Key Points

Spasticity Outcome Measures

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.

Passive Movement-based Approaches for Reducing 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 Movement-based Approaches for Reducing Spasticity

Active exercise interventions such as hydrotherapy and FES-assisted cycling and walking may produce short-term reductions in spasticity.

Direct Muscle Stimulation for Reducing Spasticity

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

Various Forms of Afferent Stimulation for Reducing Spasticity

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

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

Other forms of afferent stimulation including massage, cryotherapy, helium-neon irradiation, and whole-body vibration may result in immediate spasticity reduction but require more research to examine long-term effects.

Direct Spinal Cord and Transcranial Magnetic Stimulation

Spinal cord stimulation may provide spasticity relief over a few months but long-term effectiveness and cost-effectiveness is less certain.
Repetitive transcranial magnetic stimulation may provide spasticity relief over the short-term but long-term effectiveness is unknown.

Neuro-Surgical Interventions for Spasticity

Dorsal longitudinal T-myelotomy may result in reduced spasticity.

Oral Baclofen

Oral baclofen reduces muscle spasticity in people with SCI.

Intrathecal Baclofen

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

Effect of Medications Other than Baclofen

Tizanidine may be useful in treating SCI spasticity.

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

The usefulness of 4-Aminopyridine in the treatment of SCI spasticity requires confirmation through additional well-designed studies.

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

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

Orphenadrine citrate may reduce spasticity in SCI but additional confirmatory research is needed.

The use of L-threonine in the treatment of SCI spasticity requires confirmation through additional well-designed studies.

Continued use of diazepam and dantrolene would benefit from controlled comparison studies.

Cannabinoids

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

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

Focal Neurolysis

Botulinum neurotoxin appears to 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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Spasticity Following Spinal Cord Injury

1.0 Introduction

Definition

Spasticity is quite commonly confused with tremor, rigidity, clonus, dystonia and various movement disorders (i.e. athetoid, ballisms, 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. Perhaps the most common definition of spasticity was put forth by Lance (1980): "spasticity is 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." 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. Most antispastic treatments are, therefore, directed at the reduction of reflex activity. In recent years, however, 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 patients (Dietz & Sinkjaer 2007).

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. Furthermore, approximately 41% (Levi et al. 1995) of these individuals 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).

Determining Impact of Treatment

Spasticity in SCI varies with location and degree depending on the injury pathophysiology. For this reason, an assessment of treatment goals must be considered with various management

strategies and cost factors. Sometimes, increased spasticity is beneficial for transfers and mobility, and the reduction of tone may negatively impact those activities of daily living. 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&b), 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 patient 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).

Outcome Measurement and Spasticity

The studies reviewed in this chapter involve a variety of outcome measures that have been summarized into 4 categories: 1) Known Clinical Measures; 2) Other Measures; 3) Electrophysiological Measures and 4) Quality of Life Measures. Among the known measures, some are validated and only a subset of those is used frequently by clinicians. It will be important to develop agreement as to well-defined, clinically meaningful outcome measures for demonstrating the efficacy of an experimental therapeutic intervention (Steeves et al 2007). The abundance of outcome measures in the other categories are not well understood by the majority of clinicians and increases the difficulties encountered when comparing studies and treatments. Outcome measure feasibility is another important consideration given that clinicians commonly do not have consistent access to 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 patients.

Table 1 Summary of Outcome Measures used in Spasticity Intervention Studies

Known Clinical Measures	Other Measures	Electrophysiological Measures	Quality of Life Measures
1. Ambulation Index 2. American Spinal Injury Assessment (ASIA; motor and sensory index) 3. Ashworth (Original and Modified) *I 4. Barthel Index Clonus (count or duration) 5. Deep Tendon Reflexes (DTR) 6. Expanded disability status scale (EDSS)	1. Adverse Event monitoring 2. "Clinical interview questionnaire" 3. "Clinical Rating Score (CRS)" 4. "Clinically significant relief of spasticity" 5. "Continuation of study drug after trial" 6. Cost effectiveness analysis. 7. Cystomanometry 8. "Evaluation of functional abilities"	1. "Electrophysiologic testing" 2. EMG/velocity ratio for any given speed – stretch reflex response 3. Flexion reflex measurement Peak isometric quad torque in response to surface electrical stimulation 4. Gait analysis 5. H-Reflex and H/M ratio (latency and amplitude) 6. Joint angular displacement	1. Hopkins symptom check list (HSCL) 2. Sickness Impact Profile (SIP) 3. Global Impression (Patient and/or Clinician)

Known Clinical Measures	Other Measures	Electrophysiological Measures	Quality of Life Measures
7. Functional Independence Measure (FIM) 8. Goal Attainment Scale 9. Grip strength (Jamar dynamometer) 10. Global Impression (Patient and/or Clinician) 11. Incapacity Status Scale* 12. Klein-Bell ADL scale 13. Jebsen Hand Function Test 14. Manual Muscle Testing 15. Nine-hole peg test (upper limb problems only) 16. Passive joint ROM 17. Patient Evaluation and Conference System (PECS) 18. Pendulum test (relaxation index; peak velocity) 19. Plantar stimulation response 20. Present Pain Intensity 21. Profile of Moods Scale 22. Rivermead Mobility Index (RMI) 23. Seven point terrible-delighted scale 24. Six point Likert scale (spasticity) 25. Smith Hand Function Evaluation 26. Spasm Frequency Scale (SFS) 27. Spasm Severity Scale (SSS) 28. Standard neurological examination 29. Timed 10 m walk test (lower limb problems only) 30. Visual Analogue Scale (VAS: Spasticity, Pain, Satisfaction)	9. "Decrease in hypertonicity" 10. "Discontinuation of other antispasticity medications" 11. "Evaluation of personal independence" 12. "Five point scale ("interference of spasticity on selected self-care activities" and weekly rate of resistance to movement) 13. "Functional disability score (FDS)" 14. "Gait spasticity and transfer activity" 15. "Impression of pain" 16. "Neurological reflex scale" 17. Outcome measure not specified. 18. "Painful Spasm Scale" 19. "Patient Caregiver subjective responses" 20. Patient/Clinician Global measure (4 point scale) 21. Patient Daily Diary or Log (spasticity, clonus, nocturnal awakenings related to spasms) 22. Subjective ratings (problem severity, spasticity assessment, pain) 23. "Telephone questionnaire regarding decrease in symptoms" 24. "Use of limbs and transfer activity (weekly)" 25. Vibratory Inhibition Index (VII)	7. Motor Evoked Potentials (MEP) 8. Polysynaptic reflex measurement 9. Quantitative assessment of ankle hypertonicity 10. Viscous and elastic stiffness to sinusoidal ankle perturbation of 5° at 3 to 12 Hz.	

Known Clinical Measures	Other Measures	Electrophysiological Measures	Quality of Life Measures
31. Weschler Memory Test [¥]Includes Spasticity sum score=average MAS for left/right/examiner 1/examiner 2 for each muscle group.			

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) patient 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 patient 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 Modified Ashworth (Bohannon & Smith 1987; Haas et al 1996) spasticity scales, the Spasm Frequency scale (Penn 1988; Priebe 1996), the Pendulum test (Nance 1994) and the Spastic Paraplegia Rating scale (Schüle et al. 2006). Please refer to Chapter 25 on outcome measures for a discussion of these measures.

> 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.

Overview of Treatments

Physical therapy, surgery, pharmacotherapy and 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 patient 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 necessary to treat focal spasticity. A combination treatment regimen can be individualized and appears to be a common approach in clinical practice.

2.0 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. 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. However, Vorrink et al. (2008) demonstrated no significant differences in spasticity as indicated by patient self-report using a visual analog scale in a study examining the effect of two different wheel choices (Vorrink et al. 2008). 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 6 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) neuro-surgical approaches. 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.

2.1 Interventions Based on 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 patients with a lesion of the upper motor neuron is equivocal (Katz 1991).

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). They are however, 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 RCT involving the use of 3 of these approaches (Bobath, Rood, Brunnstrom) in combination with Baclofen therapy to reduce spasticity.

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; 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 (Lechner et al. 2003; 2007).

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 21.1 (i.e., other than Odeen & Knutsson, 1981) which outlines the specific investigations of effectiveness of these "passive" approaches. The individuals examined in all 3 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 2 Studies of Passive Movement-based Approaches for Reducing Spasticity

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Li et al. 2007 China PEDro = 6 RCT N=28	**Population:** SCI: Mean age: 56 yrs; Gender: males = 17, females = 11; Level of injury: paraplegic, thoracic; Severity of injury: complete = 16, incomplete = 12; Time since injury = 38 days; Chronicity = acute. **Treatment:** Control Group: Routine Therapy (undefined). Intervention group: Routine Therapy + oral Baclofen (initial dosage=5mg, increase by 5mg every 5 days to maximum of 60 mg) + neural facilitation (Rood, Brunnstrom and Bobath techniques) for 1-2 40 minute sessions 6 days/week for 6 weeks. **Outcome Measures:** Modified Ashworth Scale; BI tested pre-post 6 weeks intervention.	1. More subjects had reduced spasticity (reduced Ashworth scores) with neural facilitation and Baclofen Grade I (n= 2 to 12 from pre to post), Grade II (n=7 to 2) and 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 treatment vs. control group in complete SCI (45.35 +/- 12.01 vs. 30.86 +/- 11.20) and incomplete SCI (57.98 +/- 11.54 vs. 42.14+/-12.75) (p<0.05).
Harvey et al. 2009 Australia PEDro = 6 RCT N = 20	**Population:** 20 tetraplegic subjects, level of injury C2-C7, who had ankle stiffness; one ankle from each subjects was designated for treatment, and the other as control **Treatment:** Passive movement of the experimental ankle, 5 days/week for 6 months **Outcome Measures:** Passive dorsiflexion of ankles; the modified Ashworth scale of the hamstring and plantar-flexor muscles; Global Impression of Change scale	1. Passive dorsiflexion increased for the experimental ankle (88+9 vs. 91+10) and decreased for the control (89+8 vs. 87+9) (p=0.002), overall difference of 4.0^o. 2. There was no significant difference in the scores for the Ashworth scale 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.
Lechner et al. 2007 Switzerland & Austria Cross-over RCT PEDro = 4 Initial N=12; Final N=11	**Population:** SCI: Mean age = 44 yrs; Gender: males = 12, females = 0; Level of injury: paraplegia = 8, tetraplegia = 4; Severity of injury: AIS: A-B; Time since injury = 13.1 yrs; Chronicity = chronic. **Treatment:** 1) Control – no intervention; 2) Intervention H – hippotherapy treatment; 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 4 weeks. **Outcome Measures:** Ashworth Scale; VAS -self rating of spasticity; Mental well-being Bf-S.	1. Overall, significant reductions in spasticity were observed as indicated by Ashworth Scale sum score changes caused by Hippotherapy vs. none for the control condition or other interventions (p<0.05). 2. Significant differences were found when comparing pre- vs. post-session Ashworth Scale 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 vs. intervention R

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
		(p<0.05) and S (p<0.05) but not for the control condition. 4. Significant spasticity reductions were found in the VAS scores before and after treatment 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.
Rayegani et al. 2011 India PEDro=4 RCT N=64	**Population:** Mean age: 43 years; Gender: 61 males, 3 females; Cause of injury: SCI; Level of injury: 63 complete, 1 incomplete, cervical (n=11), thoracic (n=51), lumbar (n=2); **Treatment:** Group 1 (controls, n=29) – physical therapy for 2 weeks; Group 2 (n=35) – electrical passive pedaling system. **Outcome Measures:** Hip, knee, ankle and range of motion, Spasticity Scale, electrodiagnostic parameters, reflex onset, latency and amplitude.	1. Spasticity scale decreased significantly after passive cycling in group 2 (p=0.003); there was no change for group 1. 2. Hip, knee, and ankle range of motion in group 2 were significantly improved after pedal exercise (range p=0.000 – 0.111); there was no change for group 1.
Sköld, 2000 Sweden Downs & Black score=15 Pre-post N=45 (Passive stretches performed on n=12)	**Population:** Age = 17-47 yrs; Gender: males = 39, females = 6; Level of injury: cervical, thoracic; Severity of injury: AIS: A-D; Time since injury = 3-26 yrs, (Passive stretches performed on n=12, thoracic AIS C, D). **Treatment:** Repetitive passive movements of standardized range of motion in 3 different positions administered with motorized table, 10 minutes per position, 20-30 movements/minute, 2 sessions/week for 6 weeks. **Outcome Measures:** self-reported VAS: "no spasticity" to "most imaginable spasticity", MAS, collected just prior and after each treatment 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 treatment was discontinued for 4 days (p<0.018).
Kakebeeke et al. 2005 Switzerland Downs & Black score=14 Pre-post N=10	**Population:** Age = 23-60 yrs; Gender: males = 9, females = 1; Level of injury: C6 to T12; Severity of injury: AIS: A & B; Time since injury = 1-25 years. **Treatment:** Passive cycling with	1. 6/10 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

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	motorized cycle for 30 minutes at 40 RPM (1 session) vs. no cycling. **Outcome Measures:** Torque resistance to movement on isokinetic dynamometer, subjective subject assessment collected just prior and following cycling (or control).	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 Downs & Black score=13 Pre-post N=32	**Population:** Mean age = 37yrs; Gender: males = 28, females = 4; Level of injury: C4-T12; Severity of injury: AIS: A-D; Time since injury = 1mth to 6 yrs. **Treatment:** Hippotherapy-K® (HTK; Kuenzle 2000): An average of 11 sessions (5-24) each lasting 25-30 minutes. Sheepskin (no saddle) on Icelander horse. **Outcome Measures:** Ashworth scale 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 treatment sessions led to lower Ashworth scores immediately after sessions. 2. Significant decrease in muscle tone as indicated by reduced Ashworth 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 ($p=0.4$).
Odeen & Knutsson, 1981 Sweden Downs & Black score=12 Pre-post N=9	**Population:** Age = 21-67 yrs; Gender males = 8, females = 1; Time since injury > 3 yrs. **Treatment:** Standing in forced dorsiflexion or plantarflexion (i.e., load applied) vs. stretch applied to plantar flexors while supine. 30 minute 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 treatment.	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 1 cycle/s than at 0.25 cycle/s, although significant reductions were still seen for both conditions of dorsiflexion stretch (i.e., standing and supine) at the slower test speed.

Note: AIS=ASIA Impairment Scale; BI=Barthel Index; Bf-S=Befindlinchkeits-Skala; EMG=eletctromyography; MAS=Modified Ashworth Scale; RPM=Rotations per minute; VAS=Visual Analog Scale

Discussion

The most prevalent therapeutic intervention involving passive movement to reduce spasticity is therapist or caregiver-mediated muscle stretching. Harvey et al. (2009) conducted a 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 1 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 modified Ashworth scale 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 modified Ashworth scale score ranged from 0 to 2 with a median score of 1. Notably, there were no participants with a score of 2 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 4° improvement was noted between the experimental and control conditions, which 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 vs. no cycling 1 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 2 different speeds of knee flexion/extension. The majority of subjects tested (i.e., 6 of 10) reported subjectively that their spasticity was reduced following cycling; however, some subjects (i.e., 3 of 10) 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 in a study 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 relevant outcome measures which identified that the passive cycling group showed a significant decrease (p=0.003) according to the spasticity scale and hip, knee and ankle range of motion also significantly improved.

Although a weaker study design (i.e., Pre-Post Trial), Sköld (2000) did employ clinically relevant outcome measures (i.e., modified Ashworth and a self-report visual analogue scale) and an intervention administered over 6 weeks. This intervention involved the evaluation of standardized, repetitive passive movements of prone and supine hip flexion/extension and lumbar lateral flexion elicited by a motorized table in a subset of subjects with AIS C and D paraplegia. These subjects were drawn from a larger study examining self- vs. clinically-rated spasticity fluctuations. Results of the study indicated that there was a significant reduction in the modified Ashworth Score and also a significant decrease in the self-report measure of spasticity immediately following passive movement. In addition, it was reported that these reductions in spasticity were partially maintained when self-report assessments (but not clinical evaluations) were 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 6 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 vs. the neural facilitation techniques was also not assessed so it is uncertain as to the degree of effectiveness associated with these manual techniques.

Lechner and colleagues have conducted two separate investigations demonstrating a short term effect of hippotherapy on decreasing spasticity of the lower extremity (Lechner et al. 2003; 2007). The more rigorous of these studies involved a low n (n=12) crossover RCT during which each subject received twice weekly 25 minute sessions over 4 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 Ashworth scores, $p<0.05$) and self-reported spasticity ($p<0.05$) in comparison to the other interventions. Significant differences were found when comparing pre- vs. post-session Ashworth Scale scores for all 3 intervention groups (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; 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 9 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 10-15º 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 a single study that passive ankle movements may not reduce lower limb muscle spasticity in persons with initial mild spasticity.

There is level 2 evidence from a single study supported by level 4 evidence from another study 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.

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.

2.2 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) (Kesiktas et al. 2004) or those associated with functional electrical stimulation (FES)-assisted cycling (Krause et al. 2008) or locomotor training programs, whether assisted by FES (Granat et al. 1993; Mirbagheri et al. 2002) or a FES-powered orthosis (Thoumie et al. 1995).

Table 3 Studies of Active Movement-based Approaches for Reducing Spasticity

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Krause et al. 2008 Germany PEDro=5 RCT N=5	**Population:** Mean age=46yrs; Gender: males=3, females=2; Level of injury: T; Severity of injury: AIS A **Treatment:** In a crossover design SCI patients were randomly assigned to FES induced leg cycling movement group vs. passive-movement with cycle ergometer. Treatments were delivered over a single session of 60-100 minutes **Outcome Measures:** Pendulum test (Relaxation index, peak velocity), Ashworth Scale conducted within 30 minutes prior or following treatment.	1. A reduction in spasticity was seen after each intervention although the effect was significantly greater for FES-assisted vs. 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

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
		leg, while in the passive session such an increase was only present in the left leg relaxation index. 4. Reduction in the modified Ashworth Scale was seen after both active FES (p<0.001) and the passive movement session (p<0.05).
Thoumie et al. 1995 France Downs & Black score=24 Pre-post N=21	**Population:** Age = 20-53 yrs; Gender: males = 20, females = 1; Level of injury: C8-T12; Time since injury = 4-72 months. **Treatment:** Fitting of a Reciprocating Gait Orthosis II (RGO) hybrid (FES-assisted) system and subsequent locomotor training program of 2 – 1 hour sessions/week for 3-14 months. **Outcome Measures:** Spasticity (subjective self-report scale) collected prior to and following the 3-14 month trial.	1. No group analysis reported for spasticity measure – No marked changes reported, decrease in spasticity for 7 subjects at 0.5-5 hours and increase in spasticity for 4 subjects at 0.5-1 hour. No long-term effects were observed.
Kesiktas et al. 2004 Turkey Downs & Black score=17 Experimental Non-RCT N=20	**Population:** Hydrotherapy group: Mean age = 32.1 yrs; Gender: males = 8, females = 2; Level of injury: C5-6 = 3, T8-9 = 7; Severity of injury: AIS: A/B-C/D = 3/3/4; Time since injury = 7.7 yrs; Control group: Mean age = 33.1 yrs; Gender: males = 7, females = 3; Level of injury: C5-6 = 3, T8-9 = 7; Severity of injury: AIS: A/B-C/D = 3/3/4; Time since injury = 8.6 yrs. **Treatment:** 20 min of underwater exercises at 71°F, 3 times/week for 10 weeks in addition to conventional rehabilitation (passive ROM exercises, oral Baclofen, psychotherapy) vs. conventional rehabilitation alone. **Outcome Measures:** Ashworth Scale, Penn Spasm Severity, FIM scores and oral Baclofen intake were recorded weekly and evaluated at the beginning and end of the treatment period.	1. Both groups showed a significant decrease in Ashworth scores (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-treatment hydrotherapy scores were reduced vs. Controls (p<0.02). 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).
Mirbagheri et al. 2002 Canada Downs & Black score=17 Pre-post (1 unplanned control, dropout from training) Initial N=9; Final N=5	**Population:** Age = 25-48.9 yrs; Gender: males = 5, females = 4; Level of injury: C5-L1, Severity of injury: AIS: C-D; Time since injury = 3.1-12.3 yrs. (1 unplanned control, dropout from training). **Treatment:** FES-assisted walking	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

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	for as much time as possible during daily living (~1-3 hours/day) for 16-18 months following 4 weeks of training. **Outcome Measures:** Reflex and intrinsic stiffness (mathematical modelled responses of torque resistance to movement), modified Ashworth scale collected prior to and following the 16-18 month trial.	non-FES subject as indicated by increased reflex stiffness and no change in intrinsic stiffness. 3. The modified Ashworth score either showed no change following the training period or was not collected (this was not clearly presented by the authors).
Granat et al. 1993 Scotland Downs & Black score=5 Pre-post N=6	**Population:** SCI: Age = 20-40 yrs; Gender: males = 3; females = 3; Level of injury: C4 to L1; Severity of injury: Frankel grade: C = 3, D = 3; Time since injury = 2-18 yrs. **Treatment:** FES-assisted locomotor training for at least half an hour each day for a minimum of 5 days/week for a minimum of 3 months. **Outcome Measures:** Spasticity (Ashworth Scale and Pendulum Test), Manual muscle tests using Oxford Scale, maximum voluntary contraction, Upright motor control, Gait Performance (Energy Cost), postural stability (Centre of Pressure) and modified Barthel Index. Spasticity tests were conducted at least 24 hours 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".

Note: AIS=ASIA Impairment Scale; FES=functional electrical stimulation; FIM=Functional Independence Measure; HR=heart rate; ROM=range of motion.

Discussion

All studies demonstrated positive benefits for at least one outcome measure associated with spasticity. However, it should be noted that results between two spasticity-related outcome measures within some studies were not always consistent although most investigators employed the Ashworth or modified Ashworth Scale to assess spasticity.

Krause et al. (2008) used a randomized, cross-over study design in which five complete ASIA A clients with 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 Modified Ashworth Scale for FES vs. passive movement (p<0.001 vs. p<0.05) respectively and 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.

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) vs. a control group (conventional rehabilitation only) on the basis of age, gender, time post-injury, injury level and severity, spasticity (Ashworth) and function (FIM). This study produced consistent results across all spasticity-related measures with spasticity reductions evident following the 10 week hydrotherapy treatment program for both Ashworth Scale 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 vs. 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 also the benefits of reduced spasticity on motor function. Kesiktas et al. (2004) did not mention how soon after the final intervention the measures were taken so there is no indication of how long the beneficial effect might be maintained.

The remaining studies using active movement-based approaches involved pre-post trial designs of FES-assisted walking with and without orthoses. Mishorbagheri et al. (2002) calculated reflex and intrinsic stiffness of the ankle by employing a mathematical model of position vs. torque resistance in response to perturbations as a means of assessing spasticity prior to and following a FES-assisted walking training program. This program involved 4 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 training while another individual with SCI, but not actively involved in FES-assisted walking, demonstrated no reduction in spasticity. Although the modified Ashworth scale was noted as an outcome measure in the methods the authors failed to report the final results associated with this clinical measure.

Granat et al. (1993), in a similar trial of FES-assisted walking in people with longstanding SCI (Frankel C or D), also found reductions in spasticity by employing a pendulum drop test but did not show any change pre- and post-training when considering Ashworth scale 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 (RGO) on spasticity following a long-term program (i.e., 3-13 months) of gait training. No group results were reported for spasticity although it appeared that no systematic effects were obtained on a customized self-report version of the Ashworth scale. Some subjects (n=7) reported decreases in spasticity in the short-term, while others reported increased spasticity (n=4).

Conclusions

There is level 2 evidence from a single study that hydrotherapy is effective in producing a short-term reduction in spasticity.

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

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).

There is no evidence describing the length and time course of the treatment effect related to spasticity for hydrotherapy or FES-assisted walking.

Active exercise interventions such as hydrotherapy and FES-assisted cycling and walking may produce short-term reductions in spasticity.

2.3 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 (PES) or patterned neuromuscular stimulation (PNS), functional electrical stimulation (FES) and transcutaneous electrical nerve stimulation (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). 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 so as 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 4 Studies of Direct Muscle Stimulation for Reducing Spasticity

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Murillo et al. 2011 Spain Downs & Black score=21 Cross-Sectional N=28	**Population:** Treated (n=19) - Mean age: 36.0 years (SD 10.6y; range 18-67); Level of injury: cervical (n=13), thoracic (n=6), ASIA A (n=9), C (n=9), D (n=1); Mean time since injury: 5.6 months (SD 1.9 mo); Control (n=9) – Mean age: 33.8 years (SD 9.4y; range 23-48), no SCI. **Treatment:** Vibration was applied	1. Patients with incomplete SCI presented higher number of cycles and longer duration of clonus than patients with complete SCI. 2. During vibration, there was a significant reduction in Modified Ashworth Scale score, duration of clonus, and an increase in range of motion in all patients.

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	with an electric vibration device at a frequency of 50 Hz during 10 min over the rectus femoris muscle. **Outcome Measures:** Modified Ashworth Scale, range of motion, duration/frequency of clonus.	
van der Salm et al. 2006 Netherlands Downs & Black score=18 Prospective Controlled Trial N=10	**Population:** Age = 21-42 yrs; Gender: males = 8, females = 2; Level of injury: C3-T11, Severity of injury: AIS: A = 9, C = 1; Time since injury = 28-275 months. **Treatment:** 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 minute session of each type of stimulation. Intensity at 3 x motor threshold for motor stimulation and 80% of motor threshold for afferent stimulation. **Outcome Measures:** MAS, clonus score, H reflex, and H/M ratios. Measurements were conducted just prior to, immediately after, 1 hour after and 2 hours after the intervention for each of the 4 conditions.	1. 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 2 hours) 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.
Robinson et al. 1988a USA Downs & Black score=15 Pre-post N=12	**Population:** Age = 21-62 yrs; Level of injury: paraplegia = 6, tetraplegia = 6; Severity of injury: complete = 6, incomplete = 6. **Treatment:** 1, 20 minute session of electrical stimulation of quadriceps with leg maintained at 60° flexion (isometric exercise). **Outcome Measures:** Normalized relaxation index obtained during Pendulum test (R2n) collected prior and immediately after stimulation.	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 patients who were the most spastic before stimulation. 3. No carry over effect of stimulation in spasticity measured 24 hours later.
Seib et al. 1994 USA Downs & Black score=14 Prospective Controlled Trial N=10	**Population:** Age = 19-73yrs; Gender: males = 6, females = 4; SCI (N=5): Time since injury = 3-16 yrs; TBI (N=5): Time of injury = 1-6 yrs. **Treatment:** 1, 20 minute session of electrical stimulation over the tibialis anterior measured in ipsilateral (treatment) and contralateral (control) leg vs. sham stimulation (control). **Outcome Measures:** Viscous and elastic ankle stiffness measured by frequency-dependent torque resistance immediately post-stimulation (n=10/9), and 24 hours post-stimulation (n=9/8), and	1. Spasticity was reduced in 9/10 participants ($p<0.05$) ($p<0.05$ for SCI subjects only) and this was sustained for 24 hours over all subjects ($p<0.01$) but not for SCI subjects only. 2. Spasticity was not reduced immediately or after 24 hours 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 hours post-simulation.

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	immediate post-stimulation subjective spasticity assessment (n=9).	
Robinson et al. 1988b USA Downs & Black score=14 Pre-post Initial N=31; Final N=8 4wk tx N=21, 8wk tx N=8	**Population:** Level of injury: paraplegia = 15, tetraplegia = 16; Severity of injury: complete, incomplete; Time since injury: <1yr (15), >1yr (16). **Treatment:** 4-8 wk quad reconditioning program of twice daily 20-minute stimulation sessions of quadriceps, which were at least 4 hours apart, six days per week. Stimulus currents were set at 120-160mA. **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 weeks (1-3 evaluations performed each time).	1. Most participants had increased spasticity after four weeks of reconditioning but not after eight weeks. 2. Twice as many legs had R2n decreases (spasticity increases) as had increases or no change. 3. Baseline vs. 4wk left and right R2n yielded a significant within subject difference between baseline and 4wk values (p=0.008).

Note: AIS=ASIA Impairment Scale; MAS=modified Ashworth Scale; R2n=index of Relaxation

Discussion

Murillo et al. (2011), 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 and were mostly absent by the next day. In particular, van der Salm et al. (2006) examined 3 different stimulation methodologies vs. a placebo condition and assessed ankle plantar flexor spasticity with the modified Ashworth scale, 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 vs. 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 modified Ashworth scale (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 modified Ashworth 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. Murillo et al. (2011) applied vibration at 50Hz to the rectus femoris muscle for 10 min, of which a siginificant reduction in Modified Ashworth Scale scores was observed in all 28 patients.

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 by 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 4–8 weeks with twice daily 20-minute sessions at least four hours apart, six days per week. Although 31 individuals initiated the study and 21 completed 4 weeks of the stimulation program, the study had severe subject retention issues with only 8 individuals continuing participation for the intended 8 weeks. Study results showed that most subjects actually had increased spasticity at four weeks but for the subjects who remained in the study for 8 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 across even just these 4 studies with respect to outcome measure selection. Within these papers there were measures that were clinical, neurophysiological, biomechanical and subject self-report in nature. The study with the strongest design (i.e., van der Salm et al. 2006) employed clinical and neurophysiological measures with the modified Ashworth scale, clonus score and H-reflex testing. Seib et al. (1994) employed a biomechanical approach by using a spasticity measurement system which monitored ankle viscoelastic stiffness through measurements of resistance torque to repetitive sinusoidal ankle movements. Robinson et al. (1988a; 1988b) used a clinical/biomechanical approach in measuring the normalized relaxation index (R2n) obtained from the pendulum drop test. Others 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 2 evidence from two prospective controlled trials supported by a single pre-post study 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).

Based on a single pre-post study, there is no evidence that a long-term program of muscle stimulation has an effect on reducing muscle spasticity and may even increase local muscle spasticity.

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

2.4 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, in particular 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 overcome an 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) and 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 5 Studies of Various Forms of Afferent Stimulation for Reducing Spasticity

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Chung et al. 2010 Hong Kong PEDro score=10 RCT N=18	**Population:** Age range: 24-82; Level of injury: C3-T12, ASIA A-D; Cause of injury: SCI, traumatic and non-traumatic; Time since injury: 4-364 weeks. **Treatment:** 60 minutes of active TENS (0.25 ms, 100 Hz, 15 mA) or 60 minutes of placebo non-electrically stimulated TENS over the common peroneal nerve. **Outcome Measures:** Composite Spasticity Score, Achilles tendon jerks.	1. Significant reductions were shown in the Composite Spasticity Score 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 treatment group; these reductions were not observed in the placebo group. 2. Between-group differences on both Composite Spasticity Score and resistance to full-range passive ankle dorsiflexion were significant (p=0.027 and p=0.024, respectively).
Aydin et al. 2005 Turkey	**Population:** SCI (n=21): Severity of injury: complete, incomplete; Cause	1. For both treatment groups a significant improvement was

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
PEDro = 6 RCT N=41	of injury = trauma; Chronicity: chronic; Health controls (n=20). **Treatment**: Either oral Baclofen (titrated up to 80 mg/day) for 8 weeks or TENS for 15 minutes/day for 15 days. **Outcome Measures:** SFS, Painful Spasm Scale, Ashworth Scale, 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 treatment (15 minutes after) and 15 minutes and 24 hours after the last TENS session.	noted immediately 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. In comparison with baseline, TENS showed a trend for a reduced Ashworth immediately after the first treatment (p=0.059), a significant reduction immediately after the last treatment (p=0.006) and a significant but lesser reduction 24 hours after the last treatment (p=0.020). Similar findings were obtained for Deep Tendon Reflex scores. Plantar Stimulus Response scores were only significantly reduced immediately following the last treatment session (p=0.034) whereas clonus scores were only significantly reduced immediately following the first treatment (p=0.046). 3. There was a significant reduction in H-reflex maximal amplitude (p=0.032) 24 hours after the final session. This reduction was even more apparent when tested only 15 minutes after the last treatment (p=0.026). There were only small (statistically non-significant) changes in other electrophysiologic variables with either Baclofen or TENS.
Laessoe et al. 2004 Denmark PEDro=6 RCT N=9	**Population:** Age = 27-67 yrs; Gender: males = 9, females = 0; Level of injury: C2-T8; Severity of injury: AIS: A – D; Time since injury = 4 months - 50 yrs. **Treatment:** Penile Vibratory stimulation for 5 minutes or to ejaculation. **Outcome Measures:** Modified Ashworth Scale, SFS, 24 hour EMG recordings of quadriceps and tibialis anterior activity. All collected pre-stimulation and 24 hours post-stimulation. The Modified Ashworth	1. There was a significant decrease in spasticity after penile stimulation as indicated by decreases in Modified Ashworth Scale (0<0.01). This was not sustained at 24 hours. 2. There was a slight reduction in the Penn Spasm Frequency Scale 24 hours after penile stimulation but this was not significant. 3. There was a significant reduction in EMG activity in the initial 3 hours after vibration, as

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	was also collected immediately after stimulation.	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 first hour after vibration, after which the events gradually decreased until no significant effect was observed following the 3rd hour after vibration.
Walker 1985 USA PEDro=4 RCT N=41	**Population:** Level of injury: T12-L2; Time since injury > 2 yrs. **Treatment:** Helium-neon laser irradiation to peripheral nerve sites (radial, median, saphenous nerves) for 20 or 40s 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 treatment and at 30-minute intervals up to 2 hours after irradiation.	1. No statistical comparisons reported. 2. 40 s of laser irradiation and 1 hour of electrical stimulation similarly produce complete suppression of clonus lasting 30 and 60 minutes after cessation of stimulation. 3. 20 s 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.
Ness et al. 2009 USA Downs & Black score=25 Cross-Sectional N=16	**Population:** Mean age: 46.9 years (range: 28-65 years); Gender: 14 males, 2 females; Cause of injury: SCI; Level of injury: C3-C6 (n=10), T4-T8 (n=6), all complete; Time since injury: >1 year. **Treatment:** Whole-body vibration (4, 45s bouts of 50Hz stimulation) 3days/week for 4 weeks. **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).
van der Salm et al. 2006 The Netherlands Downs & Black score=18 Pre-post N=10	**Population:** Age = 21-42 yrs; Gender: males = 8, females = 2; Level of injury: C3-T11; Severity of injury: AIS: A = 9, C = 1; Time since injury = 28-275 months. **Treatment:** 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 minute session of each type of stimulation. Intensity @ 3 x motor threshold for motor stimulation and 80% of motor	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 2 hours) 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

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	threshold for afferent stimulation. **Outcome Measures:** MAS, clonus score, H reflex, and H/M ratios. Measurements were conducted just prior to, immediately after, 1 hour after and 2 hours after the intervention for each of the 4 conditions.	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 Downs & Black score=17 Pre-post N=9	**Population:** Age = 21-41 yrs; Gender: males = 6, females = 3; Level injury: paraplegia = 3, tetraplegia = 6; Severity of injury: Frankel grade: A = 4, B = 5; Time since injury = 0.5-15 yrs. **Treatment:** At least 6 sessions of Rectal Probe Electrical Stimulation (RPES) 6 times spaced 1-4 weeks apart. Each session consisted of 7 or 15 stimulations of ~1 second duration and lasted 5-10 min. Three subjects underwent a placebo with probe insertion but no stimulation. **Outcome Measures:** Ashworth 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 stimulation, within 1 hour after and 2-4 hours after. Subject self-reports was collected every 2 hours up to 24 hours after stimulation. Pendulum tests were collected on 4 subjects and somatosensory evoked potentials (SSEPs) on 2 subjects pre and post.	1. Spasticity was reduced as indicated by reduced Ashworth scores assessed within 1 hour post-stimulation ($p<0.01$). 2. Spasticity relief as indicated by self-report was for 7.8/9.5 hours (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 any significant correlation with the amount of relief provided.
Alaca et al. 2005 Turkey Downs & Black score=16 Pre-post N=10	**Population:** Age = 22-35 yrs; Gender: males = 10; Level of injury: C8-L1; Severity of injury: AIS A; Time post-injury = 1.1-9 yrs. **Treatment:** Penile Vibratory stimulation for 6, 3 minute periods (separated by 1 minute) or to ejaculation. **Outcome Measures:** Ashworth 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 and 48 hours post-stimulation.	1. There was a significant decrease in spasticity after penile stimulation as indicated by decreases in the Ashworth Scale ($0<0.001$). This was significantly lower than baseline at hour 3 ($p=0.001$) and 6 ($p=0.03$) with a trend lower at 24 hours ($p=0.08$). 2. There were slight (non-significant) reductions in the SFS and clonus scores at hour 3. 3. There were no changes in painful spasms, plantar stimulation responses, deep tendon reflexes and effect on function scale scores with penile vibration.
Goulet et al. 1996 Canada Downs & Black score=16 Pre-post N=14	**Population:** Age = 21-54 yrs; Gender: males = 13, females = 1; Level of injury: C4-T12; Severity of injury: AIS: A-D; Time since injury = 2-194 mo.	1. Significant decreases were seen in clinical measures of spasticity as seen by reductions in modified Ashworth ($p=0.04$), ATR ($p=0.01$), and global spasticity

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Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	Treatment: TENS stimulation (i.e., low threshold afferent nerve stimulation) over the common peroneal nerve for 30 minutes. **Outcome Measures:** Modified Ashworth scale, 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.	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).
Goldberg et al. 1994 Canada Downs & Black score=15 Pre-post N=17	**Population:** Study 2 (N=10): Age = 21-33 yrs; Gender: males = 9, females = 1; Level of injury: C4-T10; Severity of injury: complete, incomplete; Time since injury = 3-11 months. Study 1 (N=7): Healthy controls. **Treatment:** One-handed petrissage (massage) applied to the belly of the triceps surae muscle group for 3 minutes. **Outcome Measures:** H-reflex peak amplitude, H-reflex latency (Study 2, SCI only), M-responses collected during massage plus 3 and 6 minutes prior and 3 and 6 minutes after massage (10 responses of each averaged).	1. Significant decrease in H-reflex amplitude during massage as compared to before and after (p=0.008). The response 3 minutes 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 decreases seen in controls in supine position were also able to be obtained in prone position which was preferred position for SCI subjects.
Possover et al. 2010 Switzerland Downs & Black score=14 Case Reports N=3	**Population:** Patient 1 – female, T10; Patient 2 – male, T5; Patient 3 – male, T7/8. **Treatment:** Continuous 20Hz TENS to the sciatic, pudendal nerves and to the sacral nerve roots S3 and S4. **Outcome Measures:** Spasticity of lower extremities, motion of the legs.	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 patients standing and alternative locomotion.
Price et al. 1993 USA Downs & Black score=12 Pre-post N=25	**Population:** 25 subjects with stroke (9), head injury (9) and SCI (7); no information provided on subject details. **Treatment:** Cryotherapy (water and ice placed on calf for 20 minutes). **Outcome Measures:** Elastic and viscous components of ankle stiffness represented by mathematical modelling of torque vs. 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	SCI Results 1. Clinically significant reductions in spasticity as indicated by a reduction in total path length of 11Nm/rad or greater were seen in 5 of 7 subjects with SCI during cryotherapy and 5 of 7 one hour after. Overall Results 1. 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. Significant differences between the baseline measure and 1 hour after treatment were noted in

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	collected prior to, during and 1 hour after cryotherapy.	spasticity as indicated by elastic path length (p=0.0198) but only a trend was noted for total path length (p=0.058).
Bajd et al. 1985 Yugoslavia Downs & Black score=10 Pre-post N= 6	**Population:** 6 in- and outpatients with SCI: Age = 11-52 yrs; Level of injury: C5-T9; Severity of injury: complete = 4, incomplete = 2; Time since injury = 5-48 months. **Treatment:** TENS stimulation over L3, 4 dermatomes. Stimulation amplitude of up to 50mA 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 hours post-stimulation.	1. Group statistical analysis was not conducted. 2. In 3 patients, spasticity decreased markedly as indicated by increased relaxation index values immediately after the stimulation and returned to pre-stimulation values at 2 hours. The remaining 3 individuals showed no change.

Note: AIS=ASIA Impairment Scale; EMG=electromyography; FES=functional electrical stimulation; FDS=Function Disability Scale; FIM=Functional Independence Measure; MAS=modified Ashworth Scale; RPES= Rectal Probe Electrical Stimulation; SFS=Spasm Frequency Scale; TENS=Trancutaneous Electrical Nerve Stimulation

Discussion

Transcutaneous Electrical Nerve Stimulation (TENS)

Aydin et al. (2005) employed a RCT design to compare oral Baclofen (N=10) and TENS (N=11) to the bilateral tibial nerves (i.e., innervating gastrocnemius muscle) in reducing lower limb spasticity. Most important, this is the only trial examining multiple applications of TENS. Fifteen 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: Ashworth Scale, Spasm Frequency Scale, 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 than those obtained following a single session.

Possover et al. (2010) examined the effect of continuous TENS to the pudenal nerves and sacral nerve roots S3 and S4. They reported that a frequency of 20 Hz was sufficient to completely control spasticity of the lower extremeties and reflex incontinence. In this study, it appears that continuous TENS was effective in reducing spinal spasticity.

Other researchers have examined the effects of TENS following a single session (Bajd et al. 1985; Goulet et al. 1996; Chung et al. 2010; Possover et al. 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 modified Ashworth scale 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 et al. (2010) also examined

the effect of 60 min TENS sessions over the common peroneal nerve. The authors reported a significant reduction on the Composite Spasticity score (p=0.017), a reduction in 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 3 subjects as indicated by increased relaxation indexes associated with the pendulum test although provided no mean data or group statistical analysis. 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 it is clear that van der Salm et al. (2006) assessed individuals as close as possible to treatment end.

Rectal Electrical Stimulation

Halstead et al. (1993) have evaluated another form of electrical stimulation, rectal electrostimulation, when they observed patients 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 6 sessions of rectal probe electrostimulation on various clinical measures of spasticity including the Ashworth scale, Penn Spasm Frequency Scale, deep tendon reflexes and ankle clonus. Although they achieved good to excellent effects in more than half of the patients examined including significant reductions in the Ashworth scale (p<0.01) and with the effects outlasting the intervention by a mean of 8.2 hours according to patient self-report further therapeutic development of this approach has not continued.

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 $\propto$-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 $\propto$-motor neuron excitability are indicative of decreased spasticity.

Penile Vibration

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, Læssoe et al. (2004) employed an unblinded, crossover RCT design (N=9) in which male participants either received penile vibration or not followed by the opposite condition. The modified Ashworth scale and Penn Spasm Frequency Scale 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 modified Ashworth scale scores (p<0.01) and a slight trend for reduced Penn Spasm Frequency Scale 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 2 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). The results of Alaca et al. (2005) confirmed the overall study findings as penile vibratory stimulation in 10 males resulted in significant reductions in Ashworth Scale 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 6, 3 minute periods of stimulation (separated by 1 minute) whereas Læssoe et al. (2004) used a single 5 minute period.

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, 5 of 7 people with SCI showed a significant reduction in spasticity both immediately following cryotherapy and also at 1 hour after the cold stimulus was removed.

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 a RCT design with a variety of small group control conditions (N=5 to 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.

It should be noted that several of the modalities noted 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 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.

Whole-Body Vibration

Ness et al. (2009) examined the effect of whole-body vibration at 50 Hz on individuals with SCI for four weeks. Sessions occurred 3 times per week with 4 bouts of vibration occurring each day for 45 second each. A significant reduction in quadriceps spasticity was reported, as determined by first swing excursion, and persisted for at least 8 days.

Conclusions

There is level 1b evidence from a single RCT and level 4 evidence from a case series that an ongoing program of TENS acts to reduce spasticity as demonstrated by clinical and electrophysiological measures.

There is level 1b evidence from a single RCT that reductions in spasticity with ongoing programs of TENS may persist for up to 24 hours.

There is level 1a evidence from two RCTs that a single treatment of TENS acts to reduce spasticity but to a lesser degree than that seen with ongoing programs of TENS. This evidence is muted somewhat by conflicting results with a null result (level 2) compared with 2 positive results (level 4).

There is level 4 evidence from a single pre-post study that several sessions of rectal probe stimulation reduces lower limb muscle spasticity for up to 8 hours.

There is level 4 evidence from a single pre-post study 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 1b evidence from 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 4 evidence from a single pre-post study that cryotherapy may reduce muscle spasticity for up to 1 hour after removal of the cold stimulus.

There is level 2 evidence from a single low quality RCT that helium-neon irradiation of sensory nerves may suppress ankle clonus for up to 60 minutes following 40 seconds of stimulation.

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

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

Other forms of afferent stimulation including massage, cryotherapy, helium-neon irradiation, and whole-body vibration may result in immediate spasticity reduction but require more research to examine long-term effects.

2.5 Interventions Based on Direct Spinal Cord or Transcranial Stimulation

Initial investigations of spinal cord stimulation were conducted in the early 1970's 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 also 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 which supplies ongoing electrical stimulation. Pinter et al. (2000) noted a declining interest with this approach in the 1990's because of technical concerns and "the realization that spinal cord stimulation was less effective in patients with severe spasms of the lower limbs" (Dimitrijevic et al. 1986b; Barolat et al. 1995).

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique used to induce changes in cortical excitability. The effects of the stimulation can last minutes to hours. Previous studies have shown rTMS to be beneficial in reduced spasticity among patient with multiple sclerosis, cerebral palsy, and spastic quadriplegia (Wassermann et al. 2001).

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

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Kumru et al. 2010 Spain Downs & Black score=30 Case Control Study N=21	**Population:** Mean age: 36.2 years (SD 15.8y); Causes of injury: traumatic and non-traumatic SCI; Level of injury: C4-T2, ASIA C/D; Mean time since injury: 7.3 months (SD 3.9mo); **Treatment:** Cases (n=14) – 5 days o 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, Visual Analogue Scale, and the Spinal Cord Injury Spasticity Evaluation Tool.	1. 8/14 patients receiving the treatment 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 treatment sessions from both lower extremities when compared with the baseline condition as measured by the Modified Ashworth Scale (p<0.006) and Visual Analogue Scale (p<0.002); these effects were maintained 1 week post treatment. 4. According to Spinal Cord Injury Spasticity Evaluation Tool, spasticity was reduced significantly after 5 days of treatment (p=0.003), and this improvement remained 1week post treatment.
Barolat et al. 1995 USA Downs & Black score=15 Pre-post N=48	**Population:** Age = 17-66 yrs; Gender: males = 90%, females = 10%; Level of injury: cervical = 67%, thoracic = 33%; Severity of injury: complete = 53%, incomplete = 47%; Time post-injury = 6 –545 months. **Treatment:** 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 months after	1. Of 48 initial subjects, 40 provided data at 3 months, 33 at 6 months, 31 at 1 year and 18 at 2 years. The remainder were discontinued due to lack of efficacy or lost to follow up. 2. Average # of spasms/hour improved = 19.9 initially, 11.3 at 3 months, 9.2 at 6 months, 8.8 at 1 year and 12.9 at 2 years. 3. A significantly greater proportion of subjects indicated reduced severity scores over time with significant differences at 6 months (p=0.0424), 1 year (p=0.0001and 2 years (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 months, 45% at 6 months, 32% at 1 year and 28% at 2 years.

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	implantation.	5. Subjective rating of spasm relief also decreased with 68% of individuals experiencing good or excellent relief at 3 months, 69% at 6 months, 70% at 1 year and 79% at 2 years.
Pinter et al. 2000 Austria & USA Downs & Black score=10 Pre-post (Pilot study) N=8	**Population:** Age = 18-34 yrs; Gender: males = 4, females = 4; Level of injury: C5-T6; Severity of injury: AIS: A – C; Time since injury = 19 –94 months. **Treatment:** Epidural spinal cord stimulation over the upper lumbar cord. Final internal placement for surgical implantation determined following an 8 week trial period during which the stimulator was external. **Outcome Measures:** Ashworth scale, Clinical Rating Scale, Pendulum test, EMG activity in response to passive stretch. Data collection schedule was not described.	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 1 hour vs. off for > 12 hours. 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 combined of the left (p=0.0040) and the right (p=0.0035). 5. Antispastic medication discontinued in all but 1 patient when continuous stimulation started. This patient had Baclofen dose reduced and tizanidine discontinued.
Midha & Schmitt, 1998 USA Downs & Black score=7 Case Series N=29	**Population:** Age = 29-63 yrs; Level of injury: C4-T10; Severity of injury: complete, incomplete; Time since injury = 6 months – 30 yrs. **Treatment:** 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 patients reported that the epidural stimulator was producing symptomatic relief. 2. The average length of time that all units produced symptomatic relief was 6 months (range 0-96 months). 3. Fourteen units were removed within 3.4 years (5 days - 7years); 9 implantations failed from the day of implantation. 4. Total cost of initial implantation (not including follow-up) is $23,600 per unit.

Note: AIS=ASIA Impairment Scale; EMG=electromyography.

Discussion

Direct Spinal Stimulation

Pinter et al. (2000) showed improvements following implantation of an epidural spinal cord stimulator with a variety of clinical measures including significant decreases in Ashworth scale 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 7 of 8 subjects and reduce the dose in the remaining subject. These positive findings were achieved in a rather small population (N=8) and further 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, although they did state that spinal cord stimulation had been conducted for a mean of 14.38 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. The spasm intensity and spasm frequency was 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=0.0001and 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 (Barolat et al. 1995).

In contrast to these findings, (Midha & 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 1 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.

Transcranial Magnetic Stimulation (TMS)

Kumru et al. (2010) examined the efficacy of rTMS on 15 individuals with incomplete SCI. rTMS was applied for 2 second-long burses at 20 Hz (40 puplses/burse) to the primary motor cortex for five 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 Modified Ashworth Scale (p<0.006). Additionally, patients reported spontaneously improved sleep quality. These results remained 1 week post-treatment.

Conclusions

There is level 4 evidence based on two pre-post studies that ongoing spinal cord stimulation may provide some relief from otherwise intractable spasticity for some time (i.e., months to years).

There is level 4 evidence based on two studies that the beneficial effects of spinal cord stimulation will subside for most initial users. This, combined with the potential for equipment failure and adverse events, suggests that spinal cord stimulation may not be a cost-effective approach for managing spasticity.

There is level 4 evidence based on one study that repetitive transcranial magnetic stimulation may be effective in relieving spasticity.

> Spinal cord stimulation may provide spasticity relief over a few months but long-term effectiveness and cost-effectiveness is less certain.
>
> Repetitive transcranial magnetic stimulation may provide spasticity relief over the short-term but long-term effectiveness is unknown.

3.0 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). 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).

Table 7 Neurosurgical Interventions for Reducing Spasticity

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Livshits et al. 2002 Israel PEDro=5 RCT Initial N=40; Final N=32	**Population:** Pourpre group: Mean age = 27.6 yrs; Gender: males = 15, females = 5; Level of injury: paraplegia; Severity of injury: complete, incomplete; Time with spasticity = 2.75 yrs; Bischof II group: Mean age = 27.1 yrs; Gender: males = 14, females = 6; Level of injury = paraplegia; Severity of injury: complete, incomplete; Time with spasticity = 2.75 yrs. **Treatment:** Longitudinal T-myelotomy by Pourpre vs. Bischof II technique. **Outcome Measures:** Short form of McGill pain questionnaire (SFM), Present Pain Intensity (PPI), Visual analogue score for pain (VAS), Ashworth scale, Penn Spasm Frequency (PSF) scale. All collected prior to surgery and 6 months, 5 years and 10 years post-surgery.	1. Authors states that "good" vs. "bad" results with respect to spasticity were obtained with the Pourpre technique in 90% of subjects at 6 months, 75% at 5 years and 64.7% at 10 years. The Bischof II technique was less effective in that "good" effects were seen in 65% of subjects at 6 months, 45% at 5 years and 40% at 10 years. The author did not specify what constituted a "good" vs. a "bad" effect other than to say it was a return of spasticity. 2. Ashworth scale scores and PSF scale scores were significantly reduced relative to pre-surgery values (p values unreported). 3. People undergoing the Pourpre technique had significantly reduced Ashworth scale 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,

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
		PPI and VAS scores at 6 months vs. 5 years vs. 10 years (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 vs. Bischof II technique.
Falci et al. 2009 USA Downs & Black score=26 Retrospective N=362	**Population:** Mean age: 40.5 years (range 16.2-73y); Level of injury: 45% cephalad to C6, 23% C-6 to T-1, and 32% caudal to T1; Injury severity: ASI A in 63.3%, B in 9.9%, C in 11.3%, D in 14%, and E in 0.6%. Cause of injury: traumatic. **Treatment:** 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.
Ewelt et al. 2010 Switzerland Downs & Black score=17 Retrospective N=15	**Population:** Mean age: 50.4 years; Gender: 13 males, 2 females; Cause of injury: traumatic syringomyelia and tethered cord (n=13), spinal ependymoma and surgical cord injury (n=2); Level of injury: paraplegia, T3-T9. **Treatment:** Laminectomy, adhesiolysis, cordectomy. **Outcome Measures:** 3-point scale for spasticity.	1. 2 patients improved in their spasticity 2. 9 patients stabilized in spasticity symptoms 3. 4 patients reported further spastic deterioration of their lower limbs.
Putty & Shapiro 1991 USA Downs & Black score=9 Case series Initial N=23; Final N=20	**Population:** SCI (N=11), MS (N=7), Others N=2); Age = 22-69 yrs; Gender: males = 12 females = 8; Level of injury: C5-T9; Severity of injury: complete, incomplete; Time since injury = 2 – 23 yrs. **Treatment:** Posterior T-myelotomy. **Outcome Measures:** Subjective clinical impression.	1. No statistical results were reported; 9 of 10 patients with SCI had relief from spasms (1 died, unrelated to surgery).

Note: AIS = ASIA impairment scale.

Discussion

Livshits et al. (2002) conducted a study comparing two approaches of dorsal longitudinal T-myelotomy technique (i.e., Pourpre vs. 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 Ashworth scale scores and Penn Spasm Frequency scale scores significantly reduced relative to pre-surgery values (p values unreported). More individuals had

positive results with the Pourpre technique vs. 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 patients 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 patients while the impact on nursing care and patient comfort was less specified.

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

Conclusions

There is level 2 evidence based on a single low quality RCT supported by a single case series study 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 based on a single low quality RCT that Pourpre's technique for dorsal longitudinal T-myelotomy is more effective in maintaining reduced levels of spasticity than the Bischof II technique.

Dorsal longitudinal T-myelotomy may result in reduced spasticity.

4.0 Pharmacological Treatment for Spasticity

4.1 Oral Baclofen

Baclofen, a derivative of gamma aminobutyric acid (GABA), 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 GABA itself and is believed to reduce spasticity by enhancing inhibitory influences on the spinal stretch reflex via increasing presynaptic inhibition (Kirshblum 1999).

In typical practice, Baclofen requires a careful dose titration period with a usual maximal recommended dose of 20 mg qid (Burchiel & Hsu 2001) which is also the dosage employed in the majority of studies involving people with SCI (Aydin et al. 2005; Nance 1994; Hinderer et al. 1990). 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). A variety

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[1] Once it has been demonstrated that additional measures are required after traditional conservative approaches such as removal of potential mitigating factors, stretching and other forms of physical therapy have been attempted (Kirshblum, 1999).

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). 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).

Table 8 Oral Baclofen for Reducing Spasticity

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Hinderer et al. 1990 USA PEDro= 9 RCT (single subject design) N=5	**Population:** SCI: Gender: males = 5; Severity of injury: complete, incomplete; Cause of injury: trauma; Chronicity = chronic. **Treatment:** Baseline placebo period of varying length (2.5-4.5 wk), followed by a 2 week dose titration period of Baclofen at half target dose (40 mg/day), followed by 2.5-4.5 weeks 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 twice per week over 9 weeks.	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 40 mg 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 PEDro = 8 RCT N=22	**Population:** SCI (N=11), MS (N=11), 3 dropouts (etiology unknown). **Treatment:** Either oral Baclofen (titrated up to 100 mg/day) for 4 weeks or identical looking placebo. **Outcome Measures:** Self-report of # of spasms, nocturnal awakenings (daily) and global impression of treatment (at end of each treatment period). Clinician also provided global impression (at end of treatment period) and also assessed resistance to movement and rated change on 5 point scale (weekly). Also rated clonus, impressions of pain, use of limbs and transfer activity (weekly).	1. Number of spasms was significantly reduced with Baclofen vs. placebo (p<.01) as was number of nocturnal awakenings (p<.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 vs. 1/22 with placebo and this was significant (p<.01). 3. No improvement in gait was seen in any of those who could walk (n=8) nor were any improvements seen in tendon jerks, strength or voluntary movement. 4. In 9 cases (41%) both patients 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 PEDro=7 RCT	**Population:** SCI (N=6): Level of injury: tetraplegic; Severity of injury: complete, incomplete; Cause of injury = trauma; Chronicity = chronic.	1. No group statistical results were provided. 2. All 6 subjects had a reduced EMG/velocity ratio for any given

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
N=6	**Treatment:** Placebo or active drug (CIBA 34,647-Ba) was titrated to a maximum of 60 mg daily over a period of 2 weeks in a crossover, double-blind design. **Outcome Measures:** Surface slope of EMG (quadriceps) vs. velocity relationship associated with passive flexion of the knee.	speed tested with Baclofen vs. placebo (e.g., decreased to 37.5% (range 0%-67%) at a velocity of 200°/s). 3. All subjects displayed clinical effects with Baclofen such as reduced stretch reflex responses.
Nance et al. 2011 USA PEDro=7 Randomized, double-blind, placebo-controlled, two-period crossover N=35	**Population:** Median age range = 35-43 years; Gender: 25 males, 15 females; Cause of injury: traumatic (91.9%) and non-traumatic (8.8%) SCI; Level of injury: ASI A (40.5%). **Treatment:** Patients received a sequence of extended-release arbaclofen placarbil tablets 10, 20 or 30mg or a placebo every 12 h for 26 days for each sequence. **Outcome Measures:** Ashworth Scale, patient-rated Severity of Spasticity Scale.	1. Arbaclofen placarbil significantly improved Ashworth scores compared to placebo over the dosing interval; least-squares mean reduction versus placebo was 0.60 for 20mg (p=0.0059) and 0.88 for 30mg (p=0.0007). 2. The difference was significant for the pre-morning dose time point, 12 h after the prior evening dose, indicating that efficacy was maintained throughout the dosing interval. 3. Treatment differences for arbaclofen placarbil 10mg versus placebo were not significant. 4. Severity of spasticity ratings were significantly reduced for the combined 20/30-mg 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 PEDro=6 RCT N=41	**Population:** SCI (N=21): Severity of injury: complete, incomplete; Cause of injury = trauma; Chronicity = chronic; Health controls (N=20). **Treatment**: Either oral Baclofen (titrated up to 80 mg/day) for 8 weeks or TENS for 15 minutes/day for 15 days. **Outcome Measures**: SFS, Painful Spasm Scale, Ashworth Scale, 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-treatment.	1. For both treatment 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=.032) 24 hours after the final session of TENS. This reduction was even more apparent when tested only 15 minutes after the last treatment

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
		(p=0.026).
Dicpinigaitis et al. 2000 USA Downs & Black score=21 Prospective controlled trial N=24	**Population:** Treatment group (n=12): Mean age=39.2yrs; Level of injury: C=12; Control group (n=12): Mean age=43.2yrs; Level of injury: C=12 **Treatment:** Both groups underwent Capsaicin cough challenge testing. The treatment group consisted of patients receiving baclofen for the relief of muscle spasm while the control group did not. **Outcome Measures:** Cough thresholds	1. Individuals in the treatment 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).
Nance 1994 Canada Downs & Black score=15 Pre-post N=25	**Population**: SCI (N=25): Gender: males = 25; Level of injury: paraplegia, tetraplegia; Severity of injury: complete, incomplete. **Treatment:** 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, 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 w/ cyproheptadine).

Note: AIS=ASIA Impairment Scale; EMG=electromyography; FDS=Functional Disability Score; FIM=Functional Independence Measure; MS=Multiple Sclerosis; SFS=Spasm Frequency Scale; TENS=Transcutaneous Electrical Nerve Stimulation; VII=Vibratory Inhibition Index

Discussion

Despite the general acceptance and clinical experience of using oral Baclofen to reduce spasticity in people with SCI, at least 2 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 n (6) so did not provide a positive assessment of the efficacy of oral Baclofen.

Since the latest report for the Cochrane Review, an additional RCT (Aydin et al. 2005) has been published (n=21) demonstrating a significant reduction in spasticity with oral Baclofen as measured using the Ashworth Scale, Spasm Frequency Scale, deep tendon reflex score, FIM and Functional Disability Scores, but not for most electrophysiological measures. Another RCT (Duncan et al. 1976) demonstrated reduced spasticity as measured by the Ashworth Scale and Spasm Frequency Scale. 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. Most recently the efficacy and safety of arbaclofen placarbil (AP) was studied (Nance et al. 2011) and found that 20/30mg of AP every 12 h 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 AP and placebo group.

In contrast to these studies, a counter-therapeutic response to Baclofen was found by Hinderer et al. (1990). In this single-subject randomized-controlled design study (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. This study illustrates one of the limitations in establishing the efficacy for any spasticity-relieving agent – the heterogeneity of 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.

Conclusions

There is Level 1a evidence that oral Baclofen improves muscle spasticity secondary to SCI. This conclusion is based on the results from four positive small-scale RCTs although is muted somewhat by a negative finding from a low n (5) single-subject design RCT and an overall lack of homogeneity in outcome measures and study participants. Additional uncontrolled cohort and case series studies also provide support for the use of oral Baclofen in reducing spasticity.

> Oral baclofen reduces muscle spasticity in people with SCI.

4.2 Intrathecal Baclofen for Reducing Spasticity

Programmable pumps can be implanted for the treatment of spasticity in SCI. The most commonly delivered drug is intrathecal Baclofen. Many of the studies looking at intrathecal Baclofen in spasticity combine different causes of spasticity such as SCI, multiple sclerosis and cerebral palsy making the results difficult to interpret for SCI. Several of the studies in this section include studies where fewer than 50% of the patients have spinal cord injury. While these individual studies may not meet the formal SCIRE criteria, it was felt that it was important to include them in this section as they represent a larger number of patients with spinal cord injuries when grouped together.

Outcome measures for intrathecal Baclofen include direct spasticity measures such as Ashworth scale and spasm frequency scale, indirect measures such as functional outcome measures, complication rates and quality of life as well as cost-benefit analyses.

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.

Table 9 Intrathecal Baclofen for Reducing Spasticity

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Nance et al. 1995 Canada PEDro=9 RCT for test dose N=7	**Population:** SCI (N=5): Level of injury: C5-T8; Severity of injury: Frankel grade: A-B; MS (N=2). **Treatment:** Test dose: A daily bolus of placebo or Baclofen (12.5 to 100 mcg titrated dose). Long-term: Intrathecal Baclofen pump implantation. **Outcome Measures:** Ashworth scale, spasm frequency score, Pendulum test, Hospital Cost Analysis, bladder and respiratory function, adverse events.	1. Test dose: Intrathecal Baclofen 50 mcg decreased the average Ashworth score. 2. Long-term: A decrease in Ashworth score mean = 1.8 (p<0.005) and spasm frequency score 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. 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 months.
Penn et al. 1989; USA PEDro=9 RCT (double blind crossover) test dose; Pre-post (Open label) long term N=20	**Population:** MS (N=10); SCI (N=10): Level of injury: C5-T9. **Treatment:** Test dose: A 3 day infusion of saline or intrathecal Baclofen (100 mcg/milliliter) via programmable pump. Long-term: An open label long-term observation of intrathecal Baclofen. **Outcome Measures:** Ashworth scale and spasm frequency scale, laboratory analysis of motor control (EMG) and patient 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 Ashworth and spasm frequency scores (p<0.01). Overall (all subjects combined), the Ashworth score decreased from 4.0 $\pm$ 1.0 to 1.2 $\pm$ 0.4 (p<0.0001) and the spasm frequency scale decreased from 3.3 $\pm$ 1.2 to 0.4 $\pm$ 0.8 (p<0.0005). 2. Long-term: For all patients combined, the Ashworth scale and spasm frequency scale decreased. 3. Follow-up ranged from 10-33 months (average 19).
Coffey et al. 1993 USA PEDro=8 RCT for test dose; Pre-post for long term N=75	**Population:** SCI (N=59), MS, Other spinal pathology. **Treatment:** *Test dose:* Randomized trial test injection Baclofen versus placebo with up-titration from 50 mcg to 100 mcg. *Long-term*: Intrathecal Baclofen pump implantation. **Outcome Measures:** Ashworth and spasm scales	1. Test dose: 88 patients (94.6%) responded to the test dose with a decrease in Ashworth and spasm scale. No patients responded to placebo. 2. Long-term: For the SCI group, the Ashworth score and spasm score decreased post-pump. 3. Patients were followed for 5-41 months (mean 19 months).
Ordia et al. 1996 USA PEDro=6 RCT for trial dose N=9 Pre-post for long-term N=66	**Population:** MS, SCI (N=27), Other causes of spinal spasticity. **Treatment:** Test dose: N=9 patients were randomized to receive normal saline or test dose intrathecal Baclofen. Subsequent test doses were not open label. Long-term: Intrathecal Baclofen	1. Test dose: All 66 patients responded positively to test bolus dose and none of the 9 randomized patients responded to placebo. 2. Long-term: A decrease in Ashworth score and improvement in decreased from

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	pump implantation. N=10 patients were studied for costs study comparing 1 year pre and post pump implantation. **Outcome Measures:** Ashworth scores, spasm frequency scale, drug tolerance, treatment complications, cost-benefit analysis.	4.3 pre-operatively to 1.4 ($p<0.0005$) at last follow-up, spasm frequency scale improved from 3.6 to 0.5 ($p<0.0005$) at last follow-up. 3. An average reduction in 2.7 hospitalization days per patient was found for a cost savings of $2500 per day institutional costs (or $6700 per patient) with the cost of the treatment paid back in <2.5 years.
Hugenholtz et al. 1992 Canada PEDro = 6 RCT (Cross-over) N=6	**Population:** MS, SCI (N=4). **Treatment:** Cross-over trial of intrathecal Baclofen or saline over the course of 11 days followed by a 30 day trial of daily intrathecal Baclofen bolus injections. **Outcome Measures:** Effects of spasticity on life questionnaire; Modified Ashworth scale; Spasm frequency score; Reflex score; Passive range of motion; Muscle strength testing; A timed dressing evaluation; the Smith Hand Function evaluation; Urodynamic studies; Neurophysiologic studies.	Cross-over phase 1. Baclofen had a significant effect on lower limb tone and reflexes, trunk and leg spasms, questionnaire scores and passive range of motion in upper and lower limb joints ($p<0.05$). 2. A clinically significant placebo effect was observed for reduced tone, spasms and reflexes in 1 subject. 30 day bolus phase: 3. Subjects sustained the clinically significant effects of Baclofen on tone, spasms and lower limb passive range of motion. However, the magnitude of the effect decreased after 30 days. The effects on passive range of motion in upper limb joints and lower limb reflexes were lost after 30 days ($p<0.05$). 4. Scores in the Smith Hand Function Evaluation & Dressing Test Evaluation did not change. Urodynamic results (bladder volume) improved in 2 subjects.
Heetla et al. 2009 Netherlands Downs & Black score=30 Retrospective N=37	**Population:** Gender: 19 males, 18 females; Cause of injury: traumatic SCI (n=10), MS (n=14), miscellaneous (n=13). **Treatment:** Prior history of use with intrathecal baclofen therapy, alter infusion mode. **Outcome Measures:** Ashworth Scale, Dose titration, Co-medication, Drug-related side effects.	1. Baclofen dose increased in the first 18 months after implantation ($p<0.05$), and then stabilized around a mean dose of 350 mcg per day. 2. Eight patients (22%) developed tolerance, defined as a dose increase of >100 mcg per year. 3. Altering the infusion mode from simple to complex continuous (n=6) had no effect on the development of tolerance. 4. Pulsatile bolus infusion (n=1) and a drug holiday (n=2) were both effective in reducing the daily baclofen dose.

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
		5. Pump-related complications occurred once per 10.5 years of intrathecal baclofen treatment. 6. Drug-related side effects (mild) had an annual risk of 13.8%.
Azouvi et al. 1996 France Downs & Black score=25 Pre-post N=18	**Population:** MS, SCI (N=12): Level of injury: C5-T11; Severity of injury: Frankel A-D. **Treatment:** Intrathecal Baclofen pump implantation. **Outcome Measures:** Ashworth, spasm frequency score, FIM.	1. Improvement in Ashworth score, spasm frequency score and at 6 months, Ashworth score was improved Z= -3.79 (p<0.001), spasm frequency score was improved Z= -3.78 (p<0.001). FIM. The most dramatic improvements were seen in the 12 patients 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 months (average 37.4)
Heetla et al. 2010 Netherlands Downs & Black score=24 Pre-Post N=4	**Population:** Age range: 20-49 years; Level of injury: T6-T10; Cause of injury: SCI, MS, CP. **Treatment:** Pulsatile bolus infusion of intrathecal baclofen on a daily dose. **Outcome Measures:** Modified Ashworth Scale.	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.
Avellino & Loeser 2000 USA Downs & Black score=18 Case series N=62	**Population:** Type of injury: SCI=38, MS=17, other spinal=7, traumatic brain injury=5, cerebral palsy=4; Overall: Mean age=38.6%; Gender: males=56%, females=44%; SCI: Mean age=35.1yrs; Gender: males=82%, females=18%; Level of injury: C=20, T=8 **Treatment:** Retrospective chart review was conducted on patients implanted with intrathecal baclofen treatment for spasticity were retrospectively reviewed **Outcome Measures:** Ashworth score, spasm score, dosage, complications	1. Significant improvement at follow up (average 33.6months) was seen in the final Ashworth score and the final spasm score for patients with SCI (p<0.001). 2. SCI patients were administered an average dosage of about 500micrograms/day. 3. 36% of SCI patients presented with complications. 4. Catheter failure was the most common complication.
Boviatsis et al. 2005 Greece	**Population:** MS, SCI (N=7): Level of injury: C4 to T11.	1. The SCI group demonstrated a lower Ashworth score (4.57 to

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Downs & Black score=18 Case Series Initial N=22; Final N=21	**Treatment:** 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 scale, Ashworth scale and Penn spasm scale, self-assessment pain scale	2.57, $p=0.0134$) and a decrease in spasm scale (3.71 to 1.28, $p=0.00006$) post pump insertion. 2. All patients reported improved function after surgery with an increase in Barthel Index Score 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 months (median 35 months).
Plassat et al. 2004 France Downs & Black score=16 Case series Initial N=41;Final N=37	**Population:** SCI (N=17), MS and cerebral spasticity. **Treatment:** intrathecal Baclofen pump placement **Outcome Measures:** VAS satisfaction score locomotion, pain, sleep, Ashworth.	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 Ashworth score decreased. 3. Follow-up average 4 years
Zahavi et al. 2004 Netherlands Downs & Black score=16 Case series (long-term) Initial N=38; Final N=21	**Population:** MS, SCI (N=6), Other spinal spasticity. **Treatment:** Intrathecal Baclofen pump implantation. **Outcome Measures:** Ashworth scale, spasm score, EDSS, AI, ISS, SIP, Hopkins symptom check list.	1. Improvement in Ashworth score from baseline 2.82 to final assessment 0.91 ($p<0.05$) and spasm score 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 groups of patient 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 weeks. 3. Follow-up ranged from 66 to 108 months with a mean of 84.9 months.
Abel & Smith 1994 USA Downs & Black score=13 Pre-post N=23	**Population:** MS, SCI (N=17): Level of injury: C4-T12; Severity of injury: AIS: A-D. **Treatment:** Intrathecal Baclofen pump implantation. **Outcome Measures:** Ashworth	1. Test dose: Decrease in Ashworth and spasm score. 2. Long-term: Decrease in Ashworth scores 3. Follow-up ranged from 2-34 months with average 16 months.

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	score and spasm score.	
Loubser et al. 1991 USA Downs & Black score=13 Randomized test dose; Pre-post long term follow-up N=9	**Population:** SCI: Gender: males = 9; Level of injury: C2-T12; Cause of injury: trauma. **Treatment:** Test dose: 5 day infusion of varying doses of Baclofen and a single 12 hour placebo infusion over a 5 day period to determine optimum intrathecal Baclofen dosage. Long-term: Intrathecal Baclofen pump implantation. **Outcome Measures:** Ashworth scale, neurological reflex scale, evaluation of functional abilities, evaluation of personal independence and global assessment scale.	1. Test dose: A decrease was seen in optimal reflex score (t=7.69, p<0.001) and the Ashworth score 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 patients benefited in functional evaluations. 2. Long-term: Only 7 subjects participated. The Ashworth score and mean reflex score decreased from 3.79 $\pm$ 0.69 to 2.00 $\pm$ 0.96 (t=12.9, p<0.001). The mean reflex score decreased from 3.85 $\pm$ 0.62 to 2.18 $\pm$ 0.43 (t=6.76, P<0.001). 3. Follow-up ranged from 3-22 months.
Penn et al. 1992 USA Downs & Black score=13 Case Series N=66	**Population:** MS, SCI (N=32). **Treatment:** Intrathecal Baclofen pump implantation. **Outcome Measures:** Ashworth score and spasm frequency scale.	1. Test dose: 64/66 patients responded to a test dose of intrathecal Baclofen with a decrease in either Ashworth or spasm frequency scale. 2. Long-term: 84% treated adequately for spasticity. 3. Follow-up average 30 months (up to 81 months).
Broseta et al. 1990 Spain Downs & Black score=11 Case series N=19	**Population:** MS, cerebral spasticity, SCI (N=5): Level of injury: T3-L1. **Treatment:** Implantation of programmable pump. **Outcome Measures:** Ashworth, spasm frequency scale, reflex assessment, cystomanometry and perineal electromyography for assessment of neurological bladder dysfunction, electrophysiological H/M ratio, total dose.	1. Reduction in Ashworth and spasm frequency scale 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 months.
Korenkov et al. 2002 Germany Downs & Black score=10 Pre-post N=12	**Population:** SCI (N=12): Gender: males = 12. **Treatment:** Intrathecal Baclofen pump implantation. **Outcome Measures:** Ashworth scale and spasm frequency score. Follow-up was 12 months.	1. Significant post-operative reduction of muscle tone and spasm (P<0.05). Ashworth decreased from 4.2 to 2.2 in the lower limbs and from 2.2 to 1.0 in the UE. Decrease in Ashworth score. 2. Self-care, nursing care, PT, transfers, sitting tolerance, muscle pain and sleeplessness were all reported as improved but no measures were reported.

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Ochs et al. 1989 Germany Downs & Black score=10 Pre-post N=28	**Population:** MS, SCI (N=10). **Treatment:** Intrathecal Baclofen pump implantation. **Outcome Measures**: Ashworth and spasm frequency scale, electrophysiological data.	1. Improvement in Ashworth and spasm frequency scale. Intrathecal Baclofen had an effect on electrophysiological data 2. Follow-up up to 2 years.
Parke et al. 1989 USA Downs & Black score=9 Pre-post N=8	**Population:** MS (N=4), SCI (N=4). **Treatment:** Intrathecal Baclofen pump implantation. **Outcome Measures:** Ashworth scale, muscle strength and modified PECS scale.	1. No statistical results were reported although all subjects showed an improvement in Ashworth. Muscle strength did not change. Improvements were also noted in the PECS scores. 2. Follow-up was at least 6 months.
Denys et al. 1998 France Downs & Black score= 8 Pre-Post N=9	**Population:** MS, SCI (N=5): Gender: males = 9; Level of injury: C4-T11; Severity of injury: AIS: A-C. **Treatment:** 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. 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 patients, and rigidity reduction was reported in 5 patients. 7. In five patients, maximum erection duration was decreased. 4/5 reported duration of less than 5 minutes. Two patients reported an increase in maximum erection duration when using Baclofen. 8. Three patients could reach ejaculation without stimulation. Two patients lost the ability to ejaculate during treatment; however, it returned when treatment was discontinued. 9. Mean follow-up was 44 months.

Note: ADL=Activities of Daily Living; AI=Ambulation Index; AIS=ASIA Impairment Scale; EDSS=Expanded Disabiliaty Status Scale; EMG=electromyography; FES=functional eletctrical stimulation; FIM=Functional Independence Measure; ISS=Incapacity Status Scale; MS=Multiple Scleroris; PECS=Patient Evaluation Conference System; PT=patient; SIP=Sickness Impact Profile; UE=Upper Extremity; VAS=Visual Analogue Scale

Discussion

There are 5 studies employing a randomized controlled trial design to evaluate the effects of test doses 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 Ashworth scale 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).

Table 10 Summary of Intrathecal Baclofen RCTs for Reducing Spasticity – Spasticity Outcome

Author Year Total Sample Size	Methods	Outcome
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 patients (94.6%) responded to the test dose with a decrease in Ashworth and spasm scale. No patients responded to placebo. **Long-term:** For the SCI group, the Ashworth score and spasm score decreased post-pump.
Loubser et al. 1991 N=9 (SCI=9)	**Test dose:** 5 day infusion of varying doses of Baclofen and a single 12 hour 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 patients benefited in functional evaluations. **Long-term:** Only 7 subjects participated. The Ashworth score and mean reflex score decreased.
Penn et al. 1989 N=20 (SCI=10)	**Test dose:** A 3 day infusion of saline or intrathecal Baclofen (100 mcg/milliliter) 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.
Ordia et al. 1996 Initial N=66; Final N=57 (SCI =27)	**Test dose:** N=9 patients 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 patients responded positively to test bolus dose and none of the 9 randomized patients responded to placebo. **Long-term:** A significant decrease in Ashworth score and spasm frequency scale at last follow-up
Nance et al. 1995 Initial N=7; Final N=6 (SCI =5)	**Test dose:** A daily bolus of placebo or Baclofen (12.5 to 100 mcg 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.

Spasticity

It is unlikely that randomized controlled trials will be undertaken to look at 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 outcomes measures being the Ashworth scale and spasm frequency scales (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). The effects of intrathecal Baclofen are more pronounced in the lower extremities than the upper extremities (Korenkov et al. 2002).

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 SCI patients grouped in combination with several other diagnoses (most often MS). 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 ASIA impairment scale (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). Tolerance to intrathecal Baclofen has 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).

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 patients who may depend on their spasticity for ambulation (Loubser et al. 1991).

Table 11 Summary of Intrathecal Baclofen Observational Studies for Reducing Spasticity – Functional Outcome

Author Year Total Sample Size	Methods	Outcome
Boviatsis et al. 2005 N=22 (SCI =7)	**Treatment:** Intrathecal Baclofen pump implantation. Subjects were implanted with an infusion pump delivering a continuous flow at a fixed rate of bolus intrathecal Baclofen.	All patients reported improved function after surgery but the degree of improvement was different according to level of lesion.
Parke et al. 1989 N=8 (SCI N=4)	**Treatment:** Intrathecal Baclofen pump implantation.	Improvements were noted in the PECS scores.
Ordia et al. 1996 N=66 (SCI =27)	**Long-term:** Intrathecal Baclofen pump implantation.	Long-term: A decrease in Ashworth score and spasm frequency scale at last follow-up.
Azouvi et al. 1996 N=18 (SCI = 12)	**Treatment:** Intrathecal Baclofen pump implantation.	Improvement in FIM at 6 months. - ≥2 FIM scores: bathing, dressing lower body, and the 3 items related to transfers.

Author Year Total Sample Size	Methods	Outcome
		Most improvement in 12 patients with thoracic or low cervical lesions.
Nance et al. 1995 Initial N=7; Final N=6 (SCI =5)	**Long-term:** Intrathecal Baclofen pump implantation.	Improvements in ADLs noted.
Broseta et al. 1990 N=19 (SCI =5)	**Treatment:** Implantation of programmable pump.	Objective improvements in transfer activities and skilled acts, improved comfort, reduced H/M ratio and improved bladder function
Plassat et al; 2004 N=41 (SCI= 17)	**Treatment:** intrathecal Baclofen pump placement	Improvements were noted in pain and sleep and Ashworth score decreased.
Zahavi et al. 2004 N=38 (SCI =6)	**Treatment:** 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 weeks.
Loubser et al. 1991 N=9 (SCI =9)	**Test dose:** 5 day infusion of varying doses of Baclofen and a single 12 hour 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 patients benefited in functional evaluations.

Note: ADL=Activities of Daily Living; AI=Ambulatory Index; EDSS=Expanded Disability Status Scale; FIM=Functional Independence Measure; ISS=Incapacity Status Scale; PECS=Patient Evaluation Conference System; SIP=Sickness Impact Profile;

Cost-Effectiveness

There is one prospective study looking at cost analysis for intrathecal baclofen pumps. Postma (1999) studied 33 subjects with MS and SCI. This study did not meet SCIRE criteria for inclusion (i.e. 7/33 SCI subjects; <50% SCI) but of note, Postma found subjects who received a pump had higher direct medical costs than subjects who did not receive a pump. However, Postma concluded that the improvement in quality of life in subjects who received a pump more than justified the direct costs associated with the pump.

There are two level 4 studies looking at cost-effectiveness with the usage of intrathecal Baclofen (Nance et al. 1995; Ordia et al. 1996). Ordia's study does not specify whether SCI or MS subjects were studied for cost-effectiveness, but does report gross cost savings with intrathecal Baclofen due to an overall reduction in hospital days post pump implantation (Ordia et al. 1996).

Nance's study also combines MS and SCI. In contrast to Ordia who looked at overall hospital days, Nance looked only at hospital days related to spasticity and found a net savings in costs related to pump implantation (Nance et al. 1995).

Table 12 Summary Intrathecal Baclofen for Reducing Spasticity – Cost Analysis

Author Year Total Sample Size	Methods	Outcome
Nance et al. 1995 Initial N=7; Final N=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.

Author Year Total Sample Size	Methods	Outcome
Ordia et al. 1996 Initial N=66; Final N=57 (SCI =27)	**Long-term:** Intrathecal Baclofen pump implantation. N=10 patients were studied for costs study comparing 1 year pre and post pump implantation.	An average reduction in 2.7 hospitalization days per patient 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 years.

Intrathecal baclofen withdrawal

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 errors in pump programming, errors in pump refills (wrong concentrations or dosages) and with failures in pumps and/or catheters. Of note, Crawley et al (2004) have presented a low dose radioisotope procedure to investigate need for surgery in cases of suspected implanted drug delivery system catheter failure. Patients with intrathecal baclofen pumps need to be educated regarding the signs and symptoms of baclofen withdrawal so that they can seek early 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 4 subjects and found improvements in signs and symptoms of withdrawal.

Table 13 Treatment of intrathecal baclofen withdrawal

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Meythaler et al. 2003 USA Downs & Black score=11 Case series N=4	**Population:** Age=32-49yrs; Gender: males=3, females=1; Type of injury: SCI=3, CP=1 **Treatment:** Patients with intrathecal baclofen withdrawal were treated with 4 to 8 mg of oral cyproheptadine every 6 to 8 hours in addition to oral diazepam every 6 to 12 hours, oral baclofen every 6 hours and/or ITB boluses. **Outcome Measures:** Signs and symptoms of intrathecal baclofen withdrawal	1. Addition of 4mg of cyproheptadine treatment resulted in a relief of itching and signs of baclofen withdrawal.

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Crawley et al. 2004 UK Downs & Black score =8 Pre-Post N=11	**Population:** Not stated **Treatment:** Low dose radioisotope procedure was used to investigate catheter failure in SCI individuals with implanted drug delivery systems and uncontrolled spasm. **Outcome Measures:** Pump functioning	1. 5 of 11 patients 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 patients, while avoiding surgery for 5.
Coffey et al. 2002 USA Downs & Black score=6 Case series N=6	**Population:** SCI=4; Level of injury: C=3, T=1; Other injury: cerebral palsy=1; MS=1 **Treatment:** Charts were reviewed of patients with severe ITB withdrawal. **Outcome Measures:** Not stated	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 SCI patients, while both non SCI patients recovered.

Note: CP=cerebral palsy; ITB=Intrathecal Baclofen; MS=Multiple Sclerosis

Conclusions

There is level 1a evidence from five small-sample RCTs that bolus or test dose intrathecal Baclofen decreases spasticity.

There is level 4 evidence from fifteen studies that support the use of long-term intrathecal Baclofen to decrease spasticity.

There is level 4 evidence from seven studies with some conflicting evidence from 2 studies that intrathecal Baclofen may improve functional outcomes.

There is level 4 evidence from thirteen studies 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 two studies that intrathecal Baclofen is a cost-effective intervention.

There is level 4 evidence from one study that adding cyprohetptadine to baclofen and benzodiazepines may be useful for the treatment of intrathecal baclofen withdrawal.

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

4.3 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.

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 MS patients (Kaman et al. 2008). As an α_2-adrenergic agonist it acts at both a spinal and supraspinal level.

Table 14 Summary of Tizanidine Studies for Reducing Spasticity

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Nance et al. 1994 USA/Canada PEDro=10 RCT (DB) N=118	**Population:** SCI with moderate spasticity. **Treatment:** Tizanidine. **Outcome Measures:** Ashworth (hip adductors, knee flexors/extensors – bilateral), Pendulum, modified Klein-Bell scale (ADL), Global evaluation of antispastic efficacy, Adverse Events.	1. Ashworth: 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 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 vs. Placebo but were not significant between groups. 5. Adverse Events significantly greater in Tizanidine vs. Placebo (P=0.002).
Mathias et al. 1989 UK Downs & Black score=14 Pre-post N=10	**Population:** SCI. **Treatment:** Single-dose (8mg), tizanidine. Three pre-drug measurements 15 minutes apart after breakfast and 30 minute equilibration. Observations continued at 0.5, 1.0, 1.5, 2.0, 3, 4, 5, 6, 12, 24 hours. These measurements were repeated on a separate occasion (except measurements of sedation and blood collection) without drug administration. **Outcome Measures:** Ashworth, Manual muscle testing, vitals, sedation, pharmacokinetics (Pk), and adverse events.	1. Ashworth: peak reduction between 1-1.5 hr (p<0.05 with spasticity returning to baseline by 4th hour; no rebound spasticity measured at 12 and 24 hours. 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; p<0.05 after 1.5hr) 4. Sedation: Sedation in tetras>paras but increased in both with considerable variability. Peak within first hour with gradual waning to fully awake by 3rd hour. 5. Pharmacokinetics – Plasma levels rose at 0.5hr and peaked by 1

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
		hour. 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±0.06hr. 6. Adverse Events: Sedation and dry mouth.
Mirbagheri et al. 2010 USA Downs & Black=20 Non-RCT Experimental N=38	**Population:** Treated - Mean age: 37.6 years (SD 13.2y); Cause of injury: SCI; Level of injury: >T10, ASIA C/D; Mean time since injury: 8.5 years (SD 4.7y). Control -no SCI. **Treatment:** Treated (=20) - perturbations were applied to the spastic ankle joint, a single oral dose of Tizanidine; Control (n=20) - 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.

Note: ADL=Activities of Daily Living

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 p<0.002, respectively; Nance et al. 1994; N=118). 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; N=10) 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. More specifically, the impact of tizanidine on the spastic muscle was examined in a study by Mirbagheri et al. (2010) who found that on average there was a 25% reduction in peak-torque in the SCI subjects. Significant decreases in reflex stiffness post-tizanidine were found but not in intrinsic muscle stiffness.

Conclusions

There is level 1b evidence based on a single RCT to support the use of tizanidine for the treatment of SCI spasticity, although it is noteworthy 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.

Tizanidine may be useful in treating SCI spasticity.

Clonidine

Clonidine, also 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 15 Summary of Clonidine Studies for Reducing Spasticity

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Stewart et al. 1991 Canada PEDro=8 RCT-DBPC N=12	**Population:** SCI: Cause of injury: trauma, non-trauma; Chronicity = chronic. **Treatment:** 2-week washout period between 4 weeks of randomly assigned clonidine or Placebo treatment. Medication was administered orally 2 or 3 times per day. Initial dosage was 0.02mg/day and systematically increased to an optimal level (0.05-0.25mg/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), and Side Effects.	1. 1/3 paretic patients 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 patients during dose titration included dryness of eyes and mouth, lethargy, mild hypotension and constipation. The majority were transient or negligible while 2 patients experienced moderate to severe lethargy and constipation.
Malinovsky et al. 2003 France Downs & Black score=18 Prospective controlled trial N=36	**Population:** Age=21-73yrs **Treatment:** Patients with urinary tract surgery under spinal anesthesia were divided into two groups: 1) those with SCI 2) normal matched patients with no neurological disease. Patients in each group were randomly assigned to receive: 10 mg of i.t. bupivacaine with 50 micrograms of i.t. clonidine, 150 micrograms of i.t. clonidine, 150 micrograms of i.m. clonidine. **Outcome Measures:** Sedation, BIS	1. In the control group, complete sensory and motor block was seen with one patient becoming hypotensive from the 150microgram group; while the SCI group was not affected by i.t. bupivacaine and clonidine. 2. 50 micrograms clonidine had no sedative effect on the SCI or control groups; while 150microgram of i.t. or i.m. clonidine resulted in sedation of all patients. 3. A significant delay in sedation was seen in SCI patients in both the i.t. or the i.m group; however the duration of sedation was not different. 4. Normal patients showed a decrease in BIS earlier than the control patients (p<0.001).
Nance et al. 1989 Canada Downs & Black=16 Prospective Controlled Trial (Single Blind) N=6	**Population:** SCI. **Treatment:** 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.

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Nance 1994 Canada Downs & Black score=15 Pre-post N =25	**Population:** SCI with at least moderate spasticity: Severity of injury: complete, incomplete; Chronicity = chronic. **Treatment:** 1 wk up-titration, 1 wk target dose (0.05mg bid clonidine; 4mg qid cyproheptadine; 20 mg qid Baclofen) , 1 wk down-titration. **Outcome Measures:** Ashworth, Pendulum, Vibratory Inhibition Index (VII).	1. Ashworth 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.
Weingarden & Belen 1992 USA Downs & Black score=13 Case Series N=17	**Population:** SCI: Cause of injury: trauma. **Treatment:** 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 Downs & Black score=13 Case Series N=55	**Population:** SCI: Level of injury: paraplegia, tetraplegia; Severity of injury: complete, incomplete. **Treatment:** Oral clonidine – 0.05mg bid and increased to 0.4mg bid if tolerated by the subject. **Outcome Measures:** Success of medication was defined as a decrease in hypertonicity.	1. Results indicate that quadriplegics responded to the medication better than the paraplegics. (p<0.033). 2. No significant difference based on complete vs. incomplete lesions. 3. 31/55 subjects responded to clonidine. 4. Many non-responders withdrew due to AEs.
Remy-Neris et al. 1999 France Downs & Black score=11 Non-randomized, placebo controlled trial N=11	**Population:** SCI: Level of injury: paraplegia; Severity of injury: incomplete. **Treatment:** Responders (walking capacity preserved) to a 60ug intrathecal test dose were scheduled for 3, 15-90ug doses of clonidine, and a placebo, by L2-3 puncture. Non-responders were given 30 and 15ug clonidine and a placebo when possible. A minimum interval of 3 days separated each injection. **Outcome Measures:** Ashworth scores (bilateral quadriceps), walking parameters, H-reflex, polysynaptic reflexes – recorded before and every hour for 4-6 hours after an i.t. injection of clonidine or placebo.	1. Significant decrease in Ashworth spasticity score (p<0.0001) at all doses levels (30, 60, 90) 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 60ug.
Yablon & Sipski 1993 USA Downs & Black score=10	**Population:** SCI: Level of injury: cervical; Cause of injury = trauma; Chronicity = sub-acute.	1. Case 1: Marked improvement noted in relief of flexor spasms; 2. Case 2: Excellent improvement

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Case Series Initial N=3; Final N=3	**Treatment:** 0.1-0.3 mg/wk Transdermal clonidine patch (Constant/continuous systemic delivery). **Outcome Measures:** Change in spasticity (no specific measure noted).	noted in both spastic hypertonia and flexor spasms; 3. Case 3: Moderate improvement in spastic hypertonia and flexor spasms.
Remy-Neris et al. 2001 France Downs & Black score=6 Prospective Controlled Trial N=15	**Population:** SCI: Severity of injury: incomplete. **Treatment:** 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 score / pendulum test, and EMG latency / amplitude of quadriceps stretch reflex.	1. FRR amplitude change significant ($P<0.02$) between 30 and 90 ug 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 minutes after injection, which lasted 4-6 hr 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 negativism and depression, sedation.
Malinovsky et al. 2003 France D&B=18 Prospective controlled trial N=36	**Population:** Age=21-73yrs **Treatment:** Patients with urinary tract surgery under spinal anesthesia were divided into two groups: 1) those with SCI 2) normal matched patients with no neurological disease. Patients in each group were randomly assigned to receive: 10 mg of i.t. bupivacaine with 50 micrograms of i.t. clonidine, 150 micrograms of i.t. clonidine, 150 micrograms of i.m. clonidine. **Outcome Measures:** Sedation, BIS	1. In the control group, complete sensory and motor block was seen with one patients becoming hypotensive from the 150microgram group; while the SCI group were not affected by i.t. bupivacaine and clonidine. 2. 50 micrograms clonidine had no sedative effect on the SCI or control groups; while 150microgram of i.t. or i.m. clonidine resulted in sedation of all patients. 3. A significant delay in sedation was seen in SCI patients in both the i.t. or the i.m group; however the duration of sedation was not different.

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
		4. Normal patients showed a decrease in BIS earlier than the control patients (p<0.001).

Note: AE=adverse events; BIS=Bispectral index ; BWS=Body Weight Supported; EMG=electromyography; VAS=Visual Analogue Scale;

Discussion

There are 2 placebo controlled trials (Stewart et al. 1991; N=12 and Remy-Neris et al. 1999; N=11) providing evidence for clonidine's effectiveness in reducing SCI spasticity. Stewart et al 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's, intrathecal clonidine study. However the latter study was not randomized and therefore was less rigorous in design. Both studies had small sample sizes. Another non-randomized, placebo controlled study with a small sample size (Nance et al. 1989; N=6) concurred with clonidine's antispasmodic properties through the use of a non-validated Vibratory Inhibition Index (VII) which is not commonly known clinically. A subsequent pre-post study by the same author (Nance 1994; N=25) using the Ashworth and Pendulum measures as well as the VII 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 VII. The remaining reports of antispastic effects of clonidine in various formulations (oral, transdermal and additional intrathecal studies) are derived from case series studies (Donovan et al. 1988, N=55; Weingarden & Belen 1992, N=17; Yablon & Sipski 1993, N=3; Remy-Neris et al. 2001, N=15). All presented results in favour of using Clonidine as an anti-spasmodic but all 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 i.m. or i.t.) in patients with traumatic spinal cord injury, regardless of the mode of administration. He concluded that patients 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 the majority 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.

Conclusions

There is limited level 1b evidence based on a single RCT and supported by two prospective controlled trials and 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 (level 2 evidence for sedation) and less than robust study designs.

4-Aminopyridine

Beginning in 1993, anecdotal reports emerged on the antispasmodic effects of a new class of K+ channel blocking drug, 4-aminopyridine (4-AP, 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 CNS and there is some evidence of its use to enhance walking ability in persons with MS (Hayes 2007).

Table 16 Summary of 4-Aminopyridine Studies for Reducing Spasticity

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Potter et al. 1998 Canada & USA PEDro=10 RCT N=29	**Population:** SCI: Chronicity = chronic. **Treatment:** 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 weeks then following a washout period they were given the alternate treatment. **Outcome Measures:** Motor index, sensory index, present pain intensity, spasm frequency, modified Ashworth scale, bowel and bladder scores, clinical interview questionnaire, global patient satisfaction questionnaire, seven point terrible delighted scale and FIM.	Significant benefit of Fampridine-SR over placebo: 1. Motor scores (adjusted to only paretic segments; p1 < 0.01). 2. Sensory scores (p1 < 0.01), including both pin prick and light touch (p1 = 0.059 and 0.058). 3. Ashworth (p2 < 0.05). 4. Patient satisfaction and quality of life scores (McNemar's test, p2 < 0.01 and <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 patients reported a wish to continue to use.
Donovan et al. 2000 USA PEDro=9 RCT N=12	**Population:** SCI: Severity of injury: complete, incomplete. **Treatment:** Drug or placebo was administered for 2 hours 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 h) **Outcome Measures:** Patients were serially examined during and after infusion clinically for – Pain (McGill questionnaire); Sensorimotor function (ASIA); Hypertonicity (Ashworth scale, 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.
Cardenas et al. 2007 USA	**Population:** SCI: Age = 19-67yrs; Gender: males = 72, females = 19; Level of injury: paraplegia = 18, tetraplegia = 73; Severity of injury:	1. Patients with an Ashworth score greater than one in Group 2 (25mg) had a significant decrease in spasticity (p=0.02),

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
PEDro = 7 RCT Initial N= 91 ; Final N=71	AIS: C = 44, D = 47; Time since injury = 1-37 yrs. **Treatment:** Group 1 – Placebo; Group 2 – 25 mg bid. Fampridine-SR; Group 3 – 40mg bid. Fampridine-SR. **Outcome Measures:** Patient Diary Questionnaire; ASIA International Standards; Ashworth Scale; Spasm Frequency Scale; Tendon Reflex Scale; Subject Global Index of Global Impressions (GGI); Subject Summary Questionnaire; Safety Evaluation.	as opposed to Group 1 (placebo). 2. AIS Grades and GGI did not significantly improve within any group. 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.
Hayes et al. 1994 Canada & USA Downs & Black score=15 Pre-post N=6	**Population:** SCI: Cause of injury = trauma; Chronicity = chronic. **Treatment:** Under fasting conditions, patients received 24-25mg 4-AP IV. Monitoring for effect pre to 2 hours post and at 24 hours post drug administration **Outcome Measures:** Neurophysiological and standard neurological examination. Adverse Event monitoring.	1. Enhanced somatosensory evoked potentials (N=3), Improved motor evoked potentials (N=4), Increased voluntary EMG interference (N=2) 2. Three of 6 patients 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. Adverse Events: aching IV site (N=6), transient lightheadedness (N=2), mild perioral paresthesia (N=1), +20mm Hg 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).
Potter et al. 1998 Canada & USA Downs & Black score=10 Pre-post N=3	**Population:** SCI: Level of injury: cervical; Severity of injury: incomplete; Cause of injury = trauma. **Treatment:** Day 1- single 10mg capsule of 4-AP followed by physical and neurophysiological examination pre and post administration up to 24 hours. Day 4: 10mg bid to tid by Day 6, if tolerated. Tolerated dosing regimen continued for 4 months with prn intermittent assessments. **Outcome Measures:** A. Physical exam: ASIA motor and sensory classification; Modified Ashworth rating of spasticity. B. Neurophysiological exam: Motor	*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).

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	evoked potentials (MEPs) following transcranial magnetic stimulation of motor cortex, quantitative assessment of ankle hypertonicity. C. Pharmacokinetics and Adverse Event monitoring.	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.

Note: AIS=ASIA Impairement Scale; BP=blood pressure; CSF=cerebrospinal fluid; FIM=Functional Independence Scale; IV=intraveneous; LE=lower extremity; UE=upper extremity

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, N=12; Potter et al. 1998, N=29; Cardenas et al. 2007, N=71). Only Potter et al. (1998), using a sustained-release formulation of 4-AP (Fampridine-SR) reported a statistically significant reduction in spasticity as measured by the Ashworth (p<0.05, McNemar's 2-tailed test). Cardenas et al. (2007), also using Fampridine-SR, relied on the Ashworth and a Patient Diary Questionnaire (primary outcome measure covering 4 functional domains including spasticity and overall patient 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 bid. treatment vs. placebo. A post hoc subgroup analysis of subjects with more marked spasticity at baseline resulted in a significant treatment (25 mg bid.) related improvement in spasticity (p<0.25) compared to placebo treatment. The 3 group comparison (40 vs. mg bid. vs. placebo) did not result in significant differences (p <0.04). A fourth study using intravenous administration of 4-aminopyridine showed marked spasticity improvement in 2 of 6 subjects (Hayes et al. 1994). A subsequent intravenous administration, study (Donovan et al. 2000) concluded that this mode of administration is not optimal based on the observation of no short term benefits. The remaining 2 pre-post studies, also not specifically designed to study spasticity alone, present only minimal evidence for the anti-spasmodic effects of 4-AP. Phase 3 clinical trial results of Fampridine-SR in chronic SCI with spasticity as the primary outcome are yet to be published. It is important to note that although statistically significant reductions in spasticity was reported in 2 RCTs using validated outcome measures to study the effects of 4-AP, neither trial was specifically designed with spasticity as the primary outcome under study. Additional studies did not further strengthen the evidence or did so minimally.

Conclusions

Limited level 1a evidence based on two RCTs in favour of the anti-spasmodic effects of a sustained-release formulation (Fampridine-SR) of 4-AP is tempered by a negative finding from a single RCT involving IV administration. Study results must be interpreted with caution given that spasticity results were secondary outcomes of the studies. Phase 3 clinical trial results of Fampridine-SR effects on spasticity, as the primary outcome, in chronic SCI are yet to be published.

Cyproheptadine

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

Table 17 Summary of Cyproheptadine Studies for Reducing Spasticity

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Wainberg et al. 1990 Canada PEDro=7 RCT N=8	**Population:** SCI: Severity of injury: incomplete; Cause of injury = traumatic, non-traumatic; Chronicity = chronic. **Treatment:** One week washout between cyproheptadine or placebo (identically appearing tablets) in random order dose-titrated over 3 weeks (1 week each at 2mg, 4mg and 8mg 5id). Four subjects also were tested after open-label long term cyproheptadine (optimized dosing) of at least 6 months. Con meds and therapies were maintained for at least 3 months 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 vs. 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.
Barbeau et al. 1982 Canada Downs & Black score=12 Case series – Pre-post N=6	**Population:** SCI and MS with spasticity of spinal origin. **Treatment:** Oral cyproheptadine progressively increased from 6 mg to 24 mg per day over 4 to 24 months, including a placebo substitution period. **Outcome Measures:** Muscle strength; EMG activity; patient log of clonus and spasms; ankle clonus	1. Muscle strength decreased in 4/6 patients. 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 D&B=11 Case series N=4	**Population:** Age=32-49yrs; Gender: males=3, females=1; Type of injury: SCI=3, CP=1 **Treatment:** Data from patients previously treated with oral cyproheptadine every 6 to 8 hours, oral diazepam every 6 to 12 hours, oral baclofen every 6 hours and ITB boluses was analyzed. **Outcome Measures:** Spasticity	1. Addition of 4mg of cyproheptadine treatment resulted in a relief of itching, anxiety, and malaise in one complete paraplegic patient. 2. A tetraplegic spastic hypertonia patient treated with ITB for 38 months was admitted with urosepsis; initially the patient was febrile (39.5 C), unresponsive and spastic. After

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
		8mg of cyproheptadine treatment, the patients fever and spasticity resolved within 2 hours of the first dose. Ashworth scale dropped to 1 and SFS dropped to 0. 3. Complete SCI patient treated with ITB pump for severe lower extremity spasticity for 6 years presented with severe spasticity and itching and was admitted for a catheter revision and a UTI. Patient 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.

Note: BWS=body weight supported; EMG=electromyography; ITB=Intrathecal Balcofen; MS=Multiple Sclerosis; SFS=Spasm Frequency Score; TA=tibialis anterior; UTI=Urinary tract infection

Discussion

Cyproheptadine performed favourably versus placebo in improving spasticity and walking in a small sample of chronic SCI patients (Wainberg et al. 1990, N=8). Although the study design 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 6 subjects confirmed this antispasmodic effect of cyproheptadine using subjective patient logs of clonus and spasms. Norman et al. 1998 (N=12) 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 (N=25) in a pre/post-test 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

Limited level 1b evidence supports the use of cyproheptadine in the treatment of spasticity in chronic SCI patients, but results should be interpreted cautiously given the small sample sizes, reliance on non-validated subjective outcome measures and inferiority of cyproheptadine when compared to baclofen.

A single level 4 report supports the use of cyrpoheptadine (along with baclofen and diazepam) as an adjunct treatment of acute intrathecal baclofen withdrawal syndrome.

<div style="border:1px solid black; padding:10px;">
Cyproheptadine may be useful in treating SCI spasticity but requires additional confirmatory research.
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Gabapentin

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

Table 18 Summary of Gabapentin Studies for Reducing Spasticity

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Gruenthal et al. 1997 USA PEDro=7 RCT N=28	**Population:** SCI: Chronicity = sub-acute to chronic. **Treatment:** Eleven day washout between 2 day gabapentin (400 mg total in 3 divided doses) or placebo with evaluations prior to, on second day within 5h of last dose and after washout for each treatment. **Outcome Measures:** Each evaluation: 1) U/LE Ashworth and 6 point Likert ratings of spasticity 2) muscle stretch reflexes, 3) presence or absence of ankle/wrist clonus 4) reflex withdrawal to noxious stimuli in finger and foot.	1. Gabapentin resulted in an 11% reduction in the median Ashworth Scale (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.

Discussion

Gruenthal et al. (1997; N=28) 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.

Conclusions

There is limited level 1b evidence from a single RCT that supports the use of gabapentin in SCI-related spasticity.   Despite the robust study design and validated outcome measures, no confidence intervals were reported and the sample size was relatively small.

<div style="border:1px solid black; padding:10px;">
Gabapentin may be useful in treating SCI spasticity but requires additional confirmatory research.
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Orphenadrine Citrate

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

Table 19 Summary of Orphenadrine Citrate Studies for Reducing Spasticity

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Casale et al. 1995 England Downs & Black score= 14 Prospective Controlled Study N=11	**Population:** SCI: Mean age = 31.2 yrs; Gender: males = 9, females = 2; Level of injury: paraplegia; Time since injury = 9-11 yrs. **Treatment:** 60mg of intravenous orphenadrine citrate. **Outcome Measures:** Threshold of flexion reflex (mAmp); Ashworth Scale; at baseline, initial injection, 10, 20, 30 and 60 minutes 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 minutes in ten patients and within 60 minutes in one patient. 3. One patient who had severe spastic hypertonia did not see an improvement in reflex threshold. 4. There was a significant decrease in the Ashworth scale for orphenadrine treatment (p<0.0001), as compared to no effect for the placebo.

Discussion

Casale et al. (1995) were able to demonstrate a significant reduction of spasticity (p<0.0001) as measured by Ashworth in favour of orphenadrine citrate vs. 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 patients and given its known side effect profile, this treatment may be appropriate for short term application.

Conclusions

There is limited level 1b evidence from a single RCT supporting the anti-spastic action of intravenous orphenadrine citrate. Father confirmatory research is needed to support its use.

Orphenadrine citrate may reduce spasticity in SCI but additional confirmatory research is needed.

Other Potential Anti-Spasmodics

Other potential anti-spasmodics which have been tested in the SCI population include L-threonine, diazepam and dantrolene and a recent investigation noted an anti-spastic effect for naxolone. L-threonine is an α-amino acid with a putative mechanism of anti-spastic action through increasing spinal glycine levels (Paisley et al. 2002). No current studies (1980 to date) were found that investigated the specific use of diazepam (valium) or dantrolene in the treatment of SCI spasticity, although both of these remain in use today. Notably, diazepam has

earlier evidence of effectiveness based on RCTs conducted in persons with SCI (Wilson et al. 1966; Corbett et al. 1972). Although Levetiracetam has been trialed in a recent RCT, it has shown no effect on neuropathic pain, evoked pain or spasms (Finnerup et al. 2009).

Table 20 Effect of Other Potential Anti-Spasmodics for Reducing Spasticity

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
L-Threonine		
Lee & Patterson 1993 USA & Ireland PEDro=8 RCT N=33	**Population:** MS and traumatic and non-traumatic SCI with spasticity of spinal origin. **Treatment:** 6g/da y- 500mg L-Threonine or Placebo capsules taken 3x/day on empty stomach. **Outcome Measures**: Ashworth (bilat). Hip adductors-flexors-extensors and knee flexors-extensors) – 6 highest summed for spasticity score, which was used throughout the study. *Secondary outcome measures:* Spasm frequency and severity score (spasm score was derived by multiplying two variables together over 2wk period using specially designed chart), BI, Kurtzke Disability Status Scale, Patient & Caregiver subjective responses, Aes, and glycine/threonine plasma concentrations. Measurements pre and post treatment. All measures conducted by a single investigator.	Modest but definite antispastic effect in favour of L-threonine vs. placebo: 1. Mean spasm score reduced for both treatments – weak correlation between spasm score and spasticity reduction. 2. No change in BI or Kurtzke with either treatment. 3. Dramatic rise in plasma threonine during active treatment 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 treatment (N=2) and Placebo (N=1). 7. Four dropouts – 2 for medical and 2 for non-medical reasons.
Naxolone		
Brackett et al. 2007 USA & Canada Downs & Black score = 8 Pre-post N=6	**Population:** SCI (N=3): Age = 30-42 yrs; Level of Injury: T6, C4 & C4; Time since injury = 5-26 yrs; Able Bodied Controls (N=3): Age = 22-37 yrs. **Treatment:** 30 hour protocol implemented: physiologic saline was injection on day 1 as a control for the infusion of naxolone on day 2. **Outcome Measures:** None listed.	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 minutes of injection and could easily be triggered, even when there was lack of an obvious stimulus.

Note: BI=Barthel Index; MS=Multiple Sclerosis

Discussion

Other potential anti-spasmodics used in SCI include L-threonine, diazepam and dantrolene. A randomized, controlled study of L-threonine (Lee & Patterson 1993; N=33) only showed minimal effects on spasticity. Nance et al. 1989 in a study of clonidine for SCI spasticity showed that effects of diazepam and placebo were not different from pre-treatment values. However, an earlier cross-over study (Corbett et al. 1972, N=19) showed that Valium was more effective than amytal and placebo in reducing spasticity (p<0.02-0.05).

An inadvertent side effect discovered during an investigation of neuroendocrine function in SCI using naloxone is the profound increase in spasticity after naloxone treatment in all 3 SCI subjects compared to no such activity in the 3 able-bodied study volunteers (Brackett et al. 2007). This interesting finding indicates a relationship between opioid receptors and spasticity that has previously been suggested in patients where morphine is found to be effective when ITB tolerance is an issue.

Conclusions

Very little recent evidence supports current use of diazepam and dantrolene for reducing SCI-related spasticity. An RCT investigating L-threonine for the treatment of SCI spasticity showed only minimal effects on spasticity.

The use of L-threonine in the treatment of SCI spasticity requires confirmation through additional well-designed studies.

Continued use of diazepam and dantrolene would benefit from controlled comparison studies.

4.4 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 sixty raw cannabinoids identified but only six are pharmacologically active. Delta 9 tetra-hydrocannabinol (THC) is the main psycho-active ingredient and it is now available in prescribable synthetic (dronabinol) and plant derived forms. Human cannabinoid receptors (CB1 and CB2) were discovered in the 1980's and 90's (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 MS 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 for the management of spasticity in SCI. Therefore, one single subject RCT study was included in the following section.

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 GABA function in the Brain (Musty and Consore 2002). These are all possible mechanisms of spasticity reduction.

Table 21 Delta-9-tetrahydrocannacinol (THC) for Reducing Spasticity

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Pooyania et al. 2010 Canada PEDro=8 Double-blind, placebo-controlled	**Population:** Mean age: 42.4 years: Gender: 11 males; Cause of injury: traumatic and non-traumatic SCI; Level of injury: 6 tetraplegia, 5	1. A significant decrease in spasticity, as measured by the Ashworth Scale, was observed for those on active treatment in

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
crossover N=11	paraplegia; Time since injury: >1 year. **Treatment:** Patients received either nabilone or placebo during the first 4-week period (0.5mg once a day with option to increase to 0.5mg twice a day); after a 2-week washout, subjects were crossed over to opposite arm. **Outcome Measures:** Ashworth Scale, Spasm Frequency Scale, Visual Analogue Scale, Wartenberg Pendulum Test, Global Impression of Change.	the most involved muscle (mean difference = 0.909 +/-0.85; p=0.003), as well as for muscles overall (p=0.001). 2. There was no significant difference in other measures. 3. Side effects were mild and tolerable.
Hagenbach et al. 2007 Switzerland PEDro score= 6 RCT with preliminary Pre-post N= 22 (RCT Phase 3 N=15)	**Population**: SCI (N=15): Age = 29-66 yrs; Gender: males = 11, females = 2; Level of injury: C4-T11; Severity of injury: AIS: A,B,C,D; **Treatment:** Oral dronabiniol vs. placebo. Phase 1 (oral) and 2 (rectal) open label trials followed by a phase 3 (oral) placebo RCT. **Outcome measures:** Spasticity sum score (SSS) using the Modified Ashworth Scale (MAS); Self rating of spasticity and side effects; at baseline, day 1, 8 & 43 for each phase of study.	1. Main comparison of RCT (dronabinol vs. 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 vs. placebo (Phase 1 vs. 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 vs. placebo (Phase 1 vs. Phase 3) there 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 treatment vs. placebo groups. 6. There was no significant increase on FIM scores, but one tetraplegic patient was able to perform CIC independently after treatment due to better motor control of the hands. 7. Drop outs were due to increased pain, anxiety, decreased compliance, decreased attention and mood.
Maurer et al. 1990 Switzerland PEDro = 3	**Population:** SCI: Gender: 1 male. **Treatment:** 50mg of codeine, 5mg of delta 9 THC or placebo,	1. Delta 9 THC demonstrated a significant decrease in all of the VAS ratings for spasticity

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Single Subject RCT N=1	randomized using an ABC design in multiple trials. **Outcome Measures:** Visual Analog Scale for spasticity, pain, sleep, micturition, ability to concentrate and mood. Rating occurred next day after treatment administered (2130hr nightly) and with respect to spasticity asked about immediate effect, effect while falling asleep, effect during the night and effect in the morning after treatment.	compared to codeine and placebo. 2. Delta 9 THC also showed a significant reduction in pain compared to placebo.
Malec et al. 1982 USA Downs & Black score=12 Observational N=43	**Population:** SCI from patient database: Age <20-60+ yrs; Gender: males = 37, females = 5; Time since injury = 6 mo-5+ yrs. **Treatment:** 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; 2. Present use of marijuana correlated positively with past use; and 3. The person's reference or peer group contributed significantly to current use. 53% reported using marijuana during last year 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). 4. Reduction in spasticity via use was reported in 88% (21/24) while 12% reported no change. 5. No correlation between Spasticity Change Index and any variable (if significant correlation, then perhaps placebo effect). 6. 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 <30y (76%, 16/21).
Kogel et al. 1995 USA Downs & Black score= 7 Pre-Post N= 5	**Population:** Age = 28-55 yrs; Gender: males = 5; Level of injury: tetraplegia; Time since injury = 6 months – 9 yrs. **Treatment:** Open label design: Oral dronabinol (initial dosage = 5mg bid,	1. Spasticity was markedly improved in 2 of 5 subjects. 2. Results fluctuated in one subject, did not change in one subject and worsened in one subject.

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	increased to 20mg tid) + current spasticity regimen. **Outcome Measures:** Pendulum Drop Test; Weschler Memory Scale (WMS); Profile of Moods Scales (POMS).	3. There was no worsening in psychological parameters and two subjects had improvements in memory testing.

Note: AIS=ASIA Impairment Scale; CIC=clean intermittent catheterization; FIM=Functional Independence Measure.

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 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. 1989) 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 trials 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 THC (dronabinol) for the treatment of SCI related spasticity. The main outcomes were the spasticity sum score (SSS) using the modified Ashworth score (MAS) as well as self-rating of spasticity. In the open label phase, significant reductions in spasticity were seen in both oral and rectal THC groups. Only oral administration was used in the placebo control phase. When comparing phase 1 to phase 3 results, mean SSS decreased significantly during active treatment compared to placebo on day one (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 2 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 THC, 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 patients Nabilone or a placebo during the first 4-weeks, 0.5mg/ 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 patient with pain and spasticity due to spinal cord injury. 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 design. Using a visual analog scale to assess spasticity after blinded treatment, delta 9 THC showed significant benefits for spasticity over placebo and codeine. However, the patient was exposed to THC use prior to the placebo control trial which may have introduced significant bias.

Kogel (1995) performed a pre-post trial in five males with paraplegia. He administered dronabinol 5mg bid to 10mg qid. 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 limited level 2 evidence based on a compromised RCT and supported by studies of various designs to support the use of oral delta 9 THC (dronabinol) in reducing both objective and subjective measures of spasticity.

There is a single RCT that provides level 1b evidence that nabilone is effective in reducing spasticity in both the involved and overall muscles.

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

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

4.5 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 botulinum toxin (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).

Botulinum Toxin

Level 1 evidence supports the use of type A (BTX-A) and type B botulinum neurotoxins in relieving focal muscle spasticity in a variety of etiologies, most notably cerebral palsy, multiple sclerosis, stroke and acquired brain injury (Snow et al. 1990; Simpson et al. 1996; Corry et al. 1997; Simpson 1997; Richardson et al. 2000; Smith et al. 2000; Hyman et al 2000; Bakheit et al. 2001; Wasiak et al. 2004). 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 botulinum neurotoxin 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 are relatively few studies directed specifically at the SCI population and only one study has been identified which meet the criteria established for the present review (i.e., English language articles with N=3 and at least half of the subjects having a SCI).[2] Therefore, we present the results of four studies which examined the effect of BTX-A on spasticity secondary to SCI but may not have entirely saisfied inclusion criteria. The successful employment of botulinum neurotoxin to overcome bladder detrusor-sphincter dyssynergia in people with SCI (Dykstra & Sidi 1990; Schurch et al. 1996; deSeze et al. 2002) is addressed separately in SCIRE chapter 13 that deals with bladder health.

Table 22 Botulinum Neurotoxin for Reducing Spasticity

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Richardson et al. 2000 England PEDro=9 RCT N=52 (6 with SCI)	**Population:** Stroke (23), Head Injury (12), SCI (6) and others with focal spasticity, details of SCI unknown. **Treatment:** EMG guided injection of BTX-A with doses and specific muscles injected based on clinical judgment. **Outcome Measures:** modified Ashworth); passive ROM; Subjective rating of Problem Severity, 9-hole peg test (upper limb problems only), timed 10 m walk test (lower limb problems only), Goal Attainment Scale, Rivermead Motor Assessment Scale at 3, 6, 9 & 12 weeks.	1. Spasticity was significantly reduced for active tx vs. placebo (as shown by modified Ashworth aggregate scores) (p<.02). The main reduction for both tx and placebo groups occurred between baseline and week 3 with little further improvement thereafter. tx group had more marked reduction than placebo group. 2. Range of Motion was significantly improved for both groups but significantly more for tx vs. placebo group (p<.03). As with modified Ashworth most marked changes were between baselines - 3 weeks. 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 vs. placebo (p<.025).
Richardson et al. 1997 England Downs & Black score=10 Case Study N=1	**Population:** Age = 23 yrs; Gender: male; Level of injury: C5/6; Severity of injury: incomplete; Time since injury = 18 months. **Treatment:** EMG guided injection of BTX-A (210 units total) (in various muscles of the hand) + wrist/thumb splint + hand exercise.	1. Spasticity was reduced (most Ashworth scores went from 3 to 1 – finger flexors to 2 for all time periods after baseline) and range of motion was increased ($70°$ to $90°$). These measures were maintained over testing period to 12 weeks. 2. Grip strength was reduced initially but

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[2] 3 non-English language articles have been identified which examined the effects of botulinum neurotoxin on muscle spasticity in SCI (Oechsner, 2002; Keren et al. 2000; Takenaga et al. 1995).

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	Outcome Measures: Ashworth Scale, grip strength (Jamar dynamometer), passive ROM, Jebsen Hand Function Test, Rivermead Motor Assessment Scale @ 3, 6, 9 & 12 weeks.	recovered close to baseline by 6 weeks. 3. Jebsen hand function deteriorated on most tasks initially, then recovered on most but remained less agile at turning cards over and stacking draughts - yet improved on picking up objects.
Hecht et al. 2008 Germany Downs & Black score=10 Case Series Initial N=19; Final N=11	**Population:** Hereditary spastic paraplegia (HSP): Mean age = 41.6 yrs; Gender: males = 14, females = 5; Time since injury = 18.5 yrs. **Treatment:** Injection of BTX-A with doses and specific muscles injected based on clinical judgment. **Outcome Measures:** Ashworth Scale; Global Subjective Assessment.	1. 17 patients had a one point improvement on the Ashworth Scale, one improved by three points, and one was not scored. 2. Of the 17, those with global subjective improvement continued BTX-A treatment (n=11). 3. 10 of the continuing 11 patients 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).
Al-Khodairy et al. 1998 Switzerland Downs & Black score=7 Case Study N=1	**Population:** Age = 50 yrs; Gender: male; Level of injury: T12; Severity of injury: AIS A; Time since injury = 22 yrs. **Treatment:** 8 successive treatments of EMG-guided BTX-A (first in gastrocnemius, then other muscles as well). **Outcome Measures:** Modified Ashworth Scale, Spasm Frequency Score, Pain Visual Analogue Scale.	1. Spasticity was reduced in that Ashworth scores went from 2-3 to 1+ and the Spasm Frequency Score went from 4 to 2. 2. Pain Visual Analog Scale Scores went from 8 to 1. 3. The subject also reported less difficulty with ADLs and better sitting tolerance. 4. Unlike preceding treatments, the final treatment (8th over 2 year period) had no beneficial clinical effect with no explanation for what may have caused this phenomenon.

Note: ADL=Activities of Daily Living; AIS=ASIA Impairment Scale; BTX-A=botulinum toxin A; EMG=electromyography; ROM=range of motion;

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 Ashworth Scale 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., 8th 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) Modified Ashworth scores demonstrated reduced spasticity across the appropriate joints when tested at 3, 6, 9 and 12 months with both active treatment and placebo although there was a

significantly greater reduction with BTX-A (p<.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 6/52 subjects had spasticity of confirmed spinal cord origin.

Limited SCI specific evidence of BTX-A benefits is provided by two studies. Hecht et al. (2007) conducted a case series of 19 chronic hereditary spastic paraplegics and reported Ashworth improvements of at least one point (one patient was not scored). Eleven of the 19 patients perceived a concurrent improvement in activities of daily living and continued treatment.

Conclusions

Based on 2 case studies and 2 case series, there is level 4 evidence that botulinum neurotoxin improves focal muscle spasticity in SCI. This is cautiously supported by an RCT where only 6/52 subjects had spasticity of confirmed spinal cord origin.

The effect of long-term administration of botulinum neurotoxin is based on the results of a single case study involving 8 treatments over 2 years (level 4 evidence). Tolerance to BTX-A may occur with prolonged administration and requires further study.

Botulinum neurotoxin appears to improve focal muscle spasticity in people with SCI.

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). Only two studies were identified that met our criteria for the treatment of spasticity in spinal cord injury.

Table 23 Phenol Neurolysis for Reducing Spasticity

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Yasar et al. 2010 Turkey Downs & Black score=25 Retrospective Case Series N=20	**Population:** Mean age: 42.9 years (SD 13.2y); Gender: 19 males, 1 female; Cause of injury: traumatic and non-traumatic SCI; Level of injury: tetraplegia (n=3), paraplegia (n=17), ASI A (n=13), B (n=7); Time since injury: 41.8 months (SD 47.2mo). **Treatment:** Phenol obturator nerve blockade. **Outcome Measures:** Hip adductor spasticity.	1. Mean hip adductor spasticity decreased significantly after (p<0.001).

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	Population: Spinal cord injury with C5 level tetraplegia with varying degrees of completeness; age mean 55.8 yrs; Gender: 7 males, 0 females; Time since injury ≥5mo. Treatment: Subscapular phenol nerve block. Outcome Measures: Shoulder range of motion, visual analog scale for pain, Ashworth scale and the 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 visual analog scale for shoulder pain which was reduced from 6.0 to 3.4 (p<0.05). 3. No significant change in the modified Ashworth scale for shoulder spasticity. 4. Eating Functional Independence Measure item score improved significantly (p<0.05).
Uchikawa et al 2009 Japan Downs & Black score=10 Case Series Initial N=7; Final N=7		

Note: AIS=ASIA impairment scale; ROM=range of motion

Discussion

Uchikawa et al. (2009) examined the use of phenol blocks for the management of painful shoulder girdle spasticity in persons with cervical level spinal cord injury. In an open label, case series, seven individuals with cervical level spinal cord injury 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 (23.71), abduction (19.41) and external rotation (16.81; P<0.05) and decreases in the visual analog scale for shoulder pain which was reduced from 6.0 to 3.4 (P<0.05). They did not however observe any significant change in the modified Ashworth scale for shoulder spasticity. The eating Functional Independence Measure item score 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.

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 in managing spasticity in SCI.

Conclusions

Based on 1 case series study there is level 4 evidence that phenol neurolysis improves pain, range of motion and function related to shoulder spasticity in the setting of tetraplegia in SCI.

Based on 1 case series study, there is level 4 evidence that phenol neurolysis reduces hip adductor spasticity in individuals with paraplegia and tetraplegia in SCI.
There is no literature to support the use of focal neurolysis with alcohol in the management of spasticity in spinal cord injury.

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.

5.0 Summary

There is level 1b evidence from a single study that passive ankle movements may not reduce lower limb muscle spasticity in persons with initial mild spasticity.

There is level 2 evidence from a single study supported by level 4 evidence from another study 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 2 evidence from a single study that hydrotherapy is effective in producing a short-term reduction in spasticity.

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

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).

There is no evidence describing the length and time course of the treatment effect related to spasticity for hydrotherapy or FES-assisted walking.

There is level 2 evidence from two prospective controlled trials supported by a single pre-post study 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).

Based on a single pre-post study, there is no evidence that a long-term program of muscle stimulation has an effect on reducing muscle spasticity and may even increase local muscle spasticity.

There is level 1b evidence from a single RCT and level 4 evidence from a case series that an ongoing program of TENS acts to reduce spasticity as demonstrated by clinical and electrophysiological measures.

There is level 1b evidence from a single RCT that reductions in spasticity with ongoing programs of TENS may persist for up to 24 hours.

There is level 1a evidence from two RCTs that a single treatment of TENS acts to reduce spasticity but to a lesser degree than that seen with ongoing programs of TENS. This evidence is muted somewhat by conflicting results with a null result (level 2) compared with 2 positive results (level 4).

There is level 4 evidence from a single pre-post study that several sessions of rectal probe stimulation reduces lower limb muscle spasticity for up to 8 hours.

There is level 4 evidence from a single pre-post study 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 1b evidence from 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 4 evidence from a single pre-post study that cryotherapy may reduce muscle spasticity for up to 1 hour after removal of the cold stimulus.

There is level 2 evidence from a single low quality RCT 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 based on two pre-post studies that ongoing spinal cord stimulation may provide some relief from otherwise intractable spasticity for some time (i.e., months to years).

There is level 4 evidence based on two studies that the beneficial effects of spinal cord stimulation will subside for most initial users. This, combined with the potential for equipment failure and adverse events, suggests that spinal cord stimulation may not be a cost-effective approach for managing spasticity.

There is level 4 evidence based on one study that repetitive transcranial magnetic stimulation may be effective in relieving spasticity.

There is level 2 evidence based on a single low quality RCT supported by a single case series study 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 based on a single low quality RCT that Pourpre's technique for dorsal longitudinal T-myelotomy is more effective in maintaining reduced levels of spasticity than the Bischof II technique.

There is Level 1a evidence that oral Baclofen improves muscle spasticity secondary to SCI. This conclusion is based on the results from four positive small-scale RCTs although is muted somewhat by a negative finding from a low n (5) single-subject design RCT and an overall lack of homogeneity in outcome measures and study participants. Additional uncontrolled cohort and case series studies also provide support for the use of oral Baclofen in reducing spasticity.

There is level 1a evidence from five small-sample RCTs that bolus or test dose intrathecal Baclofen decreases spasticity.

There is level 4 evidence from fifteen studies that support the use of long-term intrathecal Baclofen to decrease spasticity.

There is level 4 evidence from seven studies with some conflicting evidence from 2 studies that intrathecal Baclofen may improve functional outcomes.

There is level 4 evidence from thirteen studies 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 two studies that intrathecal Baclofen is a cost-effective intervention.

There is level 4 evidence from one study that adding cyprohetptadine to baclofen and benzodiazepines may be useful for the treatment of intrathecal baclofen withdrawal.

There is level 1b evidence based on a single RCT to support the use of tizanidine for the treatment of SCI spasticity, although it is noteworthy 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.

There is limited level 1b evidence based on a single RCT and supported by two prospective controlled trials and 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 (level 2 evidence for sedation) and less than robust study designs.

Limited level 1a evidence based on two RCTs in favour of the anti-spasmodic effects of a sustained-release formulation (Fampridine-SR) of 4-AP is tempered by a negative finding from a single RCT involving IV administration. Study results must be interpreted with caution given that spasticity results were secondary outcomes of the studies. Phase 3 clinical trial results of Fampridine-SR effects on spasticity, as the primary outcome, in chronic SCI are yet to be published.

Limited level 1b evidence supports the use of cyproheptadine in the treatment of spasticity in chronic SCI patients, but results should be interpreted cautiously given the small sample sizes, reliance on non-validated subjective outcome measures and inferiority of cyproheptadine when compared to baclofen.

A single level 4 report supports the use of cyrpoheptadine (along with baclofen and diazepam) as an adjunct treatment of acute intrathecal baclofen withdrawal syndrome.

There is limited level 1b evidence from a single RCT that supports the use of gabapentin in 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 limited level 1b evidence from a single RCT supporting the anti-spastic action of intravenous orphenadrine citrate. Father confirmatory research is needed to support its use.

Very little recent evidence supports current use of diazepam and dantrolene for reducing SCI-related spasticity. An RCT investigating L-threonine for the treatment of SCI spasticity showed only minimal effects on spasticity.

There is limited level 2 evidence based on a compromised RCT and supported by studies of various designs to support the use of oral delta 9 THC (dronabinol) in reducing both objective and subjective measures of spasticity.

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

Based on 2 case studies and 2 case series, there is level 4 evidence that botulinum neurotoxin improves focal muscle spasticity in SCI. This is cautiously supported by an RCT where only 6/52 subjects had spasticity of confirmed spinal cord origin.

The effect of long-term administration of botulinum neurotoxin is based on the results of a single case study involving 8 treatments over 2 years (level 4 evidence). Tolerance to BTX-A may occur with prolonged administration and requires further study.

Based on 1 case series study there is level 4 evidence that phenol neurolysis improves pain, range of motion and function related to shoulder spasticity in the setting of tetraplegia in SCI.

Based on 1 case series study, there is level 4 evidence that phenol neurolysis reduces hip adductor spasticity in individuals with paraplegia and tetraplegia in SCI.
There is no literature to support the use of focal neurolysis with alcohol in the management of spasticity in spinal cord injury.

References

Abel NA, Smith RA. Intrathecal baclofen for treatment of intractable spinal spasticity. Arch Phys Med Rehabil 1994;75:54-58.

Adams MM, Hicks AL. Spasticity after spinal cord injury. Spinal Cord 2005;43(10):577-586.

Al-Khodairy AT, Gobelet C, Rossier AB. Has botulinum toxin type A a place in the treatment of spasticity in spinal cord injury patients? Spinal Cord 1998;36(12):854-858.

Alaca R, Goktepe AS, Yildiz N, Yilmaz B, Gunduz S. Effect of penile vibratory stimulation on spasticity in men with spinal cord injury. Am J Phys Med Rehabil 2005;84(11):875-879.

Albert TA, Yelnik A, Bonan I, Lebreton F, Bussel B. Effectiveness of femoral nerve selective block in patients with spasticity: preliminary results. Arch Phys Med Rehabil. 2002 May;83(5):692-6.

Anderson KD, Borisoff JF, Johnson RD, Stiens SA, Elliott SL. Long-term effects of spinal cord injury on sexual function in men: implications for neuroplasticity. Spinal Cord 2007;45(5):338-348.

Anderson KD, Borisoff JF, Johnson RD, Stiens SA, Elliott SL. Spinal cord injury influences psychogenic as well as physical components of female sexual ability. Spinal Cord 2007;45(5):349-359.

Ashworth B. Preliminary trial of carisoprodol in multiple sclerosis. Practitioner 1964;192:540-542.

Avellino AM, Loeser JD. Intrathecal baclofen for the treatment of intractable spasticity of spine or brain etiology. Neuromodulation 3(2)()(pp 75-81), 2000 Date of Publication: 2000 2000;(2):75-81.

Aydin G, Tomruk S, Keles I, Demir SO, Orkun S. Transcutaneous electrical nerve stimulation versus baclofen in spasticity: clinical and electrophysiologic comparison. Am J Phys Med Rehabil 2005;84(8):584-592.

Azouvi P, Mane M, Thiebaut JB, Denys P, Remy-Neris O, Bussel B. Intrathecal baclofen administration for control of severe spinal spasticity: functional improvement and long-term follow-up. Arch Phys Med Rehabil 1996;77:35-39.

Bajd T, Gregoric M, Vodovnik L, Benko H. Electrical stimulation in treating spasticity resulting from spinal cord injury. Arch Phys Med Rehabil 1985;66(8):515-517.

Baker D, Pryce G, Croxford JL, Brown P, Pertwee RG, Makriyannis A et al. Endocannabinoids control spasticity in a multiple sclerosis model. FASEB J 2001;15(2):300-302.

Bakheit AM, Pittock S, Moore AP, Wurker M, Otto S, Erbguth F et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of botulinum toxin type A in upper limb spasticity in patients with stroke. Eur J Neurol 2001;8(6):559-565.

Barbeau H, Richards CL, Bedard PJ. Action of cyproheptadine in spastic paraparetic patients. J Neurol Neurosurg Psychiatry 1982;45(10):923-926.

Barolat G, Myklebust JB, Wenninger W. Effects of spinal cord stimulation on spasticity and spasms secondary to myelopathy. Appl Neurophysiol 1988;51(1):29-44.

Barolat G, Singh-Sahni K, Staas WE, Jr., Shatin D, Ketcik B, Allen K. Epidural spinal cord stimulation in the management of spasms in spinal cord injury: a prospective study. Stereotact Funct Neurosurg 1995;64(3):153-164.

Bennegard GM, Karlsson AK. Higher glucose uptake in paralysed spastic leg. Spinal Cord 2008;46(2):103-106.

Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther 1987;67(2):206-207.

Bohannon RW. Tilt table standing for reducing spasticity after spinal cord injury. Arch Phys Med Rehabil 1993;74(10):1121-1122.

Boviatsis EJ, Kouyialis AT, Korfias S, Sakas DE. Functional outcome of intrathecal baclofen administration for severe spasticity. Clin Neurol Neurosurg 2005;107(4):289-295.

Brackett NL, Ibrahim E, Krassioukov A, Lynne CM. Systemic naloxone infusion may trigger spasticity in patients with spinal cord injury: case series. J Spinal Cord Med 2007;30(3):272-275.

Brashear A. Gordon MF, Elovic, et. Al. Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after stroke. N Engl J Med. 2002; 347: 395-400.

Brin MF. Dosing, administration, and a treatment algorithm for use of botulinum toxin A for adult-onset spasticity. Spasticity Study Group. Muscle Nerve Suppl 1997;6:S208-S220.

Brin MF. Botulinum toxin: chemistry, pharmacology, toxicity, and immunology. Muscle Nerve Suppl 1997;6:S146-S168.

Broseta J, Garcia-March G, Sanchez-Ledesma MJ, Anaya J, Silva I. Chronic intrathecal baclofen administration in severe spasticity. Stereotact Funct Neurosurg 1990;54-55:147-153.

Burbaud P, Wiart L, Dubos JL et. Al. A randomised, double blind, placebo controlled trial of botulinum toxin in the treatment of spastic foot in hemiparetic patients. J Neurol Neurosurg Psychiatry. 1996; 61: 265-269.

Burchiel KJ, Hsu FP. Pain and spasticity after spinal cord injury: mechanisms and treatment. Spine 2001;26(24 Suppl):S146-S160.

Burke D, Gillies JD, Lance JW. An objective assessment of a gamma aminobutyric acid derivative in the control of spasticity. Proc Aust Assoc Neurol 1971;8:131-134.

Canadian Paraplegic Association. Workplace participation national survey of Canadians with SCI. Canadian Paraplegic Association http://www.canparaplegic.org/en/Employment_and_Education_24/EMPLOYMENT_6/14.html. 1996; Last accessed: 9-15-2008.

Cardenas DD, Ditunno J, Graziani V, Jackson AB, Lammertse D, Potter P et al. Phase 2 trial of sustained-release fampridine in chronic spinal cord injury. Spinal Cord 2007;45(2):158-168.

Casale R, Glynn CJ, Buonocore M. Reduction of spastic hypertonia in patients with spinal cord injury: a double-blind comparison of intravenous orphenadrine citrate and placebo. Arch Phys Med Rehabil 1995;76(7):660-665.

Chen SC, Chen YL, Chen CJ, Lai CH, Chiang WH, Chen WL. Effects of surface electrical stimulation on the muscle-tendon junction of spastic gastrocnemius in stroke patients. Disabil Rehabil 2005;27:105-110.

Chou R, Peterson K, Helfand M. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review. J Pain Symptom Manage 2004;28(2):140-175.

Chung BP, Cheng, BK. Immediate effect of transcutaneous electrical nerve stimulation on spasticity in patients with spinal cord injury. Clinical Rehabilitation, 2010;24:202-210.

Clark J. (2002) Alternative Pharmacologic Therapies. In: Gelber DA, Jeffery DR, editors. Current Clinical Neurology: Clinical Evaluation and Management of Spasticity. Totowa, NJ: Humana Press, Inc., 151-158.

Coffey JR, Cahill D, Steers W, Park TS, Ordia J, Meythaler J et al. Intrathecal baclofen for intractable spasticity of spinal origin: results of a long-term multicenter study. J Neurosurg 1993;78:226-232.

Coffey RJ, Edgar TS, Francisco GE, Graziani V, Meythaler JM, Ridgely PM, Sadiq SA, Turner MS. Abrupt withdrawal from intrathecal baclofen: Recognition and management of a potentially life threating syndrome. Arch Phys Med Rehabil 2002;83:735-741.

Cook AW, Weinstein SP. Chronic dorsal column stimulation in multiple sclerosis. Preliminary report. N Y State J Med 1973;73(24):2868-2872.

Corbett M, Frankel HL, Michaelis L. A double blind, cross-over trial of Valium in the treatment of spasticity. Paraplegia 1972;10(1):19-22.

Corry IS, Cosgrove AP, Walsh EG, McClean D, Graham HK. Botulinum toxin A in the hemiplegic upper limb: a double-blind trial. Dev Med Child Neurol 1997;39(3):185-193.

Denys P, Mane M, Azouvi P, Chartier-Kastler E, Thiebaut JB, Bussel B. Side effects of chronic intrathecal baclofen on erection and ejaculation in patients with spinal cord lesions. Arch Phys Med Rehabil 1998;79(5):494-496.

deSeze M, Petit H, Gallien P, de Seze MP, Joseph PA, Mazaux JM et al. Botulinum a toxin and detrusor sphincter dyssynergia: a double-blind lidocaine-controlled study in 13 patients with spinal cord disease. Eur Urol 2002;42(1):56-62.

Devane WA, Dysarz FA, Johnson MR, Melvin LS, Howlett AC. Determination and characterization of a cannabinoid receptor in rat brain. Mol Pharmacol 1988;34:605-613.

Dietz V. Spastic movement disorder. Spinal Cord 2000;38:389-393.

Dietz V, Sinkjaer T. Spastic movement disorder: Impaired reflex function and altered muscle mechanics. Lancet Neurol. 2007;6:725-733.

Dimitrijevic MM, Dimitrijevic MR, Illis LS, Nakajima K, Sharkey PC, Sherwood AM. Spinal cord stimulation for the control of spasticity in patients with chronic spinal cord injury: I. Clinical observations. Cent Nerv Syst Trauma 1986;3(2):129-144.

Dimitrijevic MR, Illis LS, Nakajima K, Sharkey PC, Sherwood AM. Spinal cord stimulation for the control of spasticity in patients with chronic spinal cord injury: II. Neurophysiologic observations. Cent Nerv Syst Trauma 1986;3(2):145-152.

Dolley JO, Black J, Williams SR et al. Acceptors for botulinum neurotoxin reside on motor nerve terminals and mediate its internalisation. Nature 1984; 307: 457-60.

Donovan WH, Carter RE, Rossi CD, Wilkerson MA. Clonidine effect on spasticity: a clinical trial. Arch Phys Med Rehabil 1988;69(3 Pt 1):193-194.

Donovan WH, Halter JA, Graves DE, Blight AR, Calvillo O, McCann MT et al. Intravenous infusion of 4-AP in chronic spinal cord injured subjects. Spinal Cord 2000;38(1):7-15.

Duncan GW, Shahani BT, Young RR. An evaluation of baclofen treatment for certain symptoms in patients with spinal cord lesions. A double-blind, cross-over study. Neurology 1976;26(5):441-446.

Dunn RB, Walter JS, Lucero Y, Weaver F, Langbein E, Fehr L et al. Follow-up assessment of standing mobility device users. Assist Technol 1998;10:84-93.

Dykstra DD, Sidi AA. Treatment of detrusor-sphincter dyssynergia with botulinum A toxin: a double-blind study. Arch Phys Med Rehabil 1990;71(1):24-26.

Eng JJ, Levins SM, Townson AF, Mah-Jones D, Bremner J, Huston G. Use of prolonged standing for individuals with spinal cord injuries. Phys Ther 2001;81:1392-1399.

Ewelt C, Stalder S, Steiger HJ, Hildebrandt G, Heilbronner R. Impact of cordectomy as a treatment option for posttraumatic and non-posttraumatic syringomyelia with tethered cord syndrome and myelopathy. *Journal of Neurosurgical Spine,* 2010;13:193-199.

Falci SP, Indeck C, Lammertse DP. Posttraumatic spinal cord tethering and syringomyelia: Surgical treatment and long-term outcome. *Journal of Neurosurgical Spine,* 2009;11:445-460.

Finnerup, N. B., Grydehoj, J., Bing, J., Johannesen, I. L., Biering-Sorensen, F., Sindrup, S. H., & Jensen, T. S. (2009). Levetiracetam in spinal cord injury pain: a randomized controlled trial. *Spinal Cord, 47*(12), 861-867.

Fogel JP, Waters RL, Mahomar F. Dorsal myelotomy for relief of spasticity in spinal injury patients. Clin Orthop Relat Res 1985;(192):137-141.

Francisco GE. Botulinum toxin: dosing and dilution. Am J Phys Med Rehabil 2004;83(10 Suppl):S30-S37.

Francisco GE, Boake C, Vaughn A. Botulinum toxin in upper limb spasticity after acquired brain injury: a randomized trial comparing dilution techniques. Am J Phys Med Rehabil. 2002; 81: 355-63.

Franzoi AC, Castro C, Cardone C. Isokinetic assessment of spasticity in subjects with traumatic spinal cord injury (ASIA A). Spinal Cord 37(6)()(pp 416-420), 1999 Date of Publication: 1999 1999;(6):416-420.

Fried GW, Fried KM. Spinal cord injury and use of botulinum toxin in reducing spasticity. Phys Med Rehabil Clin N Am 2003;14(4):901-910.

Goldberg J, Seaborne DE, Sullivan SJ, Leduc BE. The effect of therapeutic massage on H-reflex amplitude in persons with a spinal cord injury. Phys Ther 1994;74(8):728-737.

Goldberg MJ. Measuring outcomes in cerebral palsy. J Pediatr Orthop 1991;11(5):682-685.

Gorgey AS, Dudley GA. Spasticity may defend skeletal muscle size and composition after incomplete spinal cord injury. Spinal Cord 2008;46(2):96-102.

Gormley ME, Jr., O'Brien CF, Yablon SA. A clinical overview of treatment decisions in the management of spasticity. Muscle Nerve Suppl 1997;6:S14-S20.

Goulet C, Arsenault AB, Bourbonnais D, Laramee MT, Lepage Y. Effects of transcutaneous electrical nerve stimulation on H-reflex and spinal spasticity. Scand J Rehabil Med 1996;28(3):169-176.

Gracies JM, Nance P, Elovic E, McGuire J, Simpson DM. Traditional pharmacological treatments for spasticity. Part II: General and regional treatments. Muscle Nerve Suppl 1997;6:S92-120.

Granat MH, Ferguson AC, Andrews BJ, Delargy M. The role of functional electrical stimulation in the rehabilitation of patients with incomplete spinal cord injury--observed benefits during gait studies. Paraplegia 1993;31(4):207-215.

Gruenthal M, Mueller M, Olson WL, Priebe MM, Sherwood AM, Olson WH. Gabapentin for the treatment of spasticity in patients with spinal cord injury. Spinal Cord 1997;35(10):686-689.

Haas BM, Bergstrom E, Jamous A, Bennie A. The inter rater reliability of the original and of the modified Ashworth scale for the assessment of spasticity in patients with spinal cord injury. Spinal Cord 1996;34(9):560-564.

Hagenbach U, Luz S, Ghafoor N, Berger JM, Grotenhermen F, Brenneisen R et al. The treatment of spasticity with Delta9-tetrahydrocannabinol in persons with spinal cord injury. Spinal Cord 2007;45(8):551-562.

Halstead LS, Seager SW. The effects of rectal probe electrostimulation on spinal cord injury spasticity. Paraplegia 1991;29(1):43-47.

Halstead LS, Seager SW, Houston JM, Whitesell K, Dennis M, Nance PW. Relief of spasticity in SCI men and women using rectal probe electrostimulation. Paraplegia 1993;31(11):715-721.

Hansebout RR, Blight AR, Fawcett S, Reddy K. 4-Aminopyridine in chronic spinal cord injury: a controlled, double-blind, crossover study in eight patients. J Neurotrauma 1993;10(1):1-18.

Harvey LA, Herbert RD, Glinsky J, Moseley AM, Bowden J. Effects of 6 months of regular passive movements on ankle joint mobility in people with spinal cord injury: a randomized controlled trial. Spinal Cord 2009;47:62-66.

Hayes KC, Potter PJ, Wolfe DL, Hsieh JT, Delaney GA, Blight AR. 4-Aminopyridine-sensitive neurologic deficits in patients with spinal cord injury. J Neurotrauma 1994;11(4):433-446.

Hayes KC. Fampridine-SR for multiple sclerosis and spinal cord injury. Expert Rev Neurother 2007;7(5):453-461.

Hecht MJ, Stolze H, uf dem BM, Giess R, Treig T, Winterholler M et al. Botulinum neurotoxin type A injections reduce spasticity in mild to moderate hereditary spastic paraplegia--report of 19 cases. Mov Disord 2008;23(2):228-233.

Heetla HW, Staal MJ, Kliphuis C, van Laar T. The incidence and management of tolerance in intrathecal baclofen therapy. *Spinal Cord,* 2009;47:751-756.

Heetla HW, Staal MJ, Kliphuis C, van Laar T. Tolerance to continuous intrathecal baclofen infusion can be reversed by pulsatile bolus infusion. *Spinal Cord,* 2010;48: 483-486.

Hinderer SR, Lehmann JF, Price R, White O, deLateur BJ, Deitz J. Spasticity in spinal cord injured persons: quantitative effects of baclofen and placebo treatments. Am J Phys Med Rehabil 1990;69(6):311-317.

Hinderer SR. The supraspinal anxiolytic effect of baclofen for spasticity reduction. Am J Phys Med Rehabil 1990;69(5):254-258.

Howlett AC, Qualy JM, Khachatrian LL. Involvement of Gi in the inhibition of adenylate cyclase by cannabimimetic drugs. Mol Pharmacol 1986;29:307-313.

Hugenholtz H, Nelson RF, Dehoux E, Bickerton R. Intrathecal baclofen for intractable spinal spasticity - a double-blind cross-over comparison with placebo in 6 patients. Can J Neurol Sci 1992;19(2):188-195.

Hyman N, Barnes M, Bhakta B, Cozens A, Bakheit M, Kreczy-Kleedorfer B et al. Botulinum toxin (Dysport) treatment of hip adductor spasticity in multiple sclerosis: a prospective, randomised, double blind, placebo controlled, dose ranging study. J Neurol Neurosurg Psychiatry 2000;68(6):707-712.

Illis LS, Read DJ, Sedgwick EM, Tallis RC. Spinal cord stimulation in the United Kingdom. J Neurol Neurosurg Psychiatry 1983;46(4):299-304.

Kakebeeke TH, Lechner H, Baumberger M et al. The importance of posture on the isokinetic assessment of spasticity. Spinal Cord 2002; 40(5):236-243.

Kakebeeke TH, Lechner HE, Knapp PA. The effect of passive cycling movements on spasticity after spinal cord injury: preliminary results. Spinal Cord 2005;43(8):483-488.

Kamen L, Henney HR, III, Runyan JD. A practical overview of tizanidine use for spasticity secondary to multiple sclerosis, stroke, and spinal cord injury. Curr Med Res Opin 2008;24(2):425-439.

Katz RT. Management of spastic hypertonia after stroke. J Neuro Rehab 1991;5:S5-S12.

Keren O, Shinberg F, Catz A, Giladi N. Botulin toxin for spasticity in spinal cord damage by treating the motor endplate. Harefuah 2000;138(3):204-208.

Kesiktas N, Paker N, Erdogan N, Gulsen G, Bicki D, Yilmaz H. The use of hydrotherapy for the management of spasticity. Neurorehabil Neural Repair 2004;18(4):268-273.

Kiminski NE, Abood ME, Kessler FK, Martin BR, Schatz AR Identification of a funcationally relevant cannabinoid receptor on mouse spleen cells that Is involved in cannabinoid-mediated immune moduleation. Mol Pharmacol 1992;42:736-742.

Kirazli Y, On AY, Kismali B, Aksit R. Comparison of phenol block and botulinus toxin type A in the treatment of spastic foot after stroke: a randomized, double-blind trial. Am J Phys Med Rehabil. 1998 Nov-Dec;77(6):510-5

Kirshblum S. Treatment alternatives for spinal cord injury related spasticity. J Spinal Cord Med 1999;22(3):199-217.

Kiser TS, Reese NB, Maresh T, Hearn S, Yates C, Skinner RD et al. Use of a motorized bicycle exercise trainer to normalize frequency-dependent habituation of the H-reflex in spinal cord injury. J Spinal Cord Med 2005;28(3):241-245.

Knutsson E, Lindblom U, Martensson A. Plasma and cerebrospinal fluid levels of baclofen (Lioresal) at optimal therapeutic responses in spastic paresis. J Neurol Sci 1974;23(3):473-484.

Kogel RW, Johnson PB, Chintam R, Robinson CJ, Nemchausky BA. Treatment of spasticity in spinal cord injury with dronabinol, a tetrahydrocannabinol derivative. Am J Ther 1995;2(10):799-805.

Korenkov AI, Niendorf WR, Darwish N, Glaeser E, Gaab MR. Continuous intrathecal infusion of baclofen in patients with spasticity caused by spinal cord injuries. Neurosurg Rev 2002;25:228-230.

Krause JS. Self-reported problems after spinal cord injury: Implications for rehabilitation practice. Topics in Spinal Cord Injury Rehabilitation 2007;12(3):35-44.

Krause P, Szecsi J, Straube A. Changes in spastic muscle tone increase in patients with spinal cord injury using functional electrical stimulation and passive leg movements. Clinical Rehabilitation 22(7)()(pp 627-634), 2008 Date of Publication: 2008 2008;(7):627-634.

Kumru H, Vidal J, Kofler M, Portell E, Valls-Sole J. Alterations in excitatory and inhibitory brainstem interneuronal circuits after severe spinal cord injury. *Journal of Neurotrauma,* 2010;27:721-728.

Kunkel CF, Scremin AM, Eisenberg B, Garcia JF, Roberts S, Martinez S. Effect of "standing" on spasticity, contracture, and osteoporosis in paralyzed males. Arch Phys Med Rehabil 1993;74:73-78.

Laessoe L, Nielsen JB, Biering-Sorensen F, Sonksen J. Antispastic effect of penile vibration in men with spinal cord lesion. Arch Phys Med Rehabil 2004;85(6):919-924.

Laitinen L, Singounas E. Longitudinal myelotomy in the treatment of spasticity of the legs. J Neurosurg 1971;35(5):536-540.

Lance JW. (1980) Symposium synopsis. In: Feldman RG, Young RR, Koella WP, editors. Spasiticity: disordered motor control. Chicago: Year Book Medical Pubs, 485-494.

Lechner HE, Feldhaus S, Gudmundsen L, Hegemann D, Michel D, Zach GA et al. The short-term effect of hippotherapy on spasticity in patients with spinal cord injury. Spinal Cord 2003;41(9):502-505.

Lechner HE, Kakebeeke TH, Hegemann D, Baumberger M. The effect of hippotherapy on spasticity and on mental well-being of persons with spinal cord injury. Arch Phys Med Rehabil 2007;88(10):1241-1248.

Lee A, Patterson V. A double-blind study of L-threonine in patients with spinal spasticity. Acta Neurol Scand 1993;88(5):334-338.

Levi R, Hultling C, Nash MS, Seiger A. The Stockholm spinal cord injury study: 1. medical problems in a regional SCI population. Paraplegia 1995;33:308-315.

Li S, Xue S, Li Z, Liu X. Effect of baclofen combined with neural facilitation technique on the reduction of muscular spasm in patients with spinal cord injury. Neural Regeneration Research 2007;2(8):510-512.

Little WJ. Course of Lections on the deformities of the human frame. Lecture IX. Lance 1843:I:350-354.

Livshits A, Rappaport ZH, Livshits V, Gepstein R. Surgical treatment of painful spasticity after spinal cord injury. Spinal Cord 2002;40(4):161-166.

Loubser PG, Narayan RK, Sandin KJ, Donovan WH, Russell KD. Continuous infusion of intrathecal baclofen: long-term effects on spasticity in spinal cord injury. Paraplegia 1991;29:48-64.

Mahoney JS, Engebretson JC, Cook KF, Hart KA, Robinson-Whelen S, Sherwood AM. Spasticity experience domains in persons with spinal cord injury. Arch Phys Med Rehabil 2007;88(3):287-294.

Malec J, Harvey RF, Cayner JJ. Cannabis effect on spasticity in spinal cord injury. Arch Phys Med Rehabil 1982;63(3):116-118.

Malinovsky J-M, Malinge M, Lepage J-Y, Pinaud M. Sedation caused by clonidine in patients with spinal cord injury. British Journal of Anaesthesia 90(6)()(pp 742-745), 2003 Date of Publication: 01 Jun 2003 2003;(6):742-745.

Mathias CJ, Luckitt J, Desai P, Baker H, el MW, Frankel HL. Pharmacodynamics and pharmacokinetics of the oral antispastic agent tizanidine in patients with spinal cord injury. J Rehabil Res Dev 1989;26(4):9-16.

Maurer M, Henn V, Dittrich A, Hofmann A. Delta-9-tetrahydrocannabinol shows antispastic and analgesic effects in a single case double-blind trial. Eur Arch Psychiatry Clin Neurosci 1990;240(1):1-4.

Maynard FM, Karunas RS, Waring WP, III. Epidemiology of spasticity following traumatic spinal cord injury. Arch Phys Med Rehabil 1990;71(8):566-569.

Mechoulam R. Cannabinoids as Therapeutic Agents. Boca Raton, Fla: CRC Press, 1986.

Merritt JL. Management of spasticity in spinal cord injury. Mayo Clin Proc 1981;56(10):614-622.

Meythaler JM, Roper JF, Brunner RC. Cyproheptadine for intrathecal baclofen withdrawal. Archives of Physical Medicine and Rehabilitation 84(5)()(pp 638-642), 2003 Date of Publication: 01 May 2003 2003;(5):638-642.

Midha M, Schmitt JK. Epidural spinal cord stimulation for the control of spasticity in spinal cord injury patients lacks long-term efficacy and is not cost-effective. Spinal Cord 1998;36(3):190-192.

Mirbagheri MM, Barbeau H, Ladouceur M, Kearney RE. Intrinsic and reflex stiffness in normal and spastic, spinal cord injured subjects. Experimental Brain Research 141(4)()(pp 446-459), 2001 Date of Publication: 2001 2001;(4):446-459.

Mirbagheri, M. M., Chen, D., & Rymer, W. Z. (2010). Quantification of the effects of an alpha-2 adrenergic agonist on reflex properties in spinal cord injury using a system identification technique. *Journal of Neuroengineering and Rehabiliation, 7,* 29.

Mirbagheri MM, Ladouceur M, Barbeau H, Kearney RE. The effects of long-term FES-assisted walking on intrinsic and reflex dynamic stiffness in spastic spinal-cord-injured subjects. IEEE Trans Neural Syst Rehabil Eng 2002;10(4):280-289.

Murillo N, Kumru H, Vidal-Samso J, Benito J, Medina J, Navarro X, Valls-Sole J. Decrease of spasticity with muscle vibration in patients with spinal cord injury. *Clinical Neurophysiology,* 2011;122:1183-1189.

Musty RE, Cansroe P. (2002) Marijuana And Cannabinoids In Spastic Disorders: An Overview Of Experimental And Clinical Research. In: Grotenhermen F, Russo E, editors. Cannabis and Cannabinoids: Pharmacology, Toxicology, and Therapeutic Potential. Philadelphia, PA: Haworth Press, 195-204.

Nance, P. W., Huff, F. J., Martinez-Arizala, A., Ayyoub, Z., Chen, D., Bian, A., & Stamler, D. (2011). Efficacy and safety study of arbaclofen placarbil in patients with spasticity due to spinal cord injury. *Spinal Cord, 49*(9), 974-980.

Nance PW, Schryvers O, Schmidt B, Dubo H, Loveridge B, Fewer D. Intrathecal baclofen therapy for adults with spinal spasticity: therapeutic efficacy and effect on hospital admissions. Can J Neurol Sci 1995;22:22-29.

Nance PW, Shears AH, Nance DM. Reflex changes induced by clonidine in spinal cord injured patients. Paraplegia 1989;27(4):296-301.

Nance PW. A comparison of clonidine, cyproheptadine and baclofen in spastic spinal cord injured patients. J Am Paraplegia Soc 1994;17(3):150-156.

Nance PW, Bugaresti J, Shellenberger K, Sheremata W, Martinez-Arizala A. Efficacy and safety of tizanidine in the treatment of spasticity in patients with spinal cord injury. North American Tizanidine Study Group. Neurology 1994;44:S44-S51.

Ness LL, Field-Fote EC. Effect of whole-body vibration on quadriceps spasticity in individuals with spastic hypertonia due to spinal cord injury. *Restorative Neurology and Neuroscience,* 2009;27:621-631.

Norman KE, Pepin A, Barbeau H. Effects of drugs on walking after spinal cord injury. Spinal Cord 1998;36(10):699-715.

O'Brien CF. Injection techniques for botulinum toxin using electromyography and electrical stimulation. Muscle Nerve Suppl 1997;6:S176-S180.

O'Brien CF. Treatment of spasticity with botulinum toxin. Clin J Pain. 2002 Nov-Dec; 18 (6suppl): S182-90).

Ochs G, Struppler A, Meyerson BA, Linderoth B, Gybels J, Gardner BP et al. Intrathecal baclofen for long-term treatment of spasticity: a multi-centre study. J Neurol Neurosurg Psychiatry 1989;52:933-939.

Odeen I, Knutsson E. Evaluation of the effects of muscle stretch and weight load in patients with spastic paraplegia. Scand J Rehabil Med 1981;13:117-121.

Oechsner M. Treatment of hip adductor spasticity with botulinum toxin type B. Nervenarzt 2002;73(12):1179-1182.

On AY, Kirazli Y, Kismali B, Aksit R. Mechanisms of action of phenol block and botulinus toxin Type A in relieving spasticity: electrophysiologic investigation and follow-up. Am J Phys Med Rehabil. 1999 Jul-Aug;78(4):344-9.

Ordia JI, Fischer E, Adamski E, Spatz EL. Chronic intrathecal delivery of baclofen by a programmable pump for the treatment of severe spasticity. J Neurosurg 1996;85:452-457.

Ozer K, Chesher SP, Scheker LR. Neuromuscular electrical stimulation and dynamic bracing for the management of upper-extremity spasticity in children with cerebral palsy. Dev Med Child Neurol 2006;48:559-563.

Paisley S, Beard S, Hunn A, Wight J. Clinical effectiveness of oral treatments for spasticity in multiple sclerosis: a systematic review. Mult Scler 2002;8(4):319-329.

Pandyan AD, Gregoric M, Barnes MP, Wood D, van WF, Burridge J et al. Spasticity: clinical perceptions, neurological realities and meaningful measurement. Disabil Rehabil 2005;27(1-2):2-6.

Parke B, Penn RD, Savoy SM, Corcos D. Functional outcome after delivery of intrathecal baclofen. Arch Phys Med Rehabil 1989;70:30-32.

Penn RD. Intrathecal baclofen for severe spasticity. Ann N Y Acad Sci 1988;531:157-166.

Penn RD, Savoy SM, Corcos D, Latash M, Gottlieb G, Parke B et al. Intrathecal baclofen for severe spinal spasticity. N Engl J Med 1989;320:1517-1521.

Penn RD. Intrathecal baclofen for spasticity of spinal origin: seven years of experience. J Neurosurg 1992;77:236-240.

Pertwee RG. Cannabinoids and multiple sclerosis. Pharmacol Ther 2002;95(2):165-174.

Pierson SH. Outcome measures in spasticity management. Muscle Nerve Suppl 1997;6:S36-S60.

Pinter MM, Gerstenbrand F, Dimitrijevic MR. Epidural electrical stimulation of posterior structures of the human lumbosacral cord: 3. Control Of spasticity. Spinal Cord 2000;38(9):524-531.

Plassat R, Perrouin Verbe B, Menei P, Menegalli D, Mathe JF, Richard I. Treatment of spasticity with intrathecal Baclofen administration: long-term follow-up, review of 40 patients. Spinal Cord 2004;42:686-693.

Pooyania, S., Ethans, K., Szturm, T., Casey, A., & Perry,D. (2010). A randomized, double-blinded, crossover pilot study assessing the effect of nabilone on spasticity in persons with spinal cord injury. *Archives of Physical Medicine and Rehabilitation, 91*(5), 703-707.

Postma TJBM, Oenema D, Terpstra S et al. Cost analysis of the treatment of severe spinal spasticity with a continuous intrathecal baclofen infusion system. PharmacoEconomics 15(4)()(pp 395-404), 1999 Date of Publication: 1999 1999;(4):395-404.

Potter PJ, Hayes KC, Segal JL, Hsieh JT, Brunnemann SR, Delaney GA et al. Randomized double-blind crossover trial of fampridine-SR (sustained release 4-aminopyridine) in patients with incomplete spinal cord injury. J Neurotrauma 1998;15(10):837-849.

Potter PJ, Hayes KC, Hsieh JT, Delaney GA, Segal JL. Sustained improvements in neurological function in spinal cord injured patients treated with oral 4-aminopyridine: three cases. Spinal Cord 1998;36(3):147-155.

Price R, Lehmann JF, Boswell-Bessette S, Burleigh A, deLateur BJ. Influence of cryotherapy on spasticity at the human ankle. Arch Phys Med Rehabil 1993;74(3):300-304.

Priebe MM, Sherwood AM, Thornby JI, Kharas NF, Markowski J. Clinical assessment of spasticity in spinal cord injury: a multidimensional problem. Arch Phys Med Rehabil 1996;77(7):713-716.

Putty TK, Shapiro SA. Efficacy of dorsal longitudinal myelotomy in treating spinal spasticity: a review of 20 cases. J Neurosurg 1991;75(3):397-401.

Raine S. The current theoretical assumptions of the Bobath concept as determined by the members of BBTA. Physiother Theory Pract 2007;23(3):137-152.

Rayegani, S. M., Shojaee, H., Sedighipour, L., Soroush, M. R., Baghbani, M., & Amirani, O. B. (2011). The effect of electrical passive cycling on spasticity in war veterans with spinal cord injury. *Frontiers in Neurology, 2*(39), 1-7.

Remy-Neris O, Barbeau H, Daniel O, Boiteau F, Bussel B. Effects of intrathecal clonidine injection on spinal reflexes and human locomotion in incomplete paraplegic subjects. Exp Brain Res 1999;129(3):433-440.

Remy-Neris O, Denys P, Bussel B. Intrathecal clonidine for controlling spastic hypertonia. Phys Med Rehabil Clin N Am 2001;12(4):939-51, ix.

Reynolds JR. Therapeutic uses and toxic effects of Cannabis indica. Lancet 1890;1:637-638.

Richardson D, Edwards S, Sheean GL, Greenwood RJ, Thompson AJ. The effect of botulinum toxin on hand function after incomplete spinal cord injury at the level of C5/6: a case report. Clin Rehabil 1997;11(4):288-292.

Richardson D, Sheean G, Werring D, Desai M, Edwards S, Greenwood R et al. Evaluating the role of botulinum toxin in the management of focal hypertonia in adults. J Neurol Neurosurg Psychiatry 2000;69(4):499-506.

Richardson RR, McLone DG. Percutaneous epidural neurostimulation for paraplegic spasticity. Surg Neurol 1978;9(3):153-155.

Robinson CJ, Kett NA, Bolam JM. Spasticity in spinal cord injured patients: 2. Initial measures and long-term effects of surface electrical stimulation. Arch Phys Med Rehabil 1988;69(10):862-868.

Robinson CJ, Kett NA, Bolam JM. Spasticity in spinal cord injured patients: 1. Short-term effects of surface electrical stimulation. Arch Phys Med Rehabil 1988;69(8):598-604.

Rosche J, Paulus C, Maisch U, Kaspar A, Mauch E, Kornhuber HH. The effects of therapy on spasticity utilizing a motorized exercise-cycle. Spinal Cord 1997;35(3):176-178.

Rosche J. Treatment of spasticity. Spinal Cord 2002;40(6):261-262.

Roussan M, Terrence C, Fromm G. Baclofen versus diazepam for the treatment of spasticity and long-term follow-up of baclofen therapy. Pharmatherapeutica 1985;4(5):278-284.

Schule R, Holland-Letz T, Klimpe S, Kassubek J, Klopstock T, Mall V et al. The Spastic Paraplegia Rating Scale (SPRS): a reliable and valid measure of disease severity. Neurology 2006;67(3):430-434.

Schurch B, Hauri D, Rodic B, Curt A, Meyer M, Rossier AB. Botulinum-A toxin as a treatment of detrusor-sphincter dyssynergia: a prospective study in 24 spinal cord injury patients. J Urol 1996;155(3):1023-1029.

Segal JL, Pathak MS, Hernandez JP, Himber PL, Brunnemann SR, Charter RS. Safety and efficacy of 4-aminopyridine in humans with spinal cord injury: a long-term, controlled trial. Pharmacotherapy 1999;19(6):713-723.

Seib TP, Price R, Reyes MR, Lehmann JF. The quantitative measurement of spasticity: effect of cutaneous electrical stimulation. Arch Phys Med Rehabil 1994;75(7):746-750.

Shahani BT, Young RR. Management of flexor spasms with Lioresal. Arch Phys Med Rehabil 1974;55(10):465-467.

Shields RK, Dudley-Javoroski S. Monitoring standing wheelchair use after spinal cord injury: a case report. Disabil Rehabil 2005;27:142-146.

Simpson DM, Alexander DN, O'Brien CF, Tagliati M, Aswad AS, Leon JM et al. Botulinum toxin type A in the treatment of upper extremity spasticity: a randomized, double-blind, placebo-controlled trial. Neurology 1996;46(5):1306-1310.

Simpson DM. Clinical trials of botulinum toxin in the treatment of spasticity. Muscle Nerve Suppl 1997;6:S169-S175.

Skold C. Spasticity in spinal cord injury: self- and clinically rated intrinsic fluctuations and intervention-induced changes. Arch Phys Med Rehabil 2000;81(2):144-149.

Smith SJ, Ellis E, White S, Moore AP. A double-blind placebo-controlled study of botulinum toxin in upper limb spasticity after stroke or head injury. Clin Rehabil 2000;14(1):5-13.

Snow BJ, Tsui JK, Bhatt MH, Varelas M, Hashimoto SA, Calne DB. Treatment of spasticity with botulinum toxin: a double-blind study. Ann Neurol 1990;28(4):512-515.

Steeves JD, Lammertse D, Curt A et al. Guidelines for the conduct of clinical trials for spinal cord injury (SCI) as developed by the ICCP panel: Clinical trial outcome measures. Spinal Cord 45(3)()(pp 206-221), 2007 Date of Publication: 30 Mar 2007 2007;(3):206-221.

Stempien L, Tsai T. Intrathecal baclofen pump use for spasticity: a clinical survey. Am J Phys Med Rehabil 2000;79:536-541.

Stewart JE, Barbeau H, Gauthier S. Modulation of locomotor patterns and spasticity with clonidine in spinal cord injured patients. Can J Neurol Sci 1991;18(3):321-332.

Takenaga S, Kawahigashi Y, Sonoda Y, Horikiri T, Hirata K, Arimura K et al. Treatment of spastic paraparesis with botulinum toxin with reference to beneficial effects, disease severity and long-term treatment. Rinsho Shinkeigaku 1995;35(3):251-255.

Tardieau G, Shentoub S, Delarue R. A la recherche d'une technique de measure de la spasticite. Revue de Neurologie (Paris) 1954;91:143-144.

Taricco M, Pagliacci MC, Telaro E, Adone R. Pharmacological interventions for spasticity following spinal cord injury: results of a Cochrane systematic review. Eura Medicophys 2006;42(1):5-15.

Thoumie P, Le CG, Beillot J, Dassonville J, Chevalier T, Perrouin-Verbe B et al. Restoration of functional gait in paraplegic patients with the RGO-II hybrid orthosis. A multicenter controlled study. II: Physiological evaluation. Paraplegia 1995;33(11):654-659.

Uchikawa K, Toikawa H, Liu M. Subscapularis motor point block for spastic shoulders in patients with cervical cord injury. Spinal Cord 47(3)()(pp 249-251), 2009 Date of Publication: March 2009 2009;(3):249-251.

van der Salm A, Veltink PH, Ijzerman MJ, Groothuis-Oudshoorn KC, Nene AV, Hermens HJ. Comparison of electric stimulation methods for reduction of triceps surae spasticity in spinal cord injury. Arch Phys Med Rehabil 2006;87(2):222-228.

Vorrink SNW, Van Der Woude LHV, Messenberg A et al. Comparison of wheelchair wheels in terms of vibration and spasticity in people with spinal cord injury. Journal of Rehabilitation Research and Development 45(9)()(pp 1269-1280), 2008 Date of Publication: 2008 2008;(9):1269-1280.

Wainberg M, Barbeau H, Gauthier S. The effects of cyproheptadine on locomotion and on spasticity in patients with spinal cord injuries. J Neurol Neurosurg Psychiatry 1990;53(9):754-763.

Walker JB. Temporary suppression of clonus in humans by brief photostimulation. Brain Res 1985;340(1):109-113.

Walter JS, Sacks J, Othman R, Rankin AZ, Nemchausky B, Chintam R et al. A database of self-reported secondary medical problems among VA spinal cord injury patients: its role in clinical care and management. J Rehabil Res Dev 2002;39:53-61.

Ward AB. A summary of spasticity management--a treatment algorithm. Eur J Neurol 2002;9 Suppl 1:48-52.

Wasiak J, Hoare B, Wallen M. Botulinum toxin A as an adjunct to treatment in the management of the upper limb in children with spastic cerebral palsy. Cochrane Database Syst Rev 2004;(4):CD003469.

Wassef MR. Interadductor approach to obturator nerve blockade for spastic conditions of adductor thigh muscles. Reg Anesth. 1993 Jan-Feb;18(1):13-7.

Wassermann EM, Lisanby SH. Therapeutic application of repetitive transcranial magnetic stimulation: a review. *Clinical Neurophysiology*. 2001;112:1367-1377.

Weingarden SI, Belen JG. Clonidine transdermal system for treatment of spasticity in spinal cord injury. Arch Phys Med Rehabil 1992;73(9):876-877.

Wilson LA, McKechnie AA. Oral diazepam in the treatment of spasticity in paraplegia a double-blind trial and subsequent impressions. Scott Med J 1966;11(2):46-51.

Wissel J, Heinen F, shenkel A. et. Al. Botulinum toxin A in the management of spastic gait disorders in children and yung adults with cerebral palsy: a randomized, double-blind study of "high-dose" versus "low-dose" treatment. Neuropediatrics 1999; 30: 120-24.

Yablon SA, Sipski ML. Effect of transdermal clonidine on spinal spasticity. A case series. Am J Phys Med Rehabil 1993;72(3):154-157.

Yadav SL, Singh U, Dureja GP, Singh KK, Chaturvedi S. Phenol block in the management of spastic cerebral palsy. Indian J Pediatr. 1994 May-Jun;61(3):249-55.

Yamada S, Perot PL, Jr., Ducker TB, Lockard I. Myelotomy for control of mass spasms in paraplegia. J Neurosurg 1976;45(6):683-691.

Yasar E, Tok F, Taskaynatan MA, Yilmaz B, Balaban B, Alaca R. The effects of phenol neurolysis of the obturator nerve on the distribution of buttock-seat interface pressure in spinal cord injury patients with hip adductor spasticity. *Spinal Cord,* 2010;48:828-831.Young RR. Treatment of spastic paresis (editorial). N Engl J Med 1989;320:1553-1555.

Young RR. Spasticity: a review. Neurology 1994;44:S12-S20.

Zahavi A, Geertzen JH, Middel B, Staal M, Rietman JS. Long term effect (more than five years) of intrathecal baclofen on impairment, disability, and quality of life in patients with severe spasticity of spinal origin. J Neurol Neurosurg Psychiatry 2004;75:1553-1557.