ashworth Scale (AS), Spasm Frequency Scale (SFS), Reflex assessment, Cystomanometry and perineal electromyography for assessment of neurological bladder dysfunction,	1. Reduction in AS and SFS improvement in hyperreflexia, objective improvements in transfer activities and skilled acts, improved comfort, reduced H/M ratio and improved bladder function. 2. Mean follow-up 11 mo.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Electrophysiological H/M ratio, Total dose.	
Gunnarsson and Samuelsson 2015 Sweden Observational N=14	**Population:** Mean age: 51.0 yr; Gender: males=8, females=6; Injury etiology: SCI=8, cerebral palsy=2, multiple sclerosis=4. **Intervention:** All individuals received intrathecal baclofen (ITB) treatment for a mean of 5.9 yr. Using an interview guide, open ended interviews concerning individuals' experiences with ITB treatment were conducted. Experiences were divided into 5 main categories: procedures before treatment, effect of ITB on daily life and activities of daily living (ADL), continuous follow-up, expected and unexpected consequences of ITB and overall satisfaction with ITB. **Outcome Measures:** Interview responses.	1. Overall individuals were satisfied with intrathecal baclofen treatment and all would choose to have a pump implanted again. 2. Patients expressed a need for more information reqarding steps in the treatment process and treatment expectations.
Borrini et al. 2014 France Observational N=158	**Population:** Mean age: 45.7 yr; Gender: males=56, females=102; Injury etiology: SCI=67, multiple sclerosis=45, brain injury=33, familial spastic paraparesis=7, other=6. **Intervention: Individuals** undergoing intrathecal baclofen therapy were implanted with spinal catheter tips in their lower thoracic region (T10-12). Data was analyzed from January 1 to December 31 2010, individuals were classified as surgical if they received an implant during 2010. **Outcome Measures:** Frequency and type of adverse event (AE): device-related AE, surgical-related AE, and drug-related AE.	1. 128 individuals underwent implantation before 2010 (non-surgical), and 30 during 2010 (surgical) of which 20 were new implants and 10 were replacements. 2. The total number of AEs was 38 of which 18 were defined as serious. 3. 28 individuals had at least one AE, 8 individuals had two AEs and 1 individual had three AEs. 4. 53% were surgical-related, 29% were device-related and 18% were drug-related. 5. Overall incidence rate of AEs per mo was 0.023: 0.012 for surgical-related AEs, 0.007 for device-related AEs and 0.004 for drug-related AEs. 6. The incidence rate of serious AEs per mo was 0.011. 7. 58% of AEs occurred during the first mo following surgery.

Discussion

Spasticity

There were six studies employing an RCT design to evaluate the effects of intrathecal baclofen in SCI. Although these studies are small and combine different etiologies of spasticity, they do provide a limited body of level 1 evidence to support the use of intrathecal baclofen test doses to decrease spasticity in SCI as measured by AS and spasm frequency score (Penn et al. 1989; Loubser et al. 1991; Coffey et al. 1993; Nance et al. 1995; Ordia et al. 1996, Hugenholtz et al. 1992).

Only one study (Kravitz et. al. 1992) examined the effects of intrathecal baclofen on the neurophysiological effects on mucle. They looked at EMG activity in six subjects in a double-blind placebo control crossover design. All six subjects had SCI. They noted a significant reduction in nocturnal EMG activity while on intrathecal baclofen. This was a small study and the study did not look at any correlation with spasticity or daily activity outcomes.

It is unlikely that RCTs will be undertaken to examine the long-term effectiveness of intrathecal baclofen given the effectiveness of test doses. However, several level 4 studies support the long term use of intrathecal baclofen to decrease spasticity with the most frequently used outcome measures being the AS and PSFS (Heetla et al. 2009; Ochs et al. 1989; Penn et al. 1989; Broseta et al. 1990; Loubser et al. 1991; Penn et al. 1992; Coffey et al. 1993; Abel & Smith 1994; Nance et al. 1995; Ordia et al. 1996; Korenkov et al. 2002; Plassat et al. 2004; Boviatsis et al. 2005; Avellino Loeser 2000; Heetla et al. 2010 and Kawano et. al. 2018). Most recently Kawano conducted a retrospective chart review on 34 individuals with spasticity due to various spinal cord disorders. All the subjects were recieving long-term baclofen. 29 of the 34 subjects had SCI. The data collected showed an average reduction in the ashworth's score of 1.92 and an average dose of intrathecal baclofen. The average followup time period was greater than 6 years and the average dose fo baclofen was 230.5 ucg per day. This review supported low complication rates and a stable dose of intrathecal baclofen in most of the individuals. This study did not include any references to function or quality of life. The effects of intrathecal baclofen are more pronounced in the lower extremities than the upper extremities (Korenkov et al. 2002).

The systematic review by McIntyre et al. (2014) summarizes the evidence from a pooled subject sample size of 162 individuals. All eight of the studies included in the review provided level 4 evidence that intrathecal baclofen decreases spasticity with a decrease in MAS from 3.1 to 4.5 at baseline to 1.0 to 2.0 at follow-up. Over time, there was an increase in the range of average daily dosing in these subjects from 57 to 187 mcg/day at baseline to 219 to 536 mcg/day at follow-up. Follow-up periods ranged from five to 41 months.

Table 14. Summary of Intrathecal Baclofen RCTs for Reducing Spasticity–Spasticity Outcomes

Author Year Total Sample Size	Methods	Outcome
Ordia et al. 1996 $N_{Initial}$=66, N_{Final}=57 (SCI=27)	**Test dose:** n=9 individuals were randomized to receive normal saline or test dose intrathecal Baclofen. Subsequent test doses were not open label. **Long-term:** Intrathecal baclofen pump implantation.	**Test dose:** All 66 individuals responded positively to test bolus dose and none of the 9 randomized individuals responded to placebo. **Long-term:** A significant decrease in Ashworth score and spasm frequency scale at last follow-up
Nance et al. 1995 $N_{Initial}$=7 N_{Final}=6 (SCI=5)	**Test dose:** A daily bolus of placebo or baclofen (12.5 to 100mcg titrated dose). **Long-term:** Intrathecal baclofen pump implantation.	**Test dose:** Intrathecal baclofen 50 mcg decreased the average Ashworth score. **Long-term:** A significant decrease in Ashworth score and spasm frequency score and an improved leg swing in pendulum test.
Coffey et al. 1993 N=75 (SCI=59)	**Test dose:** Randomized trial test injection baclofen versus placebo with up-titration from 50 mcg to 100 mcg. **Long-term:** Intrathecal baclofen pump implantation.	**Test dose:** 88 individuals (94.6%) responded to the test dose with a decrease in Ashworth and spasm scale. No individuals responded to placebo. **Long-term:** For the SCI group, the Ashworth score and spasm score decreased post-pump.
Hugenholtz et al. 1992 N=6 (SCI=4)	**Test dose:** Randomized trial test injection baclofen versus placebo over 11 days. **Long-term:** 30-day trial of daily intrathecal baclofen bolus injections.	**Test dose:** Baclofen had a significant effect on lower limb tone and reflexes, trunk and leg spasms, questionnaire scores and passive range of motion in upper and lower limb joints ($p<0.05$). A clinically significant placebo effect was observed for reduced tone, spasms and reflexes in 1 subject. **Long-term:** Subjects sustained the clinically significant effects of baclofen on tone, spasms and lower limb passive range of motion. However, the magnitude of the effect decreased after 30 days. The effects on passive range of motion in upper limb joints and lower limb reflexes were lost after 30 days ($p<0.05$).
Loubser et al. 1991 N=9 (SCI=9)	**Test dose:** 5-day infusion of varying doses of baclofen and a single 12-hr placebo infusion over a 5 day period to determine optimum intrathecal baclofen dosage. **Long-term:** Intrathecal baclofen pump implantation.	**Test dose:** At optimum intrathecal baclofen dosage, 8/9 individuals benefited in functional evaluations. **Long-term:** Only 7 subjects participated. The Ashworth score and mean reflex score decreased.

Author Year Total Sample Size	Methods	Outcome
Penn et al. 1989 N=20 (SCI=10)	**Test dose:** A 3-day infusion of saline or intrathecal baclofen (100 mcg/ml) via programmable pump. **Long-term:** An open label long-term observation of intrathecal baclofen.	**Test dose & Long-term:** Overall (all subjects combined), significant decreases for the Ashworth score and the spasm frequency scale decreased as a result of intrathecal baclofen.

Table 15. Systematic Reviews of Intrathecal Baclofen for Spasticity

Authors Year Country Date included in the review Score Total Sample Size	Method Level of evidence Questions	Conclusions
McIntyre et al. 2014 Canada Review of published articles up to and including February 2012 AMSTAR=7 N=8	**Method:** Comprehensive literature search of English RCT, prospective-controlled trials, cohort studies, case control studies, pre-post studies, post-test, case series, observational studies, clinical consensus and case reports. **Databases:** Pub Med, EMBASE, CINAHL. **Level of evidence:** *Level 1:* RCTs with PEDro ≥6; *Level 2:* RCTs with PEDro<6, Prospective-controlled trials and cohort studies; *Level 3*: case control studies; *Level 4*: pre-post studies, post-test and case series. *Level 5*: observational studies, clinical consensus and case reports. **Questions/measures/hypothesis:** Review the effectiveness of continuous spinal intrathecal baclofen in the treatment of spasticity more than 6 mo post SCI.	1. No RCTs and 8 non-RCTs met inclusion criteria for a pooled subject sample of 162 individuals. 2. All of the included studies provided level 4 evidence that ITB decreases spasticity with a decrease in MAS from 3.1-4.5 at baseline to 1.0 to 2.0 at follow-up. 3. There was an increase in the range of average daily dosing from 57 to 187 mcg/day at baseline to 219 to 536 mcg/day at follow-up. 4. Several complications were reported, especially due to catheters. 5. Follow-up periods ranged from 5 to 41 mo.

Functional Outcome

The effects of intrathecal baclofen on functional outcomes are much harder to summarize. Most studies are observational, pre-post studies with small numbers of individuals with SCI grouped in combination with several other diagnoses (most often multiple sclerosis). In addition, there is a lack of standardized outcome measures used to study functional outcomes. Finally, the majority of studies are not stratified by SCI level or AIS.

There are several observational studies looking at the short-term and long-term complication rates seen with intrathecal baclofen. Overall, complication rates are low and can be categorized

as medication related or pump related. However, complications can be severe and include death (Heetla et al. 2009; Loubser et al. 1991; Penn et al. 1992; Coffey et al. 1993; Abel & Smith 1994; Nance et al. 1995; Azouvi et al. 1996; Ordia et al. 1996; Stempien & Tsai 2000; Korenkov et al. 2002; Plassat et al. 2004; Avellino & Loeser 2000; Heetla et al. 2010).

Borrini et al. (2014) conducted a prospective study of adverse events in a mixed group of individuals with SCI (42%), multiple sclerosis (28%) and other diagnoses resulting in spasticity. Among 128 individuals with pre-existing pumps and 30 individuals undergoing new pump implantation, they found an overall incidence rate of event of 0.023 adverse events per month. The majority of adverse events (58%) occurred within the first month post surgery (new implantation or pump replacement). Furthermore, in a retrospective review of 130 individuals with SCI (38%) and multiple sclerosis (62%), Draulans et al. (2013) found an adverse event rate of 0.011 events per month with the majority (75%) of complications related to catheter problems. Finally, Stetkarova et al. (2015) reported a complication rate of 0.01 per month with an acute withdrawal rate of 0.004 per month.

Tolerance to intrathecal baclofen has also been observed (Ochs et al. 1989; Coffey et al. 1993; Abel & Smith 1994; Ordia et al. 1996; Heetla et al. 2009). Intrathecal baclofen has been shown to decrease sexual function as measured by self-reported penile rigidity, duration of erection and ejaculation. The effect of intrathecal baclofen on ejaculation appears to be reversible based on a small number of cases (Denys et al. 1998).

In a recent pre-post study, Calabro et al. (2014) demonstrated a decrease in erectile function in men following intrathecal baclofen pump implantation, especially at higher dosages.

Overall, there is level 4 evidence to suggest that functional outcomes as measured by scales such as Barthel index scale and FIM improve with intrathecal baclofen (Parke et al. 1989; Broseta et al. 1990; Nance et al. 1995; Azouvi et al. 1996; Ordia et al. 1996; Plassat et al. 2004; Boviatsis et al. 2005). However, it is notable that Zahavi et al. (2004) reports a small statistically significant deterioration in disability as measured by the expanded disability status scale, ambulation index and incapacity status scale. The article notes that this may not be a clinically significant deterioration (Zahavi et al. 2004). Loubser reports the potential for decreased functional outcomes especially with respect to ambulatory status in individuals who may depend on their spasticity for ambulation (Loubser et al. 1991).

Finally, in a recent qualitative study by Gunnarsson and Samuelsson (2015), individuals reported an overall satisfaction with intrathecal baclofen treatment and all 14 individuals stated that they would undergo pump implantation again.

Table 16. Summary of Intrathecal Baclofen Observational Studies for Reducing Spasticity–Functional Outcomes

Author Year Total Sample Size	Methods	Outcome
Boviatsis et al. 2005 N=22 (SCI=7)	**Intervention:** Intrathecal baclofen pump implantation. Subjects were implanted with an infusion pump delivering a continuous flow at a fixed rate of bolus intrathecal baclofen.	All individuals reported improved function after surgery but the degree of improvement was different according to level of lesion.
Azouvi et al. 1996 N=18 (SCI=12)	**Intervention:** Intrathecal baclofen pump implantation.	Improvement in FIM at 6 mo ≥2 FIM scores: bathing, dressing lower body, and the 3 items related to transfers. Most improvement in 12 individuals with thoracic or low cervical lesions.
Plassat et al. 2004 N=41 (SCI=17)	**Intervention:** Intrathecal baclofen pump placement.	Improvements were noted in pain and sleep and Ashworth score decreased.
Zahavi et al. 2004 N=38 (SCI=6)	**Intervention:** Intrathecal baclofen pump implantation.	Worsening in EDSS, AI and ISS and the psychosocial aspect of the perceived health status scale (SIP) were seen when compared from baseline and at 26 wk.
Korenkov et al. 2002 N=12 (SCI=12)	**Intervention**: Intrathecal baclofen pump implantation.	Self-care, nursing care, PT, transfers, sitting tolerance, muscle pain and sleeplessness were all reported as improved but no measures were reported.
Loubser et al. 1991 N=9 (SCI=9)	**Test dose:** 5-day infusion of varying doses of baclofen and a single 12 hr placebo infusion over a 5-day period to determine optimum intrathecal baclofen dosage. **Long-term:** Intrathecal baclofen pump implantation.	At optimum intrathecal baclofen dosage, 8/9 individuals benefited in functional evaluations.
Broseta et al. 1990 N=19 (SCI=5)	**Intervention:** Implantation of programmable pump.	Objective improvements in transfer activities and skilled acts, improved comfort, reduced H/M ratio and improved bladder function
Parke et al. 1989 N=8 (SCI=4)	**Intervention:** Intrathecal baclofen pump implantation.	Improvements were noted in the PECS scores.

Cost-Effectiveness

There has been one prospective study that performed a cost analysis for intrathecal baclofen pumps but this study did not meet SCIRE criteria for inclusion (i.e., <50% SCI subjects). However, without other cost analysis studies involving individuls with SCI, findings by Postma

(1999) are presented here since intrathecal baclofen cost effectiveness is an important consideration. Postma (1999) studied 33 subjects with multiple sclerosis and SCI and found subjects who received a pump had higher direct medical costs than subjects who did not receive a pump. However, Postma (1999) concluded that the improvement in quality of life in subjects who received a pump more than justified the direct costs associated with the pump.

A more recent review of intrathecal baclofen cost analysis, which was funded by a pump manufacturer, Medtronic, noted significant cost benefit, proportionate to the duration of pump use (Saulino et al. 2015). Again, this review did not meet the SCIRE criteria for inclusion (i.e., <50% individuals with SCI). To illustrate the potential cost savings of intrathecal baclofen treatment, Saulino et al. (2015) reported that by 7 years post pump implant, the average cumulative savings was more than USD $22,000 per patient.

There are two level 1b studies examining cost-effectiveness with the usage of intrathecal baclofen (Nance et al. 1995; Ordia et al. 1996). Ordia et al. (1996) did not specify whether SCI or individuals with multiple sclerosis were studied for cost-effectiveness, but the authors did report gross cost savings with intrathecal baclofen due to an overall reduction in hospital days post pump implantation (Ordia et al. 1996).

Nance et al. (1995) also combines subjects with multiple sclerosis and SCI subjects. In contrast to Ordia et al. (1996) who examined overall hospital days, Nance et al. (1995) examined only hospital days related to spasticity and found a net savings in costs related to pump implantation.

Table 17. Summary Intrathecal Baclofen for Reducing Spasticity – Cost Analysis

Author Year Total Sample Size	Methods	Outcome
Ordia et al. 1996 $N_{Initial}$=66, N_{Final}=57 (SCI=27)	**Long-term:** Intrathecal baclofen pump implantation. Ten individuals were studied for costs study comparing 1yr pre- and post pump implantation.	An average reduction in 2.7 hospitalization days per individual was found for a cost savings of $2500 per day institutional costs (or $6700 per patient) with the cost of the treatment paid back in <2.5 yr.
Nance et al. 1995 $N_{Initial}$=7, N_{Final}=6 (SCI=5)	**Long-term:** Intrathecal baclofen pump implantation.	N=6 were included in the cost analysis. Overall savings of $153,120 were calculated based on a reduction in hospital related spasticity treatment following pump implantation.

Intrathecal Baclofen Withdrawal and Overdose

With sudden withdrawal of intrathecal baclofen, there is a risk of an acute life-threatening baclofen withdrawal syndrome. The signs and symptoms of acute intrathecal baclofen withdrawal include increased spasticity, itching, fever, altered mental status, rhaobdomyolysis, seizures and death.

Withdrawal can occur with human errors in pump programming, errors in pump refills (wrong concentrations or dosages) and with mechanical failures in pumps and/or catheters. Of note,

Miracle et al. (2011) reviewed varying types of imaging as an approach to the evaluation of intrathecal pump and catheter systems in the event of withdrawal symptoms. Individuals with intrathecal baclofen pumps need to be educated regarding the pump alarm sounds and the signs and symptoms of baclofen withdrawal so that they can seek early assessment and treatment. The differential diagnosis for baclofen withdrawal includes autonomic dysreflexia, neuromalignant syndrome and malignant hyperthermia (Coffey 2002).

Initial treatment for intrathecal baclofen withdrawal is the reestablishment of intrathecal baclofen treatment as soon as possible. If this is not possible, then oral baclofen, dantrolene and intravenous benzodiazepines are used to help manage the withdrawal syndrome (Coffey 2002).

Acute baclofen withdrawal syndrome shares many characteristics with serotonergic syndrome. Meythaler (2003) added cyproheptadine, a serotonin antagonist, to the management of acute intrathecal baclofen withdrawal in four subjects and found improvements in signs and symptoms of withdrawal.

Intrathecal baclofen overdose is less common and is most often due to errors at the time of pump refills or programming errors (Watve 2011). Symptoms include hypotonia, hypotension, somnolence, seizures and respiratory depression. Acute overdose is managed with cessation of baclofen treatment, supportive treatment and withdrawal of cerebrospinal fluid (and subsequent reduction of circulating intrathecal baclofen). Once intrathecal bacofen treatment has been stopped and the overdose symptoms have been treated, individuals need to be monitored closely for the development of of intrathecal baclofen withdrawal. Treatment with itrathecal baclofen should be resumed as early as possible.

Table 18. Treatment of intrathecal baclofen withdrawal and overdose

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Crawley et al. 2004 UK Pre-Post N=11	**Population:** N/R. **Intervention:** Low dose radioisotope procedure was used to investigate catheter failure in individuals with SCI with implanted drug delivery systems and uncontrolled spasm. **Outcome Measures:** Pump functioning.	1. 5 of 11 individuals had normal pump function; while 6 had a blocked catheter, 4 of which had a proximal block. 2. The isotope test was able to indicate the need for surgery and inspection of the equipment in 6 individuals, while avoiding surgery for 5.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Meythaler et al. 2003 USA Case Series N=4	**Population:** Age range: 32-49 yr; Gender: males=3, females=1; Injury etiology: SCI=3, cerebral palsy=1. **Intervention:** Individuals with intrathecal baclofen withdrawal were treated with 4 to 8mg of oral cyproheptadine every 6-8 hr in addition to oral diazepam every 6-12 hr, oral baclofen every 6 hr and/or ITB boluses. **Outcome Measures:** Signs and symptoms of intrathecal baclofen withdrawal.	1. Addition of 4 mg of cyproheptadine treatment resulted in a relief of itching and signs of baclofen withdrawal.
Coffey et al. 2002 USA Case Series N=6	**Population:** Injury etiology: SCI=4, cerebral palsy=1, MS=1; Level of injury: C=3, T=1. **Intervention:** Charts were reviewed of individuals with severe ITB withdrawal. **Outcome Measures:** Withdrawal symptoms.	1. Most subjects (4/6) reported withdrawal symptoms by the 1st day of ITB cessation. 2. Treatment for withdrawal included oral baclofen, valium and enteral diazepam. 3. Misdiagnosis or late diagnosis resulted in the death of all individuals with SCI, while both individuas without SCI recovered.

Table 19. Systematic Reviews of Inthrathecal Baclofen Withdrawl and Overdose

Author Year Country Date included in the review Score Total Sample Size	Method Level of evidence Questions	Conclusions
Watve et al. 2011 United Kingdom Review of published articles between 1989-2010 AMSTAR=9 N=36	**Method:** Comprehensive literature search of articles on acute intrathecal baclofen therapy (ITB) overdose and ITB withdrawal. Articles were restricted to English and subjects >18 yr of age. **Databases:** MEDLINE, EMBASE, PUBMED, COCHRANE. **Level of evidence:** Case series, Case reports.	1. 13 studies on ITB overdose and 23 studies on ITB withdrawal were identified. 2. Cause and management of ITB overdose: a. Overdose was closely associated with filling procedures or is iatrogenic in 26/29 ipatients (refilling of the pump (n=14), intrathecal bolus (n=6), dose titration (n=2)).

	Question: Consolidation of available evidence and development of treatment pathways for acute ITB overdose and withdrawal states.	3. Cause and management of ITB withdrawal: a. Patients experience withdrawal symptoms close to their refill dates. 40% are catheter related, other causes are infected pump removal, empty reservoir volume, end of battery life and iatrogenic programming errors.

Conclusion

There is level 1a evidence (from six small-sample RCTs; Ordia et al. 1996; Nance et al. 1995; Coffey et al. 1993; Hugenholtz et al. 1992; Loubster et al. 1991; Penn et al. 1989) that bolus or test dose intrathecal baclofen decreases spasticity.

There is level 4 evidence (from several studies; see Table 13) that support the use of long-term intrathecal baclofen to decrease spasticity.

There is conflicting level 4 evidence (from several studies; see Table 15) that intrathecal baclofen may improve functional outcomes.

There is level 1b evidence (from two RCTs; Ordia et al. 1996; Nance et al. 1995) that intrathecal baclofen is a cost-effective intervention for treating post SCI spasticity.

There is level 4 evidence (from several studies; see Table 13) that complication rates with the long-term use of intrathecal baclofen are relatively low although complications can occasionally be severe.

There is level 4 evidence (from one case series; Meythaler et al. 2003) that adding cyprohetptadine to baclofen and benzodiazepines may be useful for the treatment of intrathecal baclofen withdrawal.

Key Points

Bolus or long-term intrathecal baclofen decreases spasticity and may improve functional outcomes with low complication rates and is a cost-effective intervention.

5.3 Effect of Medications Other Than Baclofen on Spasticity After SCI

Although baclofen is the most widely used drug for the treatment of spasticity in SCI, other drugs used as anti-spasmodics include tizanidine, cyproheptadine, diazepam, gabapentin, L-threonine, cannabis, dantrolene, clonidine (oral, transdermal and intrathecal), 4-aminopyridine (intravenous, intrathecal, immediate and sustained release) and others that will each be discussed briefly.

5.3.1 Tizanidine

Tizanidine is an orally-administered imadazoline-based compound that is widely used to reduce spasticity in a variety of conditions with most evidence for its effectiveness coming from trials with individuals with multiple sclerosis (Kaman et al. 2008). As an α_2-adrenergic agonist it acts at both a spinal and supraspinal level.

Table 20 Summary of Tizanidine Studies for Reducing Spasticity

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Chu et al. 2014 USA RCT Crossover PEDro=7 N=10	**Population:** Mean age: 48.9 yr; Gender: males=10, females=0; Level of severity: AIS C=4, AIS D=6; Mean time since injury: 138.7 mo. **Intervention:** Individuals were randomly allocated to the order in which they received oral administration of baclofen (30 mg), tizanidine (4 mg), and placebo (10 mg). Assessments were done at baseline and 90 to 120 min after the administration of each drug. **Outcome Measures:** Ankle stretch reflex torque, Isokinetic knee extension torque, Isometric knee extension torque.	1. There was a significant decrease in stretch reflex torque after tizanidine (p=0.034) but not baclofen (p=0.116) compared to placebo. 2. Peak knee flexion torque during extension decreased significantly after baclofen (p<0.001) but not after tizanidine (p=0.20) when compared to placebo. 3. Peak knee extension torque during flexion decreased significantly after baclofen (p=0.014) and tizanidine (p<0.001) compared to placebo. 4. No significant changes in isokinetic knee torque were shown for either drug compared to placebo (p=0.179). 5. Knee flexion torque significantly increased after tizanidine compared to placebo (p=0.033). 6. Compared to placebo, there was a significant increase in isometric knee extension torque for both baclofen (p<0.001) and tizanidine (p=0.001). 7. Changes in peak torque for baclofen (p=0.066) and tizanidine (p=0.99) did not differ significantly from placebo.
Nance et al. 1994 USA/Canada RCT PEDro=10 N=118	**Population:** SCI with moderate spasticity. **Intervention:** Tizanidine. **Outcome Measures:** Ashworth Scale (AS) (hip adductors, knee flexors/extensors–bilateral), Pendulum, modified Klein-Bell scale (ADL), Global evaluation of	1. AS: Tizanidine produced significantly (p<0.0001) greater decreases in muscle tone from baseline to end of titration (T3), end of plateau (P2) and end point (EP) as compared with placebo. 2. Pendulum: Tizanidine produced significantly greater decreases in the swing parameters from based to

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	antispastic efficacy, Adverse Events (AE).	T3 ($p<0.0135$), P2 ($p<0.0401$) and EP ($p<0.0038$) as compared to placebo. 3. Modified Klein-Bell showed no change from baseline in their ADL score. 4. Global changes were larger in Tizanidine versus Placebo but were not significant between groups. 5. AEs significantly greater in Tizanidine versus Placebo ($p=0.002$).
Mirbagheri et al. 2013b USA Prospective Controlled Trial N=50	**Population**: Individuals with SCI with ankle spasticity and incomplete loss of movement. Control group was age-matched to the intervention group. **Intervention:** Individuals were given 2 mg of tizanidine 4x/day for 4 wk. Dosage began low and progressively ramped up to the full dosage during the first wk. Outcomes were assessed at baseline, 1, 2 and 4 wk. **Outcome Measures:** Intrinsic ankle stiffness, Reflex ankle stiffness.	1. Tizanidine produced a decrease in reflex ankle stiffness over four wk. 2. Tizanidine produced a decrease in intrinsic ankle stiffness in some individuals. 3. A reduction in spasticity can decrease intrinsic ankle stiffness.
Mirbagheri et al. 2010 USA Prospective Controlled Trial N=38	**Population:** *SCI group (n=20):* Mean age: 37.6 yr; Level of injury: >T10; Level of severity: AIS C/D; Mean time since injury: 8.5 yr. *Control group (no SCI; n=20).* **Intervention:** Intervention group-perturbations were applied to the spastic ankle joint, a single oral dose of Tizanidine; Control-perturbations were applied to the spastic ankle joint, no dose of Tizanidine given. **Outcome Measures:** Joint torque, Peak torque, Reflex stiffness, Intrinsic muscle stiffness.	Treated Group: 1. Stretch evoked joint torque at the ankle decreased significantly ($p<0.001$). 2. The peak-torque was reduced between 15% and 60% among the spinal cord injured subjects, and the average reduction was 25%. 3. Reflex stiffness decreased significantly across a range of joint angles ($p<0.001$) after using tizanidine. 4. There were no significant changes in intrinsic muscle stiffness after the administration of tizanidine.
Mathias et al. 1989 UK Pre-Post N=10	**Population:** Injury etiology: SCI=10. **Intervention**: Single-dose (8 mg), tizanidine. Three pre-drug measurements 15 min apart	1. AS: peak reduction between 1-1.5 hr ($p<0.05$) with spasticity returning to baseline by 4th hr; no rebound spasticity measured at 12 and 24 hr.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	after breakfast and 30 min equilibration. Observations continued at 0.5, 1.0, 1.5, 2.0, 3, 4, 5, 6, 12, 24 hr. These measurements were repeated on a separate occasion (except measurements of sedation and blood collection) without drug administration. **Outcome Measures:** Ashworth Scale (AS), Manual muscle testing, Vitals, Sedation, Pharmacokinetics (Pk), Adverse events (AE).	2. Muscle power: no effects on impaired or unimpaired muscles at any stage of the study. 3. No significant changes to vitals except with heart rate (decrease in HR; 0.05 after 1.5 hr) 4. Sedation: Sedation in tetras>paras but increased in both with considerable variability. Peak within first hr with gradual waning to fully awake by 3rd hr. 5. Pk–Plasma levels rose at 0.5 hr and peaked by 1 hr. At 6 hr, level was at 85% peak and still detectable but low levels at 12 and 24 hr. Plasma half-life was 2.7±0.06 hr. 6. AE: Sedation and dry mouth.

Discussion

A randomized, placebo-controlled trial specifically conducted to elucidate the anti-spasmodic effect of tizanidine revealed significant spasticity improvements in favour of tizanidine over placebo where Ashworth and Pendulum were the primary measures used ($p<0.0001$ and 0.002, respectively; Nance et al. 1994). Although this study represents level 1b evidence, it is noteworthy to mention that 34% of subjects who received study treatment and discontinued prematurely due to adverse events, lack of efficacy and other reasons not specified, were not included in the study analysis. Another single dose, pre-post test study (Mathias et al. 1989) presented evidence to corroborate the reduction in spasticity as measured by Ashworth and furthermore revealed that muscle power was not affected at any stage in the study. That tizanidine did not have a negative impact on muscle strength was also reported by Chu et al. (2014). Tizanidine was found to have a stronger inhibitory effect on knee extensors and plantar flexors when compared to baclofen (Chu et al. 2014). The reverse was true for antispastic effects on knee flexors (Chu et al. 2014). More specifically, the impact of tizanidine on the spastic muscle was examined in a non-RCT (Mirbagheri et al. 2010) where there was an average of 25% reduction in peak-torque in the SCI subjects. Significant decreases in reflex stiffness post-tizanidine were found but not in intrinsic muscle stiffness. The latter was clarified in subsequent work of Mirbagheri et al. (2013) where several spasticity reduction patterns were observed: continuous reduction over the 4-week treatment period; more pronounced reduction during the first week of treatment, significant reduction only over time; or no improvement in intrinsic stiffness. This suggests that tizanidine reduces reflex stiffness and intrinsic stiffness for a subset of individuals.

Conclusion

There is level 1a evidence (from two RCTs and one prospective controlled trial; Chu et al. 2014; Nance et al. 1994; Mirbagheri et al. 2013b) to support the use of tizanidine in reducing spasticity.

Key Points

Tizanidine is likely useful in treating SCI spasticity.

5.3.2 Clonidine

Clonidine, an α_2-adrenergic agonist (selective, central acting), has historically been used as an anti-hypertensive agent although studies demonstrating suppression of muscle activity in rats has led to its investigation as a possible antispastic agent in human SCI (Clark 2002).

Table 21. Summary of Clonidine Studies for Reducing Spasticity

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Stewart et al. 1991 Canada RCT PEDro=8 N=12	**Population:** Injury etiology: traumatic/non-traumatic SCI; Chronicity: chronic. **Intervention:** 2 wk washout period between 4 wk of randomly assigned clonidine or Placebo treatment. Medication was administered orally 2 or 3x/day. Initial dosage was 0.02 mg/day and systematically increased to an optimal level (0.05-0.25 mg/day). **Outcome Measures:** BWS treadmill assisted walking with surface EMG, Footswitch and video recordings. Spasticity assessments: VAS subject self-report, daily spasticity diary, tonic stretch reflex (TSR) assessment at the ankle/knee and assessment of ankle clonus), Side Effects.	1. 1/3 paretic individuals had marked progression from non-ambulation to limited independent ambulation. The other 2 paretics who presented limited spasticity showed minimal changes while on clonidine. 2. Spasticity-/+/0: VAS 6/1/2, Daily spasms 2/0/2, Daily clonus 4/0/1, Ankle TSR 5/2/2, Knee TSR 5/0/2, Evoked clonus 3/1/5. 3. Side Effects in 8/9 individuals during dose titration included dryness of eyes and mouth, lethargy, mild hypotension and constipation. The majority were transient or negligible while 2 individuals experienced moderate to severe lethargy and constipation.
Malinovsky et al. 2003 France	**Population:** Age range: 21-73 yr. **Intervention:** Individuals with urinary tract surgery under spinal anesthesia were divided into two groups: 1) those with SCI 2) normal	1. In the control group, complete sensory and motor block was seen with one individual becoming hypotensive from the 150-mcg group; while the SCI group was not

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Prospective Controlled Trial N=36	matched individuals with no neurological disease. Individuals in each group were randomly assigned to receive: 10 mg of bupivacaine with 50 mcg of intrathecal clonidine, 150 mcg of intrathecal clonidine, 150 mcg of intramuscular clonidine. **Outcome Measures:** Sedation, Bispectral Index (BIS).	affected by intrathecal bupivacaine and clonidine. 2. 50 mcg clonidine had no sedative effect on the SCI or control groups; while 150 mcg of intrathecal or intramuscular clonidine resulted in sedation of all individuals. 3. A significant delay in sedation was seen in individuals with SCI in both the intrathecal and the intramuscular group; however, the duration of sedation was not different. 4. Normal individuals showed a decrease in BIS earlier than the control individuals ($p<0.001$).
Remy-Neris et al. 2001 France Prospective Controlled Trial N=15	**Population:** Injury etiology: SCI=15; Level of severity: incomplete=15. **Intervention:** Intrathecal clonidine injection (30/60/90 ug). **Outcome Measures:** Amplitude and stimulation threshold of flexor reflex responses (FRR) in tibialis anterior after posterior tibial nerve stimulation; Ashworth Scale (AS)/pendulum test, EMG latency/amplitude of quadriceps stretch reflex.	1. FRR amplitude change significant ($p<0.02$) between 30 and 90ug IT Clonidine but not significant between 30 and 50 ug between 30 and 90, NS for 30/60). 2. FRR stimulation threshold significantly increased for each Clonidine dose compared to pre-injection. ($p<0.05$ for dose-dependent effect; no change in placebo effects showing no effect of lumbar puncture). 3. Decrease in Ashworth score appeared a few min after injection, which lasted 4-6hr after a single 60ug dose. 4. Latencies of the quadriceps stretch showed a significant increase in the latency after clonidine in all but 1 subject. 5. Amplitudes of the quadriceps stretch showed a significant decrease in the latency after clonidine in all subjects. 6. Parallel results seen in integrated rectified EMG observed with pendulum test. 7. Reported AEs include hypotension, feelings of

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		negativism and depression, sedation.
Remy-Neris et al. 1999 France Prospective Controlled Trial N=11	**Population:** Injury etiology: SCI=11; Level of injury: paraplegia=11; Level of severity: incomplete=11. **Intervention:** Responders (walking capacity preserved) to a 60 µg intrathecal test dose were scheduled for 3, 15-90 µg doses of clonidine, and a placebo, by L2-3 puncture. Non-responders were given 30 and 15µg clonidine and a placebo when possible. A minimum interval of 3 days separated each injection. **Outcome Measures:** Ashworth Scale (AS) (bilateral quadriceps), Walking parameters, H-reflex, Polysynaptic reflexes–recorded before and every hr for 4-6 hr after an intrathecal injection of clonidine or placebo.	1. Significant decrease in AS ($p<0.0001$) at all dose levels (30, 60, 90 µg) with no consistent significant differences detected in reflexes. 2. Statistically significant increase in the velocity at maximal overground speed ($p=0.03$) due to an increase in the stride amplitude ($p=0.0009$), without any significant decrease in the cycle duration ($p=0.28$). 3. 90 and 120 µg doses did not produce significant improvement in 3 subjects able to walk after 60 µg.
Nance et al. 1989 Canada Prospective Controlled Trial N=6	**Population:** Injury etiology: SCI=6. **Intervention:** Clonidine, clonidine and desipramine, diazepam, placebo. **Outcome Measures:** Vibratory inhibition index (VII) of the H-reflex, Achilles reflex, Duration of clonus.	1. VII significantly reduced by clonidine ($p<0.001$) but not the other interventions. 2. Achilles reflex not affected by any intervention. 3. Duration of clonus not affected by any intervention.
Nance 1994 Canada Pre-Post N=25	**Population:** Injury etiology: SCI=25; Level of severity: complete, incomplete; Chronicity: chronic. **Intervention:** 1 wk up-titration, 1 wk target dose (0.05 mg bid clonidine; 4 mg qid cyproheptadine; 20 mg qid baclofen), 1 wk down-titration. **Outcome Measures:** Ashworth Scale (AS), Pendulum, Vibratory Inhibition Index (VII).	1. AS and Pendulum correlated well ($r=0.88$) in no-drug condition. 2. Ashworth significantly reduced, significantly increased first swing amplitude, and increased VII in all three drug conditions ($p<0.0001$, all 3 outcome measures) with baclofen showing the most improvement ($p=0.06$). 3. No difference between treatments ($p=0.2618$) for Ashworth and Pendulum. 4. Cyproheptadine and baclofen produced a greater reduction in the VII than Clonidine ($p=0.01$).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Yablon & Sipski 1993 USA Case Series N=3	**Population:** Injury etiology: traumatic SCI=3; Level of injury: cervical=3; Chronicity: sub-acute. **Intervention:** 0.1-0.3 mg/wk Transdermal clonidine patch (Constant/continuous systemic delivery). **Outcome Measures:** Change in spasticity (no specific measure noted).	1. Case 1: Marked improvement noted in relief of flexor spasms; 2. Case 2: Excellent improvement noted in both spastic hypertonia and flexor spasms. 3. Case 3: Moderate improvement in spastic hypertonia and flexor spasms.
Weingarden & Belen 1992 USA Case Series N=17	**Population:** Injury etiology: traumatic SCI=17. **Intervention:** Transdermal clonidine. **Outcome Measures:** Clinically significant relief of spasticity, Continuation of study drug after trial, Discontinuation of other anti-spasticity medications.	1. 5/17 had clinically significant relief. 2. 12/15 continued to use the medication. 3. 10/15 were able to decrease or discontinue their current antispasticity medications.
Donovan et al. 1988 USA Case Series N=55	**Population:** Injury etiology: SCI=55; Level of injury: paraplegia, tetraplegia; Level of severity: complete, incomplete. **Intervention:** Oral clonidine–0.05 mg bid and increased to 0.4 mg bid if tolerated by the subject. **Outcome Measures:** Success of medication was defined as a decrease in hypertonicity, Adverse Events (AE).	1. Results indicate that quadriplegics responded to the medication better than the paraplegics. ($p<0.033$). 2. No significant difference based on complete versus incomplete lesions. 3. 31/55 subjects responded to clonidine. 4. Many non-responders withdrew due to AEs.

Discussion

There have been two placebo-controlled trials (Stewart et al. 1991; Remy-Neris et al. 1999) providing evidence for clonidine's effectiveness in reducing SCI spasticity. Stewart et al. (1991) used oral clonidine in a randomized trial but the spasticity outcome measures are not validated or well-known clinically compared to the Ashworth measure used by Remy-Neris et al. 1999). However, the latter study was not randomized; therefore, it was less rigorous in design. Both studies had small sample sizes. In another non-randomized, placebo-controlled study by Nance et al. (1989) with a small sample size (N=6), the results concurred with clonidine's antispasmodic properties through the use of a non-validated vibratory inhibition index which is not commonly known clinically. A subsequent pre-post study by the same author (Nance 1994) using the Ashworth and Pendulum measures as well as the vibratory inhibition index compared clonidine

with cyproheptadine and baclofen for their anti-spastic properties. Although all three treatments were significantly beneficial in reducing spasticity as measured by the Ashworth and Pendulum tests, clonidine was significantly inferior to baclofen and cyproheptadine as measured by the vibratory inhibition index. The remaining reports of antispastic effects of clonidine in various formulations (oral, transdermal and additional intrathecal studies) were derived from case series studies (Donovan et al. 1988; Weingarden & Belen 1992; Yablon & Sipski 1993; Remy-Neris et al. 2001). All presented results in favour of using clonidine as an anti-spasmodic but the outcome measures chosen for each study were not specified and there were reports of several adverse events (Donovan et al. 1988). A 2003 study by Malinovsky presented evidence of the systemic and sedating effect of clonidine (150 ug intramuscularly or intrathecally) in individuals with traumatic SCI, regardless of the mode of administration. He concluded that individuals receiving treatment for spasticity may be susceptible to this sedating effect because of an altered susceptibility rather than a delayed cephalad spread of medication. Although most of studies presented results in favour of clonidine for the treatment of spasticity, the evidence is not entirely convincing given the use of small sample size, predominantly non-validated outcome measures, reports of adverse events and less robust study designs. Furthermore, when directly compared to baclofen, clonidine was significantly inferior to baclofen in its anti-spastic properties.

Conclusion

There is level 1b evidence (from one RCT, two prospective controlled trials; Stewart et al. 1991; Malinovsky et al. 2003; Remy-Neris et al. 1999) supported by several non-controlled studies in favour of using clonidine as a SCI anti-spasmodic although this must be interpreted cautiously given small study sample sizes, inadequate outcome measure selection, occurrence of adverse events and less than robust study designs.

Key Points

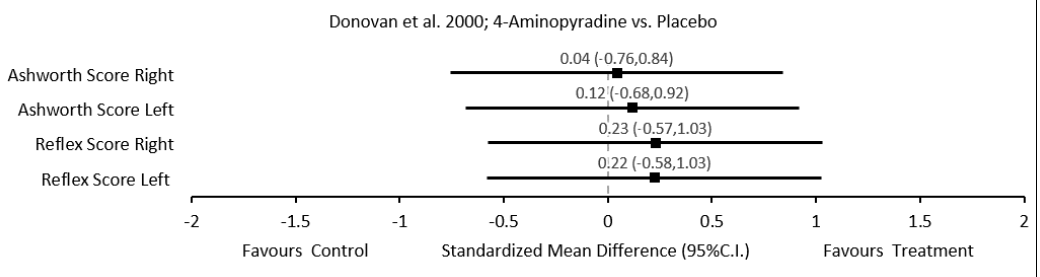
Clonidine may be effective in treating SCI spasticity but more evidence is required to support its routine use.

5.3.3 Fampridine (4-Aminopyridine)

Beginning in 1993, anecdotal reports emerged on the antispasmodic effects of a new class of K+ channel blocking drug, 4-aminopyridine (, immediate release oral and IV; Hansebout et al. 1993; Hayes et al. 1994; Potter et al. 1998a; Segal et al. 1999). This drug, with a putative mechanism of overcoming conduction deficit associated with demyelination, has potential wide-ranging effects within the central nervous system and there is some evidence of its use to enhance walking ability in persons with multiple sclerosis (Hayes 2007).

Table 22. Summary of 4-Aminopyridine Studies for Reducing Spasticity

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Cardenas et al. 2014 US and Canada RCT PEDro=6 Study SCI-F301 N=213 Study SCI-F302 N=204	**Population: Individuals** with incomplete chronic SCI from two identical double-blinded, placebo-controlled studies (SCI-F301 and SCI-F302), from 45 and 33 centres, respectively, in the US and Canada. Both individual populations were balanced at baseline rendering comparability of individual populations. SCI-F301: *Placebo (n=98):* Mean age: 40.1 yr; Gender: males=85, females=13. *Fampridine-SR (n=114)*: Mean age: 41.6 yr, Gender: males=100, females=14. SCI-F301: *Placebo (n=100)*: Mean age: 40.5 yr. *Fampridine-SR (n=103)*: Mean age: 41.3 yr. **Intervention.** Individuals were randomly assigned to either fampridine-SR 25 mg or placebo, twice daily for 2 wk in addition to a 2 wk titration, 12 wk of stable dosing, 2 wk of downward titration and 2 wk of untreated follow-up. Within intervention groups, individuals were further stratified by concomitant antispasmodic medication within the two intervention groups. **Outcome Measures:** Ashworth Spasticity Scale (AS) scores for bilateral knee flexors and extensors, Subject Global Impression (SGI), Penn Spasm Frequency Scale (SFS), International Index of Erectile Function (IIEF), Bowel and Bladder assessments, Sexual function.	1. Results from both studies showed that individuals who received famipridine-SR demonstrated greater improvements in spasticity, though differences between intervention groups in change from baseline for both primary endpoints were small and not statistically significant in both studies (Spasticity: p=0.439 for SCI-F301 and p=0.069 for SCI-F302; SGI: p=0.623 for SCI-F301 and p=0.310 for CI-F302). 2. The only statistically significant difference between treatments was on the Upper Extremity subscale in SCI-F302There were no significant between-group differences observed for bladder and bowel function in SCI-F301. The number of bowel movements was statistically significantly greater in fampridine-SR compared to placebo in SCI-F302. 3. There were no significant between-treatment differences except for an improvement among men treated with fampridine-SR on two IIEF domains, erectile function (p=0.016) and orgasmic function (p=0.032) in SCI-F301.
Cardenas et al. 2007 USA RCT PEDro=7	**Population:** Age range: 19-67 yr; Gender: males=72, females=19; Level of injury: paraplegia=18, tetraplegia=73; Level of severity: AIS C=44, AIS D=47; Time since injury range: 1-37 yr. **Intervention:** Group 1–Placebo; Group 2–25mg bid. Fampridine-SR;	1. Patients with an AS greater than one in Group 2 (25 mg) had a significant decrease in spasticity (p=0.02), as opposed to Group 1 (placebo). 2. ASIA Grades and GGI did not significantly improve within any group.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
$N_{Initial}$=91, N_{Final}=71	Group 3–40mg bid. Fampridine-SR. **Outcome Measures: Individual** Diary Questionnaire, ASIA International Standards, Ashworth Scale (AS), Spasm Frequency Scale (SFS), Tendon Reflex Scale; Subject Global Index of Global Impressions (GGI), Subject Summary Questionnaire, Safety Evaluation.	3. 71 (78%) of initial participants finished the study. 13/20 that dropped out were in Group 3 (40mg). 4. 18 subjects were lost due to adverse effects. The most common adverse events that occurred were hypertonia, generalized spasm, insomnia, pain, headache, constipation, dizziness and asthenia. Seizure and gastrointestinal bleeding occurred in two participants as well.
Donovan et al. 2000 USA RCT PEDro=9 N=12	**Population:** Injury etiology: SCI=12; Level of severity: complete, incomplete. **Intervention:** Drug or placebo was administered for 2 hr through an indwelling venous catheter attached to an infusion pump (4-AP reached doses of 30 to 80 ng/ml at the end of a 2 hr). **Outcome Measures:** Individuals were serially examined during and after infusion clinically for–Pain (McGill questionnaire), Sensorimotor function (ASIA), Hypertonicity (Ashworth scale (AS), Reflex scale), Electrophysiological measurements (Brain motor control assessment), Blood and CSF sampling.	1. No significant differences were noted pre-post infusion between 4-AP and the placebo. No differences between the motor incomplete and the motor complete groups. 2. The intravenous route may not be the best way to administer this drug as no short-term benefits were observed.
	Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- and post-intervention data. 	
Potter et al. 1998a	**Population:** Injury etiology: SCI=29; Chronicity: chronic.	Significant benefit of Fampridine-SR over placebo:

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Canada RCT PEDro=10 N=29	**Intervention:** Subjects were randomized into one of two treatments and given either Fampridine-SR (12.5 mg bid to start with an increase to 17.5 mg bid) or placebo over a period of 2 wk then following a washout period they were given the alternate treatment. **Outcome Measures:** Motor index, Sensory index, Present pain intensity, Spasm Frequency Scale (SFS), Modified Ashworth Scale (MAS), Bowel and bladder scores, Clinical interview questionnaire, Global individual satisfaction questionnaire, Seven-point terrible delighted scale, Functional Independence Measure (FIM).	1. Motor scores (adjusted to only paretic segments; p<0.01). 2. Sensory scores (p<0.01), including both pin prick and light touch (p=0.059 and p=0.058). 3. Ashworth (p<0.05). 4. Patient satisfaction and quality of life scores (McNemar's test, p<0.01 and p<0.05). 5. No statistical significance on measures of pain, bowel/ bladder/sexual function or FIM. 6. Side effects: lightheadedness and nausea–transient/trivial relative to efficacy. 7. ~30% of individuals reported a wish to continue to use.
Potter et al. 1998b Canada Pre-Post N=3	**Population:** Injury etiology: traumatic SCI=3: Level of injury: cervical=3; Level of severity: incomplete=3. **Intervention:** Day 1-single 10 mg capsule of 4-AP followed by physical and neurophysiological examination pre-and post administration up to 24 hr. Day 4: 10mg bid to tid by Day 6, if tolerated. Tolerated dosing regimen continued for 4 mo with prn intermittent assessments. **Outcome Measures:** A. Physical exam: ASIA motor and sensory classification; Modified Ashworth Scale (MAS). B. Neurophysiological exam: Motor evoked potentials (MEPs) following transcranial magnetic stimulation of motor cortex, quantitative assessment of ankle hypertonicity. C. Pharmacokinetics and Adverse Event monitoring.	*A. Physical Exam:* 1. Improved bladder function (n=1). 2. Improved spasticity (UE n=1, LE n=2). 3. Reduced pain (n=1). 4. Improved motor function (n=3). 5. Improved gait (n=2). 6. Improved sensory function (n=1), 7. Improved penile tumescence (n=1) and a 8. Nonspecific but consistently "renewed vigour" (n=2). *B. Neurophysiological Results;* 9. MEPs increased in amplitude (n=1). 10. Ankle hypertonicity reduced (n=1). *C. Pharmacokinetics and Adverse Events:* 11. Pk: 1-1.5 h Tmax; 75.05-121.27 ng/ml Cmax; 5.21-12.61L/h CL; 139.84-306.84 /L Vss; 16.9-19.08h t1/2. 12. Wakefulness (1 case limited to bid rather than tid dosing) and transient light-headedness.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Hayes et al. 1994 Canada Pre-Post N=6	**Population:** Injury etiology: traumatic SCI=6; Chronicity: chronic. **Intervention:** Under fasting conditions, individuals received 24-25 mg 4-AP IV. Monitoring for effect pre-to 2 hr post and at 24 hr post drug administration. **Outcome Measures:** Neurophysiological and standard neurological examination, Adverse Event (AE).	1. Enhanced somatosensory evoked potentials (n=3), Improved motor evoked potentials (n=4), Increased voluntary EMG interference (n=2). 2. Three of 6 individuals reported neurological benefits of the drug (n=2 for reduced spasticity; n=1 for pain; n=1 for increased sensation; n=3 for increased limb movement and n=1 for restored bowel control. 3. AE aching IV site (n=6), transient lightheadedness (n=2), mild perioral paresthesia (n=1), +20mmHg in systolic BP after 24 mg 4-AP (n=2), exacerbation of ankle phlebitis pain (n=1) and facial flushing after waking 1 day after the trial (n=1).

Discussion

Three randomized, placebo-controlled trials for 4-Aminopyridine all employed the Ashworth measure of spasticity but none of the studies were specifically designed to study spasticity (Donovan et al. 2000; Potter et al. 1998a; Cardenas et al. 2007). Using a sustained-release formulation of 4-Aminopyridine (Fampridine-SR), only Potter et al. (1998a) reported a statistically significant reduction in spasticity as measured by the Ashworth ($p<0.05$, McNemar's two-tailed test). Cardenas et al. (2007), also using Fampridine-SR, relied on the Ashworth and an Individual Diary Questionnaire (primary outcome measure covering four functional domains including spasticity and overall individual reported health status). A Subject Global Impression quality of life rating was used to confirm any benefits detected with the functional measures and resulted in a significant difference ($p<0.02$) in favour of 25 mg twice a day treatment versus placebo. A post-hoc sub-group analysis of subjects with more marked spasticity at baseline resulted in a significant treatment (25 mg twice a day) related improvement in spasticity ($p<0.25$) compared to placebo treatment. The three-group comparison (25 mg versus 40 mg twice a day versus placebo) did not result in significant differences ($p<0.04$). The third RCT used intravenous administration (Donovan et al. 2000) and concluded that this mode of administration is not optimal based on the observation of no short-term benefits; however, a fourth study using intravenous administration of 4-aminopyridine in a pre-post study design showed marked spasticity improvement in two of six subjects (Hayes et al. 1994). While Hayes et al. (1994) and Potter et al. (1998b) present evidence for the anti-spasmodic effects of 4-Aminopyridine, their contribution is mnimized gien these pre-post studies were not specifically designed to study spasticity alone.

Just one phase three clinical trial of Fampridine-SR (25 mg twice a day) was studied by Cardenas et al. (2014) among individuals with chronic SCI with moderate to severe spasticity as the primary outcome and reported no significant differences between groups.

Conclusion

There is level 1a evidence (from two large-scale RCTs; Cardenas et al. 2014; Cardenas et al. 2007) that indicate no significant anti-spasmodic effects of Fampridine-SR compared to placebo; however, this is tempered by positive findings from level 1b evidence (from one small RCT and one pre-post study; Potter et al. 1998a; Potter et al. 1998b) on the beneficial anti-spasmodic effects of Fampridine-SR. Study results must be interpreted with caution given that spasticity results were secondary outcomes of all studies except the phase 3 clinical trial results from Cardenas et al. (2007).

There is conflicting level 1b evidence (from one RCT and one pre-post study; Donovan et al. 2000; Hayes et al. 1994) that intravenous administration of Fampridine has no significant anti-spasmodic effect. Study results must be interpreted with caution given that spasticity results were secondary outcomes of the studies.

Key Points

Fampridine-SR is not significantly efficacious for the treatment of spasticity in chronic SCI.

Intravenous Fampridine is not significantly efficacious for the treatment of spasticity in chronic SCI.

5.3.4 Cyproheptadine

Cyproheptadine is a non-selective serotonergic antagonist and antihistamine that has been reported to improve spasticity in SCI.

Table 23. Summary of Cyproheptadine Studies for Reducing Spasticity

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Thompson et al. 2013 USA RCT Crossover PEDro=7 N=12	**Population:** Medan age: 50.5 yr; Gender: males=10, females=2; Level of injury: cervical=9, thoracic=3; Level of severity: AIS C=5, AIS D=7, AIS C-D=1; Median time since injury: 93 mo.	1. The median LEMS, MAS, and SCATS between cyproheptadine and escitalopram differed significantly ($p<0.05$, $p<0.01$, $p<0.01$). 2. The median change from baseline for the LEMS, MAS, and SCATS was significantly different between

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Intervention: Cyproheptadine (8 mg) and escitalopram oxalate (10 mg) were administered in a randomized order, separated by washout period of 14 days. **Outcome Measures:** Lower Extremity Motor Score (LEMS), Modified Ashworth Scale (MAS), Spinal Cord Assessment Tool for Spasticity (SCATS), Gait velocity, Stride length, Cadence.	cyproheptadine and escitalopram ($p<0.05$, $p<0.05$, $p<0.01$). 3. Following cyproheptadine, the median gait velocity and the stride length decreased significantly (both $p<0.05$), but cadence was unaffected. 4. No significant change in gait velocity, stride length, and cadence were found following escitalopram.
Wainberg et al. 1990 Canada RCT PEDro=7 N=8	**Population:** Injury etiology: traumatic/non-traumatic SCI; Level of severity: incomplete; Chronicity: chronic. **Intervention:** 1 wk washout between cyproheptadine or placebo (identically appearing tablets) in random order dose-titrated over 3 wk (1 wk each at 2 mg, 4 mg and 8 mg 5 id). Four subjects also were tested after open-label long term cyproheptadine (optimized dosing) of at least 6mo. Con meds and therapies were maintained for at least 3 mo prior to the study. **Outcome Measures:** Treadmill walking without overhead harness BWS when possible or 40% BWS- Temporal distance, Surface EMG, Joint angular displacement, Spasm severity in 2 positions, Spasticity diary.	Improvements in favour of cyproheptadine versus placebo (descriptive statistics only; no p-values provided): 1. Spasticity: all subjects reported a decrease in the severity and frequency of involuntary movements. 2. Walking pattern: A) Marked decrease in forward trunk flexion but no major changes for medial ham and TA EMG burst activity B) Maximum comfortable walking speed increased over control speed: decrease in cycle duration, percentage stance and associated decrease in the % double support duration.
Nance 1994 Canada Pre-Post N=25	**Population**: Gender: males=25, females=0; Injury etiology SCI=25; Level of injury: paraplegia, tetraplegia; Level of severity: complete, incomplete. **Intervention:** 1 wk up-titration, 1 wk target dose (0.05 mg bid clonidine; 4 mg qid cyproheptadine; 20 mg qid baclofen), 1 wk down-titration	1. A significant reduction in spasticity was seen with baclofen in all 3 outcome measures-as with the other 2 drugs tested ($p<0.0001$). 2. Generally, baclofen results were among the most improved as compared to the other 2 drugs although this was only significant for the pendulum test ($p=0.06$) and VII ($p<0.0007$–along w/ cyproheptadine).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Outcome Measures: Ashworth Scale (AS), Pendulum test, VII.	
Barbeau et al. 1982 Canada Pre-Post N=6	**Population:** Injury etiology: SCI, MS **Intervention:** Oral cyproheptadine progressively increased from 6 mg to 24 mg/day over 4 to 24 mo, incl. a placebo substitution period. **Outcome Measures:** Muscle strength, EMG activity, Individual log of clonus and spasms, Ankle clonus.	1. Muscle strength decreased in 4/6 individuals. 2. EMG activity decreased in 3/6. 3. Patient log of clonus and spasms showed decreased spontaneous spasms in 5/6. 4. Ankle clonus decreased in 6/6.
Meythaler et al. 2003 USA Case Series N=4	**Population:** Age range: 32-49 yr; Gender: males=3, females=1; Injury etiology: SCI=3, cerebral palsy=1. **Intervention:** Data from individuals previously treated with oral cyproheptadine every 6-8 hr, oral diazepam every 6-12 hr, oral baclofen every 6 hr and ITB boluses was analyzed. **Outcome Measures:** Ashworth Scale (AS), Spasticity Frequency Scale (SFS).	1. Addition of 4 mg of cyproheptadine treatment resulted in a relief of itching, anxiety, and malaise in one complete paraplegic patient. 2. A tetraplegic spastic hypertonia individual treated with ITB for 38 mo was admitted with urosepsis; initially the individual was febrile (39.5°C), unresponsive and spastic. After 8mg of cyproheptadine treatment, the individual's fever and spasticity resolved within 2hr of the first dose. AS dropped to 1 and SFS dropped to 0. 3. Complete SCI individual treated with ITB pump for severe lower extremity spasticity for 6yr presented with severe spasticity and itching and was admitted for a catheter revision and a UTI. Individual was prescribed 4mg of cyproheptadine, 5mg of diazepam, and 20mg of baclofen and found his spasticity and itching improve. Once the catheter was replaced only ITB was prescribed, other medications were discontinued.

Discussion

Acute administration of cyproheptadine (5-HT antagonis) was found to decrease clinical measures of strength (Lower Extremity Motor Score) and spasticity/spasms (SCATS and modified Ashworth). (Thompson & Hornby 2013). Comfirming the modulatory effect of 5HT on

both voluntary and involuntary force generation is the finding that SSRI administration increased strength and spasticity/spasms. (Thompson & Hornby 2013).

Cyproheptadine performed favourably versus placebo in improving spasticity and walking in a small sample of individuals with chronic SCI (Wainberg et al. 1990). Thompson and Hornby (2013) were unable to demonstrate that cyproheptadine improved walking but postulated that their individuals in this small sample (n=12) may have subjectively opted to walk at slower more stable speeds. Although the study by Wainberg et al. (1990) was randomized and placebo controlled, reductions in spasticity were only subjectively measured as subject reports of severity and frequency of involuntary movements. Similarly, Barbeau et al. (1982) in a case series study involving six subjects confirmed this antispasmodic effect of cyproheptadine using subjective individual logs of clonus and spasms. Norman et al. (1998) corroborated the reduction in ankle clonus in a study of various drugs and gait in SCI. Validated outcome measures (i.e., Ashworth and Pendulum tests) were used by Nance (1994) in a pre-post study that provided statistically significant evidence supporting the use of cyproheptadine in treating SCI spasticity.

Primary reliance on subjective outcome measures, in RCT and non-RCT designs, with small sample sizes provides weak evidence in favour of cyproheptadine for the treatment of spasticity and walking. Although spasticity was reduced when using cyproheptadine, it was found to be inferior to baclofen. Nevertheless, cyproheptadine as an adjunct treatment (along with baclofen and diazepam) was found to be useful in relieving spasticity and other complications of acute intrathecal baclofen withdrawal syndrome.

Conclusions

There is level 1b evidence (from one RCT and one pre-post study; Thompson et al. 2013; Nance et al. 1994) that supports the use of cyproheptadine in the treatment of spasticity in individuals with chronic SCI.

There is level 4 evidence (from one case series; Meythaler et al. 2003) supporting the use of cyproheptadine (along with baclofen and diazepam) as an adjunct treatment of acute intrathecal baclofen withdrawal syndrome.

Key Points

Cyproheptadine may be useful in treating SCI spasticity but requires additional confirmatory trials using rigorous study design.

5.3.5 Gabapentin

The effect of gabapentin, an anticonvulsant developed for treating epilepsy but used mostly in the management of neuropathic pain, has been investigated as an antispastic in SCI (Clark 2002).

Table 24. Summary of Gabapentin Studies for Reducing Spasticity

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Gruenthal et al. 1997 USA RCT PEDro=7 N=28	**Population:** Injury etiology: SCI=28; Chronicity: sub-acute- chronic. **Intervention:** 11-day washout between 2-day gabapentin (400 mg total in 3 divided doses) or placebo with evaluations prior to, on second day within 5 hr of last dose and after washout for each treatment. **Outcome Measures:** U/LE Ashworth Scale (AS), 6-point Likert ratings of spasticity, Muscle stretch reflexes, Presence or absence of ankle/wrist clonus, Reflex withdrawal to noxious stimuli in finger and foot.	1. Gabapentin resulted in an 11% reduction in the median AS (z=2.011, p=0.044) and a 20% reduction in the median Likert Scale score (z=3.214, p=0.013) when compared to placebo. 2. Other measures did not yield significant differences. 3. No treatment order effect. 4. No significant changes in any measure seen when placebo compared to baseline. 5. No Adverse Events.

5.3.5.1 Discussion

Gruenthal et al. (1997) conducted a randomized, placebo-controlled trial and were able to reveal modest improvements as measured by Ashworth and Likert Scale scores (p=0.044 and 0.013, respectively). Despite the robust study design, no confidence intervals were reported and the sample size was relatively small.

Conclusion

There is level 1b evidence (from one RCT; Gruenthal et al. 1997) that supports the use of gabapentin for SCI-related spasticity. Despite the robust study design and validated outcome measures, no confidence intervals were reported and the sample size was relatively small.

Key Points

Gabapentin may be useful in treating SCI spasticity but requires additional confirmatory research.

5.3.6 Other Anti-spasmodics

Other potential anti-spasmodics which have been tested in the SCI population include traditional Chinese medicine, Riluzole, L-threonine, and orphenidrine citrate.

Traditional Chinese medicine is believed to have medical benefits and scientific documentation of these benefits, specifically with respect to spasticity, pain and sleep, have begun.

Riluzole is an antiglutamatergic agent approved to slow the progression of Amyotrophic Lateral Sclerosis. Due to its spinal locus of activity where it acts more strongly on polysynaptic reflex pathways but not on direct motoneuron excitabilty, riluzole was investigated and shown to decrease spastic flexion reflexes in response to cutaneous stimuli in spinal cord injured rats (Kitzman 2009).

L-threonine is an α-amino acid with a putative mechanism of anti-spastic action through increasing spinal glycine levels (Paisley et al. 2002).

Orphenadrine citrate is a non-competitive NMDA-type (N-Methyl-D-aspartate) glutamate antagonist which acts centrally as an anticholinergic and non-opioid analgesic (Clark 2002).

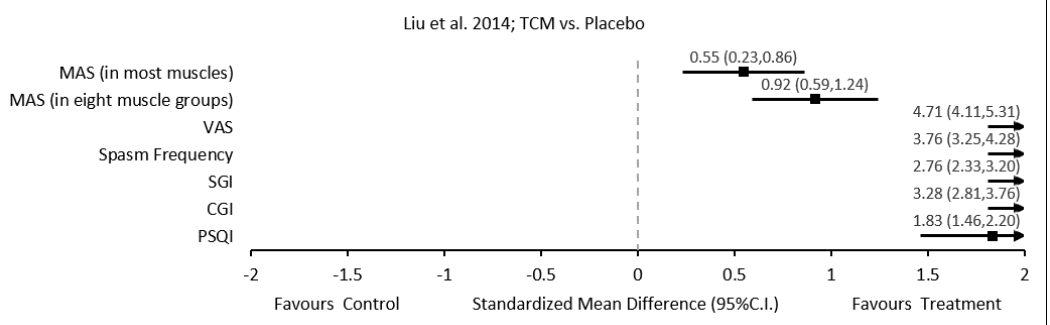
Although diazepam and dantrolene continue to be used in SCI spasticity, no new evidence is available to support continued recommendation for use in the presence of current first line treatments.

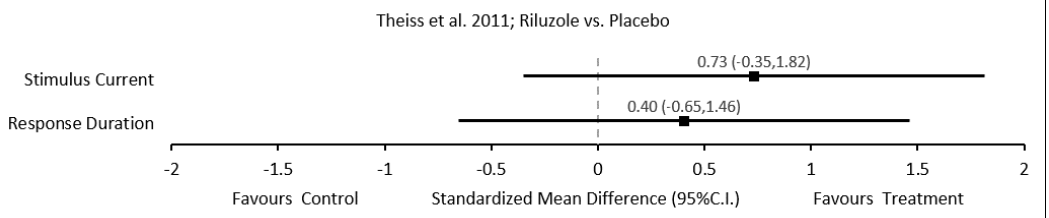
Other drugs that have been assessed against spasticity treatment in SCI include the opioid antagonist, Naloxone and the anti-epileptic, levetiracetam.

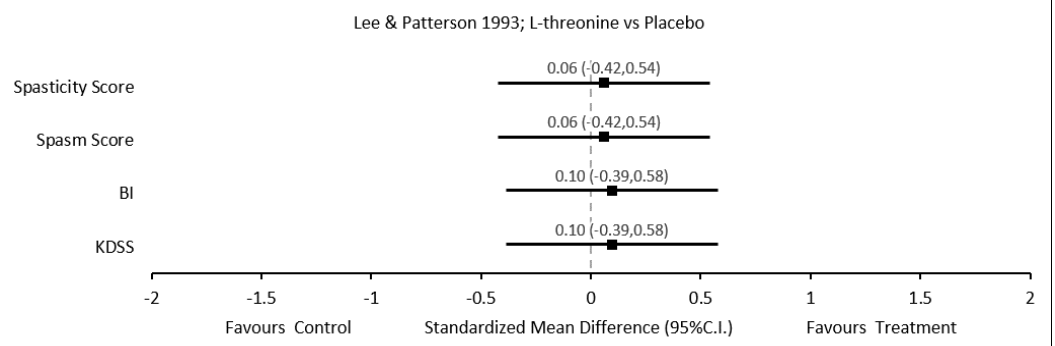
Table 25. Effect of Other Potential Anti-spasmodics for Reducing Spasticity

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Traditional Chinese Medicine		
Liu et al. 2014 China RCT PEDro=7 N=160	**Population:** Age range: 18-65yr; Level of Injury: C5; Level of severity: AIS A-D. **Intervention**: Individuals were randomized into perfume-water administered placebo (n=80) and traditional Chinese medicine (TCM; n=80) treated groups (TCM formula was composed of six kinds of herbs). All individuals received 1 yr treatment. Bath barrels (500L) were filled with either perfume water or TCM in which individuals bathed for 30 min every 3 days at a constant temperature for 1-yr. **Outcome Measures:** Ashworth Scale (AS), Spasm Frequency Scale (SFS), Visual Analog Scale (VAS), Subject Global Impression of Change (SGIC), Clinician's Global Impression of Change (CGIC), Pittsburgh Sleep Quality Index (PSQI), Regular Sleep-Wake Rhythm, Skin Allergies.	1. Post-intervention AS in the most involved muscle group of the body (as chosen by the subject and clinician) significantly improved ($p<0.05$) in the TCM group (7.10±0.79) when compared to the placebo group (7.56±0.89). 2. Post-intervention sum of the AS in both upper and lower extremities (including the elbow flexors and extensors, the wrist and finger flexors, the hip adductors, the knee flexors and extensors, and the foot plantar flexors) in the TCM group (25.38±3.11) was below ($p>0.05$) that of the placebo group (28.34±3.35). 3. Post-intervention SFS was significantly improved ($p<0.05$) in the TCM group (2.86±0.12)

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Outcomes were assessed post-intervention.	when compared to the placebo group (3.55±0.23). 4. Post-intervention VAS significantly improved in the TCM group when compared to the placebo group (p<0.01). 5. Post-intervention VAS significantly improved (p<0.01) in the TCM group (40.34±2.89) when compared to the placebo group (55.89±3.67). 6. Post-intervention SGIC significantly improved (p<0.01) in the TCM group (2.99±0.17) when compared to the placebo group (3.75±0.35). 7. Post-intervention CGIC significantly improved (p<0.01) in the TCM group (3.21±0.16) compared to the placebo group (3.88±0.24). 8. No skin allergies were found. 9. Post-intervention PSQI significantly improved (p<0.01) in the TCM group (5.8±0.97) when compared to the placebo group (7.7±1.1). 10. There was a significant difference (p<0.01) between the 18.75% (15/80) of individuals in the placebo group and the 43.75% (35/80) of individuals in the TCM group who reported better sleep quality and a more regular sleep-wake rhythm.
	Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- and post-intervention data.	

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		
Orphenadrine		
Casale et al. 1995 England Prospective Controlled Study N=11	**Population:** Mean age:31.2 yr; Gender: males=9, females=2; Injury etiology: SCI=11; Level of injury: paraplegia=11; Time since injury range: 9-11 yr. **Intervention:** 60 mg of intravenous orphenadrine citrate. **Outcome Measures:** Threshold of flexion reflex (mAmp); Ashworth Scale (AS); at baseline, initial injection, 10, 20, 30 and 60 min post injection.	1. A significant difference was observed when comparing the use of orphenadrine and placebo ($p<0.0001$). 2. Orphenadrine increased the flexion reflex threshold within 30 min in ten individuals and within 60min in one patient. 3. One individual who had severe spastic hypertonia did not see an improvement in reflex threshold. 4. There was a significant decrease in the AS for orphenadrine treatment ($p<0.0001$), as compared to no effect for the placebo.
Riluzole		
Theiss et al. 2011 USA RCT Crossover PEDro=8 N=7	**Population:** Mean age: 43.7 yr; Gender: males=6, females=1; Level of injury: cervical=5, thoracic=2; Level of severity: AIS C=2, AIS D=4, AIS C-D=1; Mean time since injury: 14.4 yr. **Intervention:** Riluzole (50 mg) and placebo (50 mg) were administered in a randomized order, separated by washout period of 7 days. **Outcome Measures:** Stimulus threshold for flexion-withdrawal reflex, Peak amplitude of torque during reflex response, H-reflex and M-wave responses, Hmax/Mmax ratio, Torque of maximum voluntary contractions (MVC), Average sustained torque, Modified Ashworth	1. The threshold stimulus intensity for the reflex response significantly increased after riluzole ($p=0.03$) but not after placebo. 2. Compared with placebo, a significant decrease in the peak amplitude of torque following riluzole was found ($p=0.0003$). 3. The torque of MVC during dorsiflexion decreased significantly after placebo ($p=0.02$) but not after riluzole. 4. The percent change in average sustained torque increased significantly with riluzole

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Scale (MAS), Spinal Cord Assessment Tool for Spasticity (SCATS).	administration compared to placebo (p=0.04). 5. The Hmax/Mmax ratio, MAS, and the SCATS scores were not significantly different between the placebo and the riluzole conditions.
	Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- and post-intervention data. 	
L-Threonine		
Lee & Patterson 1993 USA & Ireland RCT PEDro=8 N=33	**Population:** Injury etiology: MS, traumatic/non-traumatic SCI. **Intervention:** 6 g/day-500 mg L-Threonine or Placebo capsules taken 3x/day on empty stomach. **Outcome Measures**: Ashworth Scale (AS) (bilat). Hip adductors-flexors-extensors and knee flexors-extensors)–6 highest summed for spasticity score, which was used throughout the study. Spasm frequency and severity score (spasm score was derived by multiplying two variables together over 2 wk period using specially designed chart), BI, Kurtzke Disability Status Scale, Individual & Caregiver subjective responses, Aes, and glycine/threonine plasma concentrations. Measurements pre- and post intervention. All measures conducted by a single investigator.	Modest but definite antispastic effect in favour of L-threonine versus placebo: 1. Mean spasm score reduced for both interventions–weak correlation between spasm score and spasticity reduction. 2. No change in BI or Kurtzke with either intervention. 3. Dramatic rise in plasma threonine during active intervention but no change in plasma glycine. 4. Weak correlation between plasma threonine and spasticity reduction. 5. Patient-carer's subjective report–6/2 threonine/placebo responders. 6. Aes included minor side effects during intervention (n=2) and Placebo (n=1). 7. Four dropouts–2 for medical and 2 for non-medical reasons.
	Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- and post-intervention data.	

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		
Naxolone		
Brackett et al. 2007 USA & Canada Pre-Post N=6	**Population:** *SCI (n=3):* Age range: 30-42 yr; Level of Injury: T6, C4 & C4; Time since injury range: 5-26 yr; *Able Bodied Controls (n=3):* Age range: 22-37 yr. **Intervention:** 30hr protocol implemented: physiologic saline was injection on day 1 as a control for the infusion of naxolone on day 2. **Outcome Measures:** N/R.	1. No spasticity was experienced in able bodied subjects during the study. 2. SCI subjects had a large increase in the duration and occurrence of spasticity. 3. This increase was only present when SCI subjects were injected with naxolone. Spastic events occurred within 30 min of injection and could easily be triggered, even when there was lack of an obvious stimulus.
Levetiracetam		
Finnerup et al. 2009 Denmark RCT Crossover PEDro=7 $N_{Initial}$=36, N_{Final}=24	**Population:** Mean age: 51.0 yr; Gender: males=21, females=3; Level of injury: cervical=10, thoracic=12, lumbar=2; Level of severity: AIS A=10, AIS C=2, AIS D=12. **Intervention:** Individuals were randomized to receive either 5-wk treatment with levetiracetam (500 mg x2 in the first week to 1000 mg x2 in the second week and 1500 mg x2 in wk 3–5) or placebo. After a 1 wk washout period subjects were crossed to the other treatment arm. **Outcome Measures:** Pain score, Penn Spasm Frequency Scale (PSFS), Modified Ashworth Scale (MAS).	1. There was no difference in the median pain intensity during levetiracetam and placebo treatment (p=0.46). 2. Levetiracetam did not significantly change PSFS or MAS scores (p>0.05).

Discussion

Traditional Chinese Medicine

Liu et al. (2014) reported significant improvements in pain, spasticity and sleep after a randomized, double blind, study comparing an herbal bath of six traditional Chinese medicines to a placebo of perfumed bath water. No treatment related side effects or allergies were observed in 160 participants during the year long study. Outcome assessments included the AS, the VAS for pain, subject and clinician global impression scales and the Pittsburg Sleep Quality Index. Liu et al. (2014) concluded that the treatment was effective and economical for long-term use. However, they acknowledge that even though the herbs used in this study are believed to have medical benefits after more than 1000 years of use, a detailed chemical analysis is needed to understand the mechanism of action.

Orphenadrine

Casale et al. (1995) were able to demonstrate a significant reduction of spasticity ($p<0.0001$) as measured by Ashworth in favour of intravenous administration orphenadrine citrate versus placebo. This anti-spasmodic effect was demonstrated by an increased flexion reflex threshold as early as 30 minutes post administration. The authors suggest that this drug, given its immediate action, could be used as a preparatory solution for physical therapy sessions in spastic individuals. Given its known side effect profile, this treatment may be appropriate for short term application.

Riluzole

Theiss et al. (2011) demonstrated significantly reduced spasticity without a generalized reduction in strength, uniformly among seven individuals with chronic, motor-complete SCI. Although the study was randomized, double-blinded and controlled, measurements were made only on a single dose and outcome assessments were not clinically feasible (e.g. stimulus thresholds and torque measurements). At least one confirmatory RCT would be beneficial before consideration that continued use of riluzole is beneficial for spasticity treatment in SCI. In the interim, riluzole may be appropriate to trial on individuals who do not respond to or tolerate other anti-spasmodics.

L-Threonine

A randomized, controlled study of L-threonine (Lee & Patterson 1993) showed minimal effects on spasticity. Interestingly there was no correlation between the reduction in spasm score and tone reduction suggesting that these components of the disordered upper motor neurone syndrome may have different pathophysiological causes and therefore may require different pharmacological treatments. This is especially important to note since many individuals do not experience satisfactory control of spasticity using first line treatments for reasons other than intolerance.

Naloxone

An inadvertent side effect discovered during an investigation of neuroendocrine function in SCI using naloxone was the profound increase in spasticity after naloxone treatment in all three SCI

subjects compared to no such activity in the three able-bodied study volunteers (Brackett et al. 2007). This interesting finding agrees with a previous suggestion that a relationship between opioid receptors and spasticity in individuals exists where morphine is found to be effective when intrathecal baclofen tolerance is an issue.

Levetiracetam

Levetiracetam, an anti-epileptic (i.e., Keppra), was studied by Finnerup et al. (2009) for its effect on neuropathic pain, evoked pain or spasms and spasticity. Although well tolerated, no effects were recorded for spasm severity or pain.

Although diazepam and dantrolene continue to be used in the treatment of SCI related spasticity, no new evidence has been found to support their continued use given that Level 1 evidence supports treatments now routinely used for spasticity in SCI (Nance et al. 1989). See Table 20 for data regarding a study focusing on clonidine in SCI. However, an earlier crossover study (Corbett et al. 1972) showed that effects of diazepam and placebo were not different from pre-treatment and that Valium was more effective than amytal and placebo in reducing spasticity ($p<0.02$-0.05).

Conclusion

There is level 1b evidence (from one RCT; Liu et al. 2014) that traditional Chinese medicine is a safe, effective and economical long-term treatment for spasticity in SCI.

There is level 2 evidence (from one prospective controlled trial; Casale et al. 1995) for short-term use of intravenous orphenadrine citrate for treatment of spasticity secondary to SCI.

There is level 1b evidence (from one RCT; Theiss et al. 2011) that riluzole is effective in treating spasticity post SCI.

There is level 1b evidence (from one RCT; Lee & Patternson 1993) that L-threonine produces minimal anti-spasmodic effects post SCI.

There is level 4 evidence (from one pre-post study; Brackett et al. 2007) that naloxone causes a profound increase in spasticity in individuals with SCI.

There is level 1b evidence (from one RCT; Finnerup et al. 2009) that Levitiracetam is not effective for treating spasm severity in SCI.

Continued use of diazepam and dantrolene for reducing SCI-related spasticity is not supported with up to date evidence and would benefit from new controlled comparison studies. Whether effective or not, replicating results in well-designed trials is warranted before alternative recommendations for new or older treatments will be accepted into current practice.

Key Points

Traditional Chinese medicine, intravenous orphenadrine cirate, riluzole, and L-threonine may be effective in treating SCI-related spasticity.

Levitiracetam, diazepam, dantrolene and naloxone may not be effective for treating SCI-related spasticity, but would benefit from confirmatory studies.

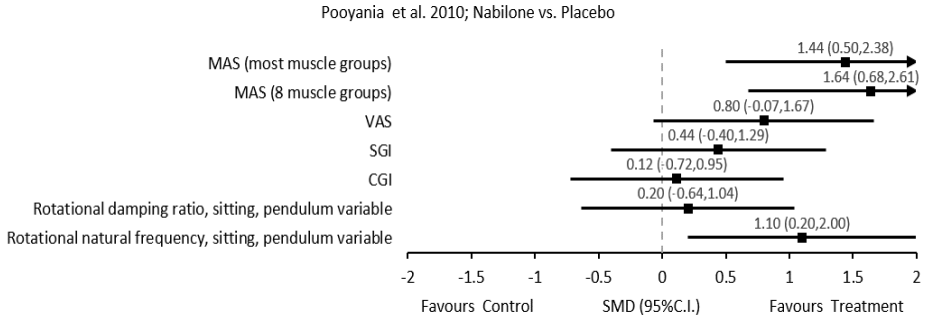
5.4 Cannabinoids for Reducing Spasticity After SCI

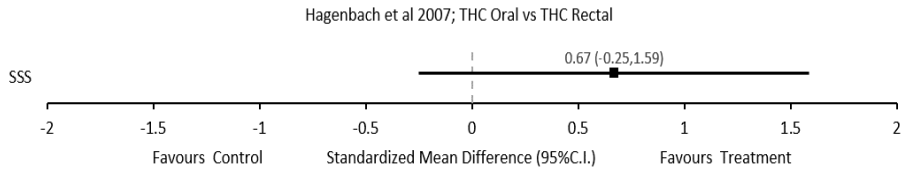
The medicinal and psychoactive properties of cannabinoids have been recognized for an estimated 5000-8000 years (Mechoulam 1986; Reynolds 1890). There are 60 raw cannabinoids identified but only six are pharmacologically active. Delta 9 tetra-hydrocannabinol is the main psycho-active ingredient and it is now available in prescribable synthetic (dronabinol, nabilone) and plant derived forms. Human cannabinoid receptors (CB1 and CB2) were discovered in the 1980s and 1990s (Howlett et al. 1986; Devane et al. 1988; Kiminski et al. 1992) along with these receptors, naturally occurring cannabinoid like substances (endocannabinoids) have been discovered in animals and humans. Baker (2001) showed that administration of CB1 agonists in an animal model for multiple sclerosis led to reduction in spasticity and tremor. In the same study the administration of CB1 antagonists not only reversed the effect of the agonist but made symptoms of spasticity and tremor worse. Since 2005, there has been an average of 20 new publications per week on the medical uses of cannabis. However, there is a paucity of literature on the use of cannabinoids specifically for the management of spasticity in SCI.

In the central nervous system cannabinoids have been shown to decrease the release of excitatory neurotransmitters, like glutamic acid, from presynaptic nerve terminals. They have also been shown to modulate calcium channels (Pertwee 2002) and enhance gamma aminobutyric acid function in the brain (Musty & Consore 2002). These are all possible mechanisms of spasticity reduction.

Table 26. Delta-9-tetrahydrocannacinol for Reducing Spasticity

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Nabilone		
Pooyania et al. 2010 Canada RCT Crossover PEDro=8	**Population:** Mean age: 42.4 yr: Gender: males=11, females=0; Injury etiology: traumatic, non-traumatic SCI; Level of injury: tetraplegia=6, paraplegia=5; Time since injury: >1yr.	1. A significant decrease in SFS, as measured by the AS, was observed for those on active treatment in the most involved muscle (mean difference=0.909±0.85; p=0.003), as well as for muscles overall (p=0.001).

<table>
<tr><th>Author Year
Country
Research Design
Score
Total Sample Size</th><th>Methods</th><th>Outcome</th></tr>
<tr><td rowspan="2">N=11</td><td>Intervention: Individuals received either nabilone or placebo during the first 4 wk period (0.5 mg 1x/day with option to increase to 0.5 mg 2x/ day); after a 2 wk washout, subjects were crossed over to opposite arm.
Outcome Measures: Ashworth Scale (AS), Spasm Frequency Scale (SFS), Visual Analog Scale (VAS), Wartenberg Pendulum Test, Global Impression of Change.</td><td>2. There was no significant difference in other measures.
3. Side effects were mild and tolerable.</td></tr>
<tr><td colspan="2">Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- and post-intervention data.
 
</td></tr>
<tr><td colspan="3">Detra-9-tetrahydrocannabinol (dronabinol)</td></tr>
<tr><td>Hagenbach et al. 2007
Switzerland
Phase 1–Pre-Post
Phase 2–RCT
PEDro=6
N=22 (RCT N=15)</td><td>Population: Age range: 29-66 yr; Gender: males=11, females=2; Injury etiology: SCI=15; Level of injury: C4-T11; Level of severity: AIS: A,B,C,D.
Intervention: Phase 1–Open labell oral and rectal detra-9-tetrahydrocannabinol (dronabinol). Phase 2- Oral detra-9-tetrahydrocannabinol (dronabinol) versus placebo.
Outcome measures: Modified Ashworth Scale (MAS), Self rating of spasticity and side effects.</td><td>1. Main comparison of RCT (dronabinol versus placebo) was not analyzed due to potential confounds associated with large group differences on SSS.
2. For the Phase I pre-post comparison of dronabinol, mean SSS decreased significantly during active treatment compared to control on day one (p=0.001), day 8 (p=0.001) and day 43 (p=0.05) of treatment.
3. When comparing dronabinol versus placebo (Phase 1 versus Phase 3), mean SSS decreased significantly relative to placebo over days 1, 8 and 43 by a mean of 4.89 as compared to baseline (p=0.001).
4. When comparing dronabinol versus placebo (Phase 1 versus Phase 3) there</td></tr>
</table>

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		was a significant decrease in self-rated spasticity on day 1 (p=0.033) but not for days 8 or 43 (p>0.05). 5. There were no significant differences on mood or psychological testing in intervention versus placebo groups. 6. There was no significant increase on FIM scores, but one tetraplegic individual was able to perform CIC independently after intervention due to better motor control of the hands. 7. Drop outs were due to increased pain, anxiety, decreased compliance, decreased attention and mood.
	Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- and post-intervention data. 	
Maurer et al. 1990 Switzerland Single Subject RCT PEDro=3 N=1	**Population:** Gender: males=1, females=0; Injury etiology: SCI=1. **Intervention:** 50 mg of codeine, 5 mg of detra-9-tetrahydrocannabinol (dronabinol) or placebo, randomized using an ABC design in multiple trials. **Outcome Measures:** Visual Analog Scale (VAS) for spasticity, pain, sleep, micturition, ability to concentrate and mood. Rating occurred next day after intervention administered (2130 hr nightly) and with respect to spasticity asked about immediate effect, effect while falling asleep, effect during the night and effect in the morning after intervention.	1. Delta 9 THC demonstrated a significant decrease in all of the VAS ratings for spasticity compared to codeine and placebo. 2. Delta 9 THC also showed a significant reduction in pain compared to placebo.
Kogel et al. 1995 USA	**Population:** Age range: 28-55 yr; Gender: males=5, females=0;	1. Spasticity was markedly improved in 2 of 5 subjects.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Pre-Post N=5	Level of injury: tetraplegia; Time since injury range: 6 mo–9 yr. **Intervention:** Open label design: Oral detra-9-tetrahydrocannabinol (dronabinol) (initial dose: 5 mg bid, increased to 20 mg tid)+current spasticity regimen. **Outcome Measures:** Pendulum Drop Test, Weschler Memory Scale (WMS), Profile of Moods Scales (POMS).	2. Results fluctuated in one subject, did not change in one subject and worsened in one subject. 3. There was no worsening in psychological parameters and two subjects had improvements in memory testing.
All Types		
Malec et al. 1982 USA Observational N=43	**Population:** Age range: <20-60+ yr; Gender: males=37, females=5; Injury etiology: 43; Time since injury range: 6 mo-5+ yr. **Intervention:** Survey to examine the perceived effects of cannabis on spasticity. **Outcome Measures:** Customized cross-sectional survey addressing demographic information (age range, sex, marital status, education, and range of time since injury), marijuana use, belief patterns associated with use, severity of spasticity associated with use/nonuse, Spasticity Change Index, computed by subtracting level of spasticity in the drug-state from the non-drug-state.	1. SCI persons reported decreased spasticity with marijuana use; present use of marijuana correlated positively with past use. 2. The person's reference or peer group contributed significantly to current use. 53% reported using marijuana during last yr with correlation to use prior to SCI ($r=0.78$, $p<0.001$, $n=43$; agrees with other studies). Also correlated with degree of use in present social reference group ($r=0.32$, $p<0.05$, $n=38$) and prior social reference group ($r=0.30$, $p<0.05$, $n=37$). Age was negatively correlated with current use ($r=-0.56$, $p<0.001$, $n=43$). 3. Reduction in spasticity via use was reported in 88% (21/24) while 12% reported no change. 4. No correlation between Spasticity Change Index and any variable (if significant correlation, then perhaps placebo effect). 5. Education moderately correlated with reported change in spasticity ($r=-0.65$, $p<0.001$, $n=23$): lower education associated with greater reported change in Spasticity Change Index. Marijuana use prevalent (53%, 23/43) among SCI surveyed and especially of SCI <30 yr (76%, 16/21).

Discussion

There continues to be a paucity of literature on the use of cannabinoids for the management of spasticity in SCI. They are often described in cases with intractable spasticity in individuals who have not responded to standard treatments which may bias studies in favor of a negative outcome. In addition to a single subject, blinded, controlled study (Maurer et al. 1990) there have been only two placebo-controlled trials (Hagenbach et al. 2007; Pooyania et al. 2010) and the remainder of the literature is limited to pre-post and observational study designs.

Hagenbach (2007) performed a trial consisting of two open label phases followed by a double-blind, randomized, placebo control phase in order to evaluate the efficacy and side effects of orally and rectally delivered delta 9-tetra-hydrocannabinol (dronabinol) for the treatment of SCI related spasticity. The main outcomes were the spasticity sum score using the MAS as well as self-rating of spasticity. In the open label phase, significant reductions in spasticity were seen in both oral and rectal tetra-hydrocannabinol groups. Only oral administration was used in the placebo control phase. When comparing phase one to phase three results, mean spasticity sum score decreased significantly during active treatment compared to placebo on day 1 ($p=0.001$), day 8 ($p=0.001$) and day 43 ($p=0.05$) of treatment. There was a significant subjective decrease in spasticity on day 1 ($p=0.033$) but not day 8 or 43. There were no significant differences found with the remaining outcome measures. Unfortunately, there were numerous dropouts within the first two phases due to increased pain, anxiety, decreased compliance, decreased attention and mood. This likely contributed to large between group differences for the baseline spasticity scores and led to a decision to abandon analysis of the active compound-placebo comparison. Therefore, despite the various findings noted above which demonstrated reduced spasticity with delta 9 tetra-hydrocannabinol, it remains unclear if placebo effects may have contributed to these findings as there was an indication of placebo effects within the comparison of open label and placebo-control results. Given the limitations associated with this study (i.e., lack of analysis of placebo-treatment analysis) it was assigned a lower level of evidence (i.e., level 2) even though it achieved a PEDro score consistent with an assignment of level 1 (i.e., PEDro≥6) according to SCIRE criteria.

The second study was a double-blind placebo-controlled crossover (Pooyania et al. 2010) which gave individuals Nabilone or a placebo during the first 4 weeks, 0.5 mg/ day with some increasing to twice a day. Following a 2-week washout, the subjects were crossed over to the opposite arm. The main finding was a significant decrease in spasticity for those on active treatment in involved ($p=0.003$) and overall muscles ($p=0.001$). Similarly, to the previous study, the other outcome measures rendered no significant differences. However, the two trials differed in reported side effects as this second study documented only mild and tolerable side effects.

Maurer et al. (1990) studied one individual with pain and spasticity due to SCI. Despite not meeting the SCIRE inclusion criteria, it was included due to the paucity of literature pertaining to cannabinoids for the management of spasticity in SCI, and because it was a randomized ABC (three period, three treatment crossover) design. Using a VAS to assess spasticity after blinded treatment, delta 9 tetra-hydrocannabinol showed significant benefits for spasticity over placebo and codeine. However, the individual was exposed to delta 9 tetra-hydrocannabinol use prior to the placebo control trial which may have introduced significant bias.

Kogel et al. (1995) performed a pre-post trial in five males with paraplegia. He administered dronabinol escalating from five mg BID to 10 mg four times each day to 20 mg three times each day. The main outcome was the pendulum test and secondary outcomes were the Weshler memory test and profile of mood states. Two of the five subjects had marked improvements in their spasticity. One showed fluctuating responses, one no change and one worsened. The psychological testing was only performed on four of the five subjects but no deleterious effects were noted and in fact two subjects improved on memory testing.

Conclusion

There is level 1b evidence (from one RCT; Pooyania et al. 2010) that nabilone is effective in reducing spasticity in both the involved and overall muscles.

There is level 2 evidence (from one compromised RCT; Hagenbach et al. 2007 and supported by one pre-post study; Kogel et al. 1995) to support the use of oral delta-9-tetrahydrocannabinol (dronabinol) in reducing both objective and subjective measures of spasticity.

Key Points

Nabilone has been shown to be effective in reducing spasticity but additional research is needed.

Oral detra-9-tetrahydrocannabinol (dronabinol) may help to reduce spasticity but requires additional evidence from controlled studies.

5.5 Focal Neurolysis for Spasticity Management

Focal neurolysis, or chemodenervation, has long been used as a management tool for spasticity. Local pharmacological therapies have traditionally included phenol and alcohol neurolysis. More recently BTX chemodenervation has gained popularity for management of focal spasticity in a number of neurologic disorders, because of its ease of administration, good side effect profile and beneficial effects (Franciso et al. 2002; Kirazli et al. 1998; Simpson et al. 1996; Smith et al. 2000; Dolley et al. 1984).

5.5.1 Botulinum Toxin

BTX is naturally occurring substance that is lethal in large doses. Several different strains have been identified (A-F) but only BTX A and B have been found to have therapeutic benefit. In the 1950s researchers found that by injecting overactive muscles with minute quantities of BTX-A they could decrease muscle activity by blocking the release of acetylcholine from the neuron (Mukherjee 2015). BTX-A does this by interfering with SNAP-25 protein. This prevents fusion of the acetylcholine containing vesicles with the nerve terminal membrane, thus preventing the release of acetylcholine into the synaptic cleft and the resultant contraction of the muscle fibers. BTX-B does this similiarly by interfering with synaptin. The effect dissipates after three to 6

months due to collateral sprouting of new nerve terminals and the eventual full recovery of the original nerve from the effects of the toxin.

There is level 1 evidence supporting the use of type A (BTX-A) and type B (BTX-B) in relieving focal muscle spasticity in a variety of etiologies, most notably stroke and acquired brain injury (SREBR 2016; ERABI 2016). In addition, there are several treatment guidelines and other information available for assisting the clinician with dosing and medication administration decisions (Brin 1997a; Brin 1997b; Gormley Jr. et al. 1997; O'Brien 1997; Ward 2002; Francisco 2004). The recommendation for the use of BTX for relieving focal muscle spasticity in individuals with SCI (Brin 1997b; Kirshblum 1999; Fried & Fried 2003) "is independent of the etiology of the spasticity, depending rather on the presence of an increase in muscle tone that interferes with function" (Brin 1997b). The advantages for its use include the ability to achieve a focal response, a relative ease of administration and avoiding the sedation common with other pharmacological alternatives (Fried & Fried 2003). In spite of this information, there continue to be relatively few studies directed specifically at the SCI population. The successful employment of botulinum neurotoxin to overcome bladder detrusor-sphincter dyssynergia in people with SCI is addressed separately in the SCIRE bladder module.

Table 27. Botulinum Neurotoxin for Reducing Spasticity

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Richardson et al. 2000 England RCT PEDro=9 N=52	**Population:** Injury etiology: stroke=23, head injury=12, SCI=6, other=11. **Intervention:** EMG guided injection of BTX-A with doses and specific muscles injected based on clinical judgment. **Outcome Measures:** Modified Ashworth Scale (MAS), Passive range of motion (ROM), Subjective rating of Problem Severity, 9-hole peg test (upper limb problems only), Timed 10 m walk test (10MWT) (lower limb problems only), Goal Attainment Scale (GAS), Rivermead Motor Assessment Scale (RMA) at 3, 6, 9 and 12 wk.	1. Spasticity was significantly reduced for active tx versus placebo (as shown by MAS aggregate scores) ($p<0.02$). The main reduction for both tx and placebo groups occurred between baseline and 3 wk with little further improvement thereafter. tx group had more marked reduction than placebo group. 2. ROM was significantly improved for both groups but significantly more for intervention versus placebo group ($p<0.03$). As with MAS most marked changes were between baselines and 3 wk. 3. In general, the various functional measures showed no systematic significant differences other than Subjective Rating of Problem Severity with aggregate outcome scores significantly better for active Tx versus placebo ($p<0.025$).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Spiegl 2014 Germany Pre-Post N=9	**Population:** Mean age: 40.0 yr; Gender: males=9, females=0; Level of severity: AIS A=8, AIS B=0, AIS C=1. **Intervention: Individuals** received botulinum toxin A injections (800-2000 U) to the affected muscles of the lower extremities after ≥3 mo of unsuccessful physiotherapeutic and oral antispastic therapy. Following injection, individuals received intensive physiotherapy of the affected muscles for 3 day. **Outcome Measures:** Modified Ashworth Scale (MAS) at 2wk and 2 yr; Difficulties during mobilization, Adverse events.	1. MAS scores 2 wk post injection decreased to ≤2 in 6 individuals with a mean reduction of 1.9. 2. MAS scores 2wk post injection showed no change in 2 individuals. 3. Decreases in spasticity were observed 2-5 days post injection with the peak decrease observed at a mean of 2 wk post injection. 4. MAS scores at 2 yr post injection were ≤2 in 3 individuals and ≤3 in 3 individuals with a mean increase of 0.6 from 2 wk to 2 yr. 5. Difficulties during mobilization were reduced in 5 individuals in areas including getting dressed or transferring to wheelchair. 6. Adverse events were reported by 2 individuals with 1 individual reporting decreased mobility due to muscle weakness for 3 mo post injection and the other reporting general muscle weakness for 3 days post injection. 7. No infections or allergic reactions were observed in individuals post injection. 8. The positive effect in 6 individuals lasted >7 mo before decreasing in all individuals.
Bernuz et al. 2012 France Pre-Post N=15	**Population:** Mean age: 43.0 yr; Gender: males=14, females=1; Mean time since injury: 10 yr; Level of injury: cervical=7, thoracic=7, lumbar=1; Level of severity: AIS D=15. **Intervention:** Injection of 200 UI of Botulinum Toxin (BoNT A) distributed in 2 points in the rectus femoris (RF) muscles. **Outcome Measures:** Isokinetic peak torque (seated and supine) during passive stretch (10 deg/sec, 90 deg/sec, 150 deg/sec) and voluntary contraction (60 deg/sec), Angle at peak torque	1. Peak torque during voluntary contraction decreased significantly (p=0.0004). 2. The angle at peak torque during passive stretch at 90 deg/s increased significantly (p=0.03). 3. The MTS grade decreased significantly (p<0.05) and the MTS angle increased significantly (p<0.01). 4. Peak knee angle during flexion, and the knee flexion velocity at toe-off increased significantly (both p<0.05). • Significant treatment increases in gait velocity (p<0.01), stride length (p<0.01), and swing phase (p<0.01).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	(seated and supine) during passive stretch (10 deg/sec, 90 deg/sec, 150 deg/sec) and voluntary contraction (60 deg/sec), Modified Tardieu Scale (MTS), Peak knee flexion, Gait velocity, Stride length, Swing phase, 6-minute walking test (6MWT), Timed stair climbing, Discomfort.	5. No significant change in the 6MWT was found. 6. The Timed stair climbing decreased significantly ($p<0.05$). 7. Main discomfort decreased significantly ($p=0.001$).
Palazon-Garcia et al. 2018 Spain Case Series N=90	**Population**: SCI (n=90): Etiology: Trauma=87, Familial spastic paraparesis=3; Mean age=41.92yr (range=18-77); Gender: males=65, females=25; Level of injury: C=51, T=23, L=13; Mean time since injury=NR; AIS scale: A=20, B=11, C=14, D=44, E=1. **Intervention:** This retrospective study examined spasticity outcomes in individuals injected with botulinum toxin. Muscles injected include the flexor carpi radialis, flexor digitorum profundus, biceps brachii, quadriceps, soleus, and tibialis posterior. **Outcome Measures:** modified Ashworth Scale (mAS).	1. Muscle tone as measured by the mAS fell from 2.38 to 1.18 post injection when considering only the injected muscles. Mean improvement in tone, as measured by the mAS was 1.3 points per muscle.
Hecht et al. 2008 Germany Case Series $N_{Initial}$=19, N_{Final}=11	**Population:** Hereditary spastic paraplegia (HSP): Mean age: 41.6 yr; Gender: males=14, females=5; Mean time since injury: 18.5 yr. **Intervention:** Injection of BTX-A with doses and specific muscles injected based on clinical judgment. **Outcome Measures:** Ashworth Scale (AS), Global Subjective Assessment (GSA).	1. 17 individuals had a one-point improvement on the AS, one improved by three points, and one was not scored. 2. Of the 17, those with GSA improvement continued BTX-A treatment (n=11). 3. 10 of the continuing 11 individuals participated in physical therapy concurrently with BTX-A injections. 4. Adverse effects: muscle weakness (n=3), pain during walking (n=1) & CK elevation (n=1).

Discussion

Richardson et al. (1997) employed EMG-guided BTX-A injections, to treat several wrist and hand muscles in a single chronic SCI subject. Spasticity was reduced as assessed by the AS and range of motion was increased with these measures maintained over the testing period to 12 weeks. Using the same technique, Al-Khodairy et al. (1998) conducted a 2-year follow-up study of a chronic incomplete paraplegic male with similar results augmented by the Spasm Frequency Score and reports of markedly reduced pain due to spasticity, less difficulty with activities of daily living, better sitting tolerance and fewer sleep disturbances. The final treatment delivered in this series (i.e., eighth over 2-year period) was without effect leaving the possibility of drug tolerance but this was not confirmed.

In a subsequent, EMG-guided BTX-A injection study of RCT design (Richardson et al. 2000) MAS scores demonstrated reduced spasticity across the appropriate joints when tested at three, six, nine and 12 months with both active treatment and placebo, although there was a significantly greater reduction with BTX-A ($p=0.02$). Despite the RCT design and the use of a validated spasticity outcome measure, the conclusions must be cautiously interpreted with respect to BTX-A use in SCI, given that only six of 52 subjects had spasticity of confirmed spinal cord origin.

Limited SCI specific evidence of BTX-A benefits is provided by Hecht et al. (2008). They studied a case series of 19 individuals with chronic hereditary spastic paraplegia and reported Ashworth improvements of at least one point (one individual was not scored). 11 of the 19 individuals perceived a concurrent improvement in activities of daily living and continued treatment.

In an open label study of 15 individuals with AIS-D SCI, Bernuz et. al. (2012) found significant decreased peak torque in the quardriceps after treatment with 200 units of BTX-A in the form of Botox® into the rectus femoris (RF). Individuals also demonstrated faster walking speeds, improvements in stride length and better performance on stairs post treatment. Individuals also reported improved comfort. There was no change in performance in the 6-minute Walk Test. The authors concluded that BTX-A injection into the RF muscle in individuals with incomplete led to improvements in impairments, functional aspects of gait, and discomfort that is related to the delay and reduction of RF spasticity in mid-swing.

Spiegl et al. (2014) examined nine male individuals with paraplegia and severe spasticity, in an open-label prospective desisgn study. Eight had complete, AIS-A injuries and one was AIS-C. All subjects had not responded to oral therapies and physiotherapy adequately. They were evaluated in a pre-post fashion. They received up to 2000 units (range 800-2000 units) of BTX-A in various muscle groups in the lower extremities. Descriptive analysis showed that six of nine individuals reported being very satisfied with the results and showed an average reduction in the Ashworth's score of 1.9. All those very satisfied with treatment had a post treatment Ashworth's score of less than two. The one study subject with incomplete, AIS-C paraplegia suffered a decline in mobility following treatment. They concluded that BTXcould be a very promising treatment for spasticity in SCI and that further studies were needed.

Most Recently Palazon-Garcia published a retrospective study of 90 individuals with incomplete SCI. As expected, the majority of subjects were male (65 of 90). Each subject was treated with BTX chemodenervation. The average reduction in the Ashworth's score was 1.7. Almost 40%

(38.9%) of subjects demonstrated an improvement in pain and 65.5 percent showed imporvents in range of motion. There were no measures for function or quality of life. Individuals with focal spasticity had the greatest improvements.

Conclusion

There is level 1b evidence (from one RCT, two pre-post studies, and one case series; Richardson et al. 2000; Spiegl 2014; Bernuz et al. 2012; Hecht et al. 2008) that BTX type A improves focal muscle spasticity in SCI. It is important to note the RCT included just six of 52 subjects with spasticity of confirmed spinal cord origin.

There is level 4 evidence that botulinum toxin improves spasticity and range of motion in persons with incomplete SCI.

There is a lack of literature looking at the impact of BTXchemodenervation on function and quality of life.

Key Points

Botulinum neurotoxin may improve focal muscle spasticity in people with SCI.

5.5.2 Phenol

Phenol is believed to reduce spasticity via direct neurolysis causing damage to the alpha motor fibers of the nerve(s) affected. Phenol neurolysis is not specific for the motor fibers and therefore can cause secondary sensory nerve damage and complications such as painful neuropathy (On et al. 1999). Phenol blocks have been used to successfully treat spasticity in a number of conditions including stroke, SCI, multiple sclerosis and cerebral palsy (Uchikawa et al. 2009; Albert et al. 2002; On et al. 1999; Kirazli et al. 1998; Yadav et al. 1994; Wassef et al. 1993).

Table 28. Phenol Neurolysis for Reducing Spasticity

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Demir et al. 2018 Turkey Pre-Post N=19	**Population**: SCI (n=19): Mean age=33±9.4yr; Gender: males=11, females=3; Level of injury: C=8, T=6; Mean time since injury=90.7±104.5mo; AIS scale: A=6, B=5, C=2, D=1. **Intervention:** All participants received 19 ultra sound-guided femoral nerve block. Femoral	1. There were significant decreases in mAS scores of hip flexor muscle tone at 1st wk and 2nd mo follow-up assessments when compared to baseline ($p<0.017$). 2. There was were significant decreases in spasticity in the mAS score of knee extensor tone at end

	neurolysis was performed with a peripheral nerve stimulator with a frequency of 1 Hz for 0.1 ms. Initial intensity was 3 mA. Three mL of 5% phenol was administered to the perineural area after stimulation. Outcome measures were assessed at baseline, end of the 1st wk, and at the end of the 2nd mo. **Outcome Measures:** modified Ashworth Scale; frequency of spasms; satisfaction.	of 1st wk and 2nd mo when compared to baseline ($p<0.017$). 3. There were significant increases in participant satisfaction regarding intervention at 1st wk and 2 mo follow-ups when compared to baseline. Moreover, satisfaction improved significantly from 1st wk to 2nd mo follow-up ($p<0.017$).
Ghai et al. 2013 India Pre-Post N=20	**Population:** Mean age: 36.7 yr; Gender: males=17, females=3; Injury etiology: SCI=16, koch's spine=2, MS=2. **Intervention:** 10 ml of 0.25% bupivacaine. If 1° MAS decrease and 20° range of motion increase were observed, obturator nerve blockade with 8-10 ml of 6% phenol was performed using the interadductor approach the next day. Outcomes were assessed at the 1st hr, 24th hr, end of 1st wk, and 1st, 2nd, and 3rd mo post intervention. **Outcome Measures**: Modified Ashworth Scale (MAS), Visual Analog Scale (VAS), Spasm Frequency Scale (SFS), Range of Motion (ROM), Hygiene score, Gait scale score.	1. All parameters with the exception of gait significantly improved ($p<0.05$) compared with the baseline during all time periods between 1 hr and 3 mo post intervention. 2. Gait score showed significant improvement ($p<0.05$) compared with the baseline between 1 wk and 3 mo post treatment. There was no significant improvement in gait score before 1 wk. 3. Adverse events: 2 participants developed dysesthesia lasting for 7 to 10 days; 1 participant developed fibrosis at the injection 20 days post-injection; no participants developed neuritis or secondary deafferentation pain
Ghai et al. 2012 India Case Series N=3	**Population:** Mean age: 18.3 yr; Gender: males=3, females=0; Level of injury: T4-6=2, C4-5=1; Level of severity: AIS D=3. **Intervention**: 8-10 ml 65% alcohol to obturator nerves with interadductor approach after successful 10 ml of 0.5% bupivacaine block. **Outcome Measures:** ROM, Pain Visual Analog Scale (VAS), Modified Ashworth Scale (MAS), Hygiene. Outcomes assessed at 1 wk, 3 mo and 4 mo post injection.	**1 wk post-injection:** **Case 1:** "Drastic" improvements in hip joint ROM, pain VAS, MAS, hygiene Duration of improvements: 3 mo for ROM, MAS, hygiene; 4 mo for pain VAS **Case 2**: "There was significant improvement in pain, spasticity, range of motion of hip joint, hygiene scores, and number of muscle spasms. It has been 6mo now, and the effect of alcohol is still persisting" **Case 3**: "Though the VAS score decreased significantly but spasticity and numbers of spasms were not much alleviated, and the participant was quite unsatisfied with the block"

Yasar et al. 2010 Turkey Retrospective Case Series N=20	**Population:** Mean age: 42.9 yr; Gender: males=19, females=1; Injury etiology: traumatic, non-traumatic SCI; Level of injury: tetraplegia=3, paraplegia=17; Level of severity: AIS A=13, AIS B=7; Mean time since injury: 41.8 mo. **Intervention:** Phenol obturator nerve blockade. **Outcome Measures:** Hip adductor spasticity.	1. Mean hip adductor spasticity decreased significantly after ($p<0.001$).
Uchikawa et al. 2009 Japan Case Series N=7	**Population:** Mean age: 55.8 yr; Gender: males=7, females=0; Injury etiology: SCI=7; Level of injury: C5=5; Time since injury: ≥5 mo. **Intervention:** Subscapular phenol nerve block. **Outcome Measures:** Shoulder Range of Motion (ROM), Visual Analog Scale (VAS) for pain, Ashworth Scale (AS), Eating functional independence measure item score.	1. Significant improvements in passive ROM in flexion (23.71), abduction (19.41) and external rotation (16.81; $p<0.05$) 2. Decreases in the VAS for shoulder pain which was reduced from 6.0 to 3.4 ($p<0.05$). 3. No significant change in the MAS for shoulder spasticity. 4. Eating Functional Independence Measure item score improved significantly ($p<0.05$).

Discussion

Phenol

Uchikawa et al. (2009) examined the use of phenol blocks for the management of painful shoulder girdle spasticity in persons with cervical level SCI. In an open label, case series, seven individuals with cervical level SCI with shoulder pain and limited range of motion were treated with phenol motor point blocks to the subscapularis muscle. They observed significant improvements in passive ROM in flexion, abduction, and external rotation and decreases in the VAS for shoulder pain ($p<0.05$ for all). However, they did not observe any significant change in the MAS for shoulder spasticity. The FIM score for eating improved significantly ($p<0.05$).

In another case series, Yasar et al. (2010) also examined the efficacy of a phenol block on the obturator nerve for the reduction of hip adductor spasticity. The authors reported a statistically significant decrease in spasticity post-treatment.

Ghai et al. (2012) reported a case series of three persons with SCI and hip adductor spasticity treated with phenol blocks of the obturator nerve. Results were variable, with two participants reporting improvement in pain, spasticity, range of motion and hygiene. The other participant reported improvement in pain but not spasticity, and was not satisfied with the results.

Ghai et al. (2013) conducted a pre-post study on the use of phenol blocks of the obturator nerve for the management of hip adductor spasticity in a population that included participants with SCI, multiple sclerosis and Koch's spine. As SCI participants comprised ≥50% of the samples, and we were unable to obtain individual level data, data pertaining to the entire subject group

were included. Ghai et al. (2013) observed significant improvements ($p<0.05$) in MAS, pain VAS, SFS, range of motion, and hygiene score, which measured the ability of nursing staff to access the perineal area. They reported an improved gait score after neurolysis as measured by the Gait Scale in three ambulatory participants. Inspection of gait after the injection revealed decreased scissoring of hips, improved balance and gait speed. All of them, however, still needed assistive devices for ambulation.

Most recently in a pre-post study, by Demir et. al. (2018), fourteen individuals with traumatic SCI and lower extremity spasticity were treated with ultrasound guided phenol blocks. A total of 19 procedures were reported on. Subjects were reported to have experiences a significant decrease in the modified Ashworth's score for hip flexors ($p<0.017$) and knee extensors ($p<0.017$) at 1 week and 2 months following treatment. This was associated with reported improvements on ease of catheterization, hygiene, and satification. Spasm frequency decreased significantly in the first week post injection, but was not sustained at the 2-month evaluations. No complications were reported. This study was limited by small numbers and the lack of a control group.

Alcohol

Alcohol neurolysis works in a manner similar to phenol. It has been studied in the management of spasticity in hemiplegia and in focal dystonias, all with some success. Our literature search failed to reveal any studies utilizing alcohol neurolysis in managing spasticity in SCI.

Conclusion

There is level 4 evidence (from one case series; Uchikawa et al. 2009) that phenol neurolysis improves pain, range of motion and function related to shoulder spasticity for individuals with tetraplegia in SCI.

There is level 4 evidence (from one pre-post study and two case series; Ghai et al. 2013; Ghai et al. 2012; Yasar et al. 2010) that phenol neurolysis reduces hip adductor spasticity in individuals with paraplegia and tetraplegia in SCI.

There is level 4 evidence (from one pre-post study; Demir et. al. 2018) that phenol neurolosis reduces spasticity in the hip flexors and knee extensors with associated improvements in ease of catheterization, hygiene and satisfaction.

There is no literature to support the use of focal neurolysis with alcohol in the management of spasticity in SCI.

Key Points

Phenol block may improve pain, range of motion and function related to shoulder spasticity in individuals with tetraplegia.

Phenol block may reduce hip adductor spasticity in individuals with paraplegia and tetraplegia.

6 Summary

Non-pharmacological Interventions for Spasticity

There is level 1b evidence (from one RCT; Fang et al. 2015) that passive ankle movements may not reduce lower limb muscle spasticity in persons with initial mild spasticity.

There is level 2 evidence (from one RCT; Lechner et al. 2007) that hippotherapy may reduce lower limb muscle spasticity immediately following an individual session.

There is level 2 evidence that electrical passive pedaling systems have an effect on spasticity and hip, knee and ankle range of motion.

There is limited level 1b evidence from a single study that a combination of a 6-week course of neural facilitation techniques (Bobath, Rood and Brunnstrom approaches) and baclofen may reduce lower limb muscle spasticity with a concomitant increase in ADL independence. More research is needed to determine the relative contributions of these therapies.

There is level 4 evidence from a single study that rhythmic, passive movements may result in a short-term reduction in spasticity.

There is level 4 evidence from a single study that externally applied forces or passive muscle stretch as are applied in assisted standing programs may result in short-term reduction in spasticity. This is supported by individual case studies and anecdotal reports from survey-based research.

There is level 1b evidence from two RCTs (Fang et al. 2015; Mirbagheri et al. 2015) robot-assisted exercise appears to decrease all components of spasticity (isometric torque, reflex and intrinsic stiffness).

There is level 4 evidence that single bouts of FES-assisted cycling ergometry, with a single level 2 study also showing that similar passive cycling movements are effective in reducing spasticity over the short-term although FES is more effective than passive movement.

There is level 1 evidence from 1 study, with conflicting evidence across two level 4 evidence studies, that show FES cycling decreases spasticity over the long-term.

There is level 4 evidence from three studies that a program of FES-assisted walking acts to reduce ankle spasticity in the short-term (i.e., ≤ 24 hours), however, a level 2 study showed no reduction across several lower limb muscles when considering an overall sustained effect.

There is no evidence to describe the optimal length and time course of FES-assisted walking for reducing spasticity.

There is level 2 evidence (from one prospective controlled trial; Sadeghi et al. 2016) that dynamic and static standing training does not reduce spasticity.

There is level 2 evidence (from one RCT; Manella & Field-Fote 2013) that electrical stimulation treadmill training and LOKOMAT robotic-assisted training decreases ankle clonus.

There is level 4 evidence (from one pre-post study; Adams et al. 2011) that use of tilt-table standing decreases extensor spasms and body-weight support treadmill training results in a reduction in passive resistance to movement and flexor spasms.

There was level 4 evidence (from one pre-post study; Boutilier et al. 2012) that showed use of a Segway device for dynamic standing results in a reduction of spasticity.

There is conflicting level 4 evidence (from two case series; Kressler et al. 2014; Del-Ama et al. 2014) that use of an exoskeleton walking device results in a reduction in spasticity.

There is level 4 evidence (from one pre-post study; Cortes et al. 2013) that use of robotic training of the wrist does not improve upper limb spasticity.

There is level 4 evidence (from one pre-post study; Kesiktas et al. 2004) that hydrotherapy is not more effective in producing a short-term reduction in spasticity than conventional rehabilitation alone.

Resistance training is not deleterious but does not decrease spasticity as evidenced by one level 1b RCT (Bye et al. 2017).

There is level 2 evidence (from 2 RCTs; Martinez et al. 2018, Estes et al. 2017, further supported by 1 small level 4 pre-post study by Gant et al. 2018)) that combination therapies do not consistently reduce spasticity. This is slightly challenged by level 4 evidence (small pre-post, Mazzoleri et al. 2017) that FES cycling followed by robotic exoskeleton training may reduce spasticity.

There is level 1b evidence (from one RCT; Sivaramakrishnan et al., 2018) that a single session of electrical stimulation with FES or TENS exerts similar anti-spasticity effects, suggesting both TENS and FES may be used as therapeutic adjuncts.

There is level 1b evidence (from one RCT; Gomez-Soriano et al., 2018) that TENS and vibration therapy may reduce plantar flexion spasticity through inhibition of the plantar tibialis anterior cutaneous reflex, rather than the soleus H reflex.

There is level 2 evidence (from two prospective controlled trials and one pre-post study; Van der Salm et al. 2006; Seih et al. 1994; Robinson et al. 1988a) that a single treatment of surface muscle stimulation reduces local muscle spasticity with agonist stimulation more effective than stimulation to the antagonist.

There is conflicting evidence for how long the effects of a single treatment of electrical stimulation on muscle spasticity persist, although they appear to be relatively short lasting (i.e., ≤ 6 hours).

There is level 4 evidence (from one pre-post study; Robinson et al. 1988b) that a long-term program of muscle stimulation does not reduce muscle spasticity and may even increase local muscle spasticity.

There is conflicting level 4 evidence (from two pre-post studies; Cart et al. 2013; Tancredo et al. 2013) that use of neuromuscular electrical stimulation decreases spasticity.

There is level 1b evidence (from one RCT; Tamburella et al. 2014) that kinesio tape has short-term effects of decreasing spasticity and improving balance and gait in individuals with chronic SCI.

There is level 1a evidence (from three RCTs; Oo 2014; Chung & Cheng 2010; Aydin et al. 2005) that an ongoing program of TENS acts to reduce spasticity as demonstrated by various clinical and electrophysiological measures.

There is level 1b evidence (from a single RCT; Aydin et al. 2005) that reductions in spasticity with ongoing programs of TENS may persist for up to 24 hours.

There is level 1a evidence (from two RCTs; Oo 2014; Aydin et al. 2005) that a single treatment of TENS acts to reduce spasticity but to a lesser degree than that seen with ongoing programs of TENS.

There is level 1b evidence (from one RCT and one pre-post study; Laessoe et al. 2004; Alace et al. 2005) a single RCT supported by a single pre-post study that a single bout of penile vibration acts to reduce spasticity lasting for at least 3 hours and possibly up to 6 hours.

There is level 2 evidence (from one RCT; Walker 1985) that helium-neon irradiation of sensory nerves may suppress ankle clonus for up to 60 minutes following 40 seconds of stimulation.

There is level 4 evidence (from one pre-post study; Halstead et al. 1993) that several sessions of rectal probe stimulation reduces lower limb muscle spasticity for up to 8 hours.

There is level 4 evidence (from one pre-post study; Van der Salm et al. 2006) that electrical stimulation of the triceps surae does not significantly reduce spasticity.

There is level 1b (In et al. 2018, N=28 RCT) evidence that reflects reduced plantar-flexor spasticity resulting after whole body vibration (16 minutes, twice daily, 5 times per week over 8 weeks).

There is level 2 (Estes et al. 2018, N-29 RCT) evidence supporting that single whole-body vibration sessions (4 or 8, 45 second bouts of 30 or 50Hz vibration) does not result in reduced quadriceps spasticity.

There is level 4 evidence (from one pre-post study; Murillo et al. 2011) that vibration over the rectus femoris muscle results in reduced knee spasticity and increased knee range of motion.

There is level 5 evidence (from one observational study; Ness & Field-Fote 2009) that (whole body vibration; 4, 45 second bouts of 50Hz vibration, 3 times per week over 4 weeks) results in reduced quadriceps spasticity over the short term.

There is level 4 evidence (from one pre-post study; Goldberg et al. 1994) that short periods of massage (e.g., 3 minutes) of the triceps surae results in reduced H-reflexes with the effect lasting no longer than a few minutes.

There is level 4 evidence (from one pre-post study; Price et al. 1993) that cryotherapy may reduce muscle spasticity for up to 1 hour after removal of the cold stimulus.

There is level 4 evidence (from one pre-post study; Altindag & Gursoy 2014) that three sessions of extracorporal shock wave therapy may reduce muscle tone over the short term.

There is level 4 evidence (from one pre-post study; Cobelijic et al. 2018) that better clinical and neurophysiological understanding is needed for galvanic vestibular stimulation responders vs nonresponders to potentially optimize galvanic vestibular stimulation stimulation parameters for responders.

There is level 4 evidence (from three pre-post studies and one case series; Hofstoetter et al. 2014; Pinter et al. 2000; Barolat et al. 1995; Dekopov et al. 2015) that ongoing spinal cord stimulation may provide some relief from otherwise intractable spasticity.

There is level 4 evidence (from one pre-post study and one case series; Hofstoetter et al. 2014; Midha & Schmitt 1998) that the beneficial effects of spinal cord stimulation may subside for most initial users over a short period of time. This, combined with the potential for equipment failure and adverse events, suggests that spinal cord stimulation may not be a feasible approach for ongoing management of spasticity.

There is level 1a evidence (from two RCTs and one case control; Nardone et al. 2014; Benito et al. 2012; Kumru et al. 2010) that rTMS decreases spasticity and improves walking speed.

There is level 1b evidence (Nardone et al. 2017; RCT) that intermittent theta-burst stimulation reduces upper extremity spasticity for up to 1 week.

Neuro-Surgical Interventions for Spasticity

There is level 2 evidence (from one RCT and one case series; Livshits et al. 2002; Putty & Shapiro 1991) that dorsal longitudinal T-myelotomy may result in reduced spasticity in those individuals initially refractory to more conservative approaches. These reductions may not always be maintained over the course of several years.

There is level 2 evidence (from one RCT; Livshits et al. 2002) that Pourpre's technique for dorsal longitudinal T-myelotomy is more effective in maintaining reduced levels of spasticity than the Bischof II technique.

Level 1b evidence (Levi et al. 2018; RCT, N=10) has not demonstrated that transplantation of human neural stem cells results in persistent spasticity reduction in participants with chronic cervical SCI.

Level 4 evidence (Vaquero et al. 2018; Pre/post, N=11) reveals that initial improvements in spasticity are not persistent as a result of intrathecal administration of autologous mesenchymal stem cells in SCI.

Pharmacological Treatment for Spasticity

There is Level 1a evidence that oral baclofen improves muscle spasticity secondary to SCI. This conclusion is based on the results from eight RCTs (Yan et al. 2018, Luo et al. 2017, Chu et al. 2014; Nance et al. 2011; Aydin et al. 2005; Duncan et al. 1976; Burke et al. 1971, Jones et al.

1970) although is minimally muted by a single negative finding from one small RCT (Hinderer et al. 1990) with an overall lack of homogeneity in outcome measures and study participants. Additional evidence from a prospective controlled trial (Dicpinigaitis et al. 2000), a cohort (Veerakumar et al. 2015) and pre-post study (Nance 1994) also provide support for the use of oral baclofen in reducing spasticity.

There is Level 1b evidence (Yan et al. 2018, N=336, Luo et al. 2017, N=150) supporting the immediate effect of baclofen for the treatment of spasticity but that at 6 weeks post treatment, baclofen is inferior to botulinumtoxin A and tolperisone.

There is level 1b evidence (Corbett et al. 1972, RCT, N=9) supported by 2 other trials (level 2 evidence (Level 2, Neill et al. 1964, Cohort, N=20) confirming that valium (diazepam) is effective in decreasing spasticity secondary to SCI.

There is level 1a evidence (from six small-sample RCTs; Ordia et al. 1996; Nance et al. 1995; Coffey et al. 1993; Hugenholtz et al. 1992; Loubster et al. 1991; Penn et al. 1989) that bolus or test dose intrathecal baclofen decreases spasticity.

There is level 4 evidence (from several studies; see Table 13) that support the use of long-term intrathecal baclofen to decrease spasticity.

There is conflicting level 4 evidence (from several studies; see Table 15) that intrathecal baclofen may improve functional outcomes.

There is level 1b evidence (from two RCTs; Ordia et al. 1996; Nance et al. 1995) that intrathecal baclofen is a cost-effective intervention for treating post SCI spasticity.

There is level 4 evidence (from several studies; see Table 13) that complication rates with the long-term use of intrathecal baclofen are relatively low although complications can occasionally be severe.

There is level 4 evidence (from one case series; Meythaler et al. 2003) that adding cyprohetptadine to baclofen and benzodiazepines may be useful for the treatment of intrathecal baclofen withdrawal.

There is level 1a evidence (from two RCTs and one prospective controlled trial; Chu et al. 2014; Nance et al. 1994; Mirbagheri et al. 2013b) to support the use of tizanidine in reducing spasticity.

There is level 1b evidence (from one RCT, two prospective controlled trials; Stewart et al. 1991; Malinovsky et al. 2003; Remy-Neris et al. 1999) supported by several non-controlled studies in favour of using clonidine as a SCI anti-spasmodic although this must be interpreted cautiously given small study sample sizes, inadequate outcome measure selection, occurrence of adverse events and less than robust study designs.

There is level 1a evidence (from two large-scale RCTs; Cardenas et al. 2014; Cardenas et al. 2007) that indicate no significant anti-spasmodic effects of Fampridine-SR compared to placebo; however, this is tempered by positive findings from level 1b evidence (from one small RCT and one pre-post study; Potter et al. 1998a; Potter et al. 1998b) on the beneficial anti-spasmodic effects of Fampridine-SR. Study results must be interpreted with caution given that spasticity

results were secondary outcomes of all studies except the phase 3 clinical trial results from Cardenas et al. (2007).

There is conflicting level 1b evidence (from one RCT and one pre-post study; Donovan et al. 2000; Hayes et al. 1994) that intravenous administration of Fampridine has no significant anti-spasmodic effect. Study results must be interpreted with caution given that spasticity results were secondary outcomes of the studies.

There is level 1b evidence (from one RCT and one pre-post study; Thompson et al. 2013; Nance et al. 1994) that supports the use of cyproheptadine in the treatment of spasticity in individuals with chronic SCI.

There is level 4 evidence (from one case series; Meythaler et al. 2003) supporting the use of cyproheptadine (along with baclofen and diazepam) as an adjunct treatment of acute intrathecal baclofen withdrawal syndrome.

There is level 1b evidence (from one RCT; Gruenthal et al. 1997) that supports the use of gabapentin for SCI-related spasticity. Despite the robust study design and validated outcome measures, no confidence intervals were reported and the sample size was relatively small.

There is level 1b evidence (from one RCT; Liu et al. 2014) that traditional Chinese medicine is a safe, effective and economical long-term treatment for spasticity in SCI.

There is level 2 evidence (from one prospective controlled trial; Casale et al. 1995) for short-term use of intravenous orphenadrine citrate for treatment of spasticity secondary to SCI.

There is level 1b evidence (from one RCT; Theiss et al. 2011) that riluzole is effective in treating spasticity post SCI.

There is level 1b evidence (from one RCT; Lee & Patternson 1993) that L-threonine produces minimal anti-spasmodic effects post SCI.

There is level 4 evidence (from one pre-post study; Brackett et al. 2007) that naloxone causes a profound increase in spasticity in individuals with SCI.

There is level 1b evidence (from one RCT; Finnerup et al. 2009) that Levitiracetam is not effective for treating spasm severity in SCI.

Continued use of diazepam and dantrolene for reducing SCI-related spasticity is not supported with up to date evidence and would benefit from new controlled comparison studies. Whether effective or not, replicating results in well-designed trials is warranted before alternative recommendations for new or older treatments will be accepted into current practice.

There is level 1b evidence (from one RCT; Pooyania et al. 2010) that nabilone is effective in reducing spasticity in both the involved and overall muscles.

There is level 2 evidence (from one compromised RCT; Hagenbach et al. 2007 and supported by one pre-post study; Kogel et al. 1995) to support the use of oral delta-9-tetrahydrocannabinol (dronabinol) in reducing both objective and subjective measures of spasticity.

There is level 1b evidence (from one RCT, two pre-post studies, and one case series; Richardson et al. 2000; Spiegl 2014; Bernuz et al. 2012; Hecht et al. 2008) that BTXtype A improves focal muscle spasticity in SCI. It is important to note the RCT included just six of 52 subjects with spasticity of confirmed spinal cord origin.

There is level 4 evidence that BTX improves spasticity and range of motion in persons with incomplete SCI.

There is a lack of literature looking at the impact of BTXchemodenervation on function and quality of life.

There is level 4 evidence (from one case series; Uchikawa et al. 2009) that phenol neurolysis improves pain, range of motion and function related to shoulder spasticity for individuals with tetraplegia in SCI.

There is level 4 evidence (from one pre-post study and two case series; Ghai et al. 2013; Ghai et al. 2012; Yasar et al. 2010) that phenol neurolysis reduces hip adductor spasticity in individuals with paraplegia and tetraplegia in SCI.

There is level 4 evidence (from one pre-post study; Demir et. al. 2018) that phenol neurolosis reduces spasticity in the hip flexors and knee extensors with associated improvements in ease of catheterization, hygiene and satisfaction.

There is no literature to support the use of focal neurolysis with alcohol in the management of spasticity in SCI.

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Abbreviations

AIS	American Spinal Injury Association Impairment Scale
AS	Ashworth Scale
BTX	Botulinum Toxin
EMG	electromyography
FES	functional electrical stimulation
FIM	Functional Independence Measure
MAS	Modified Ashworth Scale
PSFS	Penn Spasm Frequency Scale
RCT	randomized controlled trial
rTMS	repetitive transcranial magnetic stimulation
SCATS	Spinal Cord Assessment Tool for Spasticity
SCI	spinal cord injury
SCI-SET	Spinal Cord Injury Spasticity Evaluation Tool
tDCS	transcranial direct current stimulation
TENS	transcutaneous electrical nerve stimulation
TMS	transcranial magnetic stimulation
VAS	visual analog scale