Spasticity Following Spinal Cord Injury

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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 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.

Active Movement-based Approaches for Reducing Spasticity
Active exercise interventions such as hydrotherapy and (FES) functional electrical stimulation-assisted 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 and helium-neon irradiation may result in immediate spasticity reduction but require more research to examine long-term effects.

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

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 useful effective in treating SCI spasticity but more evidence is required to support it 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 research is needed to determine its use.

The use 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 destra-9-tetrahydrocannabinol (dronabinol) may help to reduce spasticity but requires additional evidence from controlled studies.

**Focal Neurolysis**

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

Phenol block improves pain, range of motion and function related to shoulder spasticity in individuals with tetraplegia.
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 forward 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 motoneuron syndrome”. Recent studies indicate that besides changes in the 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 fibre, 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 are 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 (eg. 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

<table>
<thead>
<tr>
<th>Known Clinical Measures</th>
<th>Other Measures</th>
<th>Electrophysiological Measures</th>
<th>Quality of Life Measures</th>
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<tr>
<td>1. Ambulation Index</td>
<td>1. Adverse Event monitoring</td>
<td>1. &quot;Electrophysiologic testing&quot;</td>
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<td>3. Ashworth (Original and Modified)</td>
<td>3. &quot;Clinical Rating Score (CRS)&quot;</td>
<td>3. Flexion reflex measurement Peak isometric quad torque in response to surface electrical stimulation</td>
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<tr>
<td>5. Clonus (count or duration)</td>
<td>5. &quot;Continuation of study drug after trial&quot;</td>
<td>5. H-Reflex and H/M ratio (latency and amplitude)</td>
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<tr>
<td>Known Clinical Measures</td>
<td>Other Measures</td>
<td>Electrophysiological Measures</td>
<td>Quality of Life Measures</td>
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<tr>
<td>10. Global Impression (Patient and/or Clinician)</td>
<td>“Evaluation of personal independence”</td>
<td>10. Viscous and elastic stiffness to sinusoidal ankle perturbation of 5° at 3 to 12 Hz.</td>
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<tr>
<td>11. Incapacity Status Scale*</td>
<td>“Five point scale” (interference of spasticity on selected self care activities” and weekly rate of resistance to movement)</td>
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<td>12. Klein-Bell ADL scale</td>
<td>“Functional disability score (FDS)”</td>
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<td>13. Jabsen Hand Function Test</td>
<td>“Gait spasticity and transfer activity”</td>
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<td>15. Nine-hole peg test (upper limb problems only)</td>
<td>“Neurological reflex scale”</td>
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<td>17. Patient Evaluation and Conference System (PECS)</td>
<td>“Painful Spasm Scale”</td>
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<td>18. Pendulum test (relaxation index; peak velocity)</td>
<td>“Patient Caregiver subjective responses”</td>
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<td>19. Plantar stimulation response</td>
<td>Patient/Clinician Global measure (4 point scale)</td>
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<td>20. Present Pain Intensity</td>
<td>Patient Daily Diary or Log (spasticity, clonus, nocturnal awakenings related to spasms)</td>
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<td>21. Profile of Moods Scale</td>
<td>Subjective ratings (problem severity, spasticity assessment, pain)</td>
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<td>22. Rivermead Mobility Index (RMI)</td>
<td>“Telephone questionnaire regarding decrease in symptoms”</td>
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<tr>
<td>23. Seven point terrible-delighted scale</td>
<td>“Use of limbs and transfer activity (weekly)”</td>
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<td>24. Six point Likert scale (spasticity)</td>
<td>Vibratory Inhibition Index (VII)</td>
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<tr>
<td>25. Smith Hand Function Evaluation</td>
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<td>26. Spasm Frequency Scale (SFS)</td>
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<tr>
<td>27. Spasm Severity Scale (SSS)</td>
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<td>28. Standard neurological examination</td>
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<tr>
<td>29. Timed 10 m walk test (lower limb problems only)</td>
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<td>30. Visual Analogue Scale (VAS: Spasticity, Pain, Satisfaction)</td>
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<tr>
<td>31. Weschler Memory Test</td>
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*Includes Spasticity sum score=average MAS for
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; 4) having a reasonable risk-benefit ratio; 5) requirement for strict adherence to test conditions and procedures; and 6) 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 scale, Spasm Frequency scale (Penn 1988; Priebe 1996), 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 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
A 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 combination 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). 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 the 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 engaging in 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

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<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Score</th>
<th>Research Design</th>
<th>Total Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
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<th>Author Year</th>
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<th>Outcome</th>
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<tbody>
<tr>
<td>Li et al. 2007</td>
<td>China</td>
<td>PEDro = 6</td>
<td>RCT</td>
<td>N=28</td>
<td><strong>Population:</strong> 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. <strong>Treatment:</strong> 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. <strong>Outcome Measures:</strong> Modified Ashworth Scale; BI tested pre-post 6 weeks intervention.</td>
<td>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&lt;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&lt;0.05).</td>
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<tr>
<td>Harvey et al. 2009</td>
<td>Australia</td>
<td>PEDro = 6</td>
<td>RCT</td>
<td>N = 20</td>
<td><strong>Population:</strong> 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 <strong>Treatment:</strong> Passive movement of the experimental ankle, 5 days/week for 6 months <strong>Outcome Measures:</strong> Passive dorsiflexion of ankles; the modified Ashworth scale of the hamstring and plantar-flexor muscles; Global Impression of Change scale</td>
<td>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°. 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.</td>
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<td>Lechner et al. 2007</td>
<td>Switzerland &amp; Austria</td>
<td>PEDro = 4</td>
<td>Cross-over RCT</td>
<td>Initial N=12; Final N=11</td>
<td><strong>Population:</strong> 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. <strong>Treatment:</strong> 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. <strong>Outcome Measures:</strong> Ashworth Scale; VAS -self rating of spasticity; Mental well-being Bf-S.</td>
<td>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&lt;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 (p&lt;0.05) and S (p&lt;0.05) but not for the control condition. 4. Significant spasticity reductions were found in the VAS scores before and after</td>
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<td>Author Year</td>
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<td>Total Sample Size</td>
<td>Methods</td>
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<td>Sköld 2000</td>
<td>Sweden</td>
<td>15</td>
<td>Pre-post</td>
<td>N=45 (Passive stretches performed on n=12)</td>
<td><strong>Population</strong>: 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). <strong>Treatment</strong>: 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. <strong>Outcome Measures</strong>: self-reported Visual Analogue Scale (VAS): &quot;no spasticity&quot; to &quot;most imaginable spasticity&quot;, MAS, collected just prior and after each treatment session.</td>
<td>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.</td>
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<td>Kakebeeke et al. 2005</td>
<td>Switzerland</td>
<td>14</td>
<td>Pre-post</td>
<td>N=10</td>
<td><strong>Population</strong>: Age = 23-60 yrs; Gender: males = 9, females = 1; Level of injury: C6 to T12; Severity of injury: AIS: A &amp; B; Time since injury = 1-25 years. <strong>Treatment</strong>: Passive cycling with motorized cycle for 30 minutes at 40 RPM (1 session) vs. no cycling. <strong>Outcome Measures</strong>: Torque resistance to movement on isokinetic dynamometer, subjective subject assessment collected just prior and following cycling (or control).</td>
<td>1. Spasticity decreased after each intervention session as indicated by VAS (p&lt;0.001) and MAS (p&lt;0.001). 2. Spasticity reductions were maintained in VAS values (albeit to a lesser degree) after treatment was discontinued for 4 days (p&lt;0.018).</td>
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<tr>
<td>Lechner et al. 2003</td>
<td>Switzerland</td>
<td>13</td>
<td>Pre-post</td>
<td>N=32</td>
<td><strong>Population</strong>: 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. <strong>Treatment</strong>: Hippotherapy-K® (HTK; Kuenzle 2000): An average of 11 sessions (5-24) each lasting 25-30 minutes. Sheepskin (no saddle) on Icelandar horse. <strong>Outcome Measures</strong>: Ashworth scale</td>
<td>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 noted as indicated by no differences with torque before and after cycling or before and after the control (no cycling) condition. 3. 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&lt;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</td>
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<td>Author</td>
<td>Year</td>
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<td>Total Sample Size</td>
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<tr>
<td>Odeen &amp; Knutsson</td>
<td>1981</td>
<td>Sweden</td>
<td>Downs &amp; Black score=12</td>
<td>Pre-post N=9</td>
<td>Population: Age = 21-67 yrs; Gender males = 8, females = 1; Time since injury &gt; 3 yrs. Treatment: Standing in forced dorsiflexion or plantarflexion (i.e., load applied) vs. stretch applied to plantarflexors 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.</td>
<td>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.</td>
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Note: AIS=ASIA Impairment Scale; BI=Barthel Index; Bf-S=Befindlichkeits-Skala; EMG=electromyography; 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 plantarflexors. 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.

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 85° with the ankle dorsiflexed by 10-15° 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 1 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 limited level 1 evidence from a single study that a combination of a 6 week course of neural facilitation techniques (Bobath, Rood and Brunstrom 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.** |

**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

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Country</th>
<th>Score</th>
<th>Research Design</th>
<th>Total Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Krause et al. 2008</td>
<td>Germany</td>
<td>PEDro=5</td>
<td>RCT</td>
<td>N=5</td>
<td><strong>Population:</strong> Mean age=46yrs; Gender: males=3, females=2; Level of injury: T; Severity of injury: AIS A <strong>Treatment:</strong> 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 <strong>Outcome Measures:</strong> Pendulum test (Relaxation index, peak velocity), Ashworth Scale conducted within 30 minutes prior or following treatment.</td>
<td>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 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&lt;0.001) and the passive movement session (p&lt;0.05).</td>
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<tr>
<td>Thoumie et al. 1995</td>
<td>France</td>
<td>Downs &amp; Black score=24</td>
<td>Pre-post</td>
<td>N=21</td>
<td><strong>Population:</strong> Age = 20-53 yrs; Gender: males = 20, females = 1; Level of injury: C8-T12; Time since injury = 4-72 months. <strong>Treatment:</strong> 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. <strong>Outcome Measures:</strong> Spasticity (Subjective self-report scale based on Ashworth scale), Cardiovascular function (HR, VO2, blood lactate), Constipation (Radiopaque markers transit). Osteoporosis (Bone mineral density) collected prior to and following the 3-14 month trial.</td>
<td>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.</td>
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<tr>
<td>Kesiktas et al. 2004</td>
<td>Turkey</td>
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<td><strong>Population:</strong> Hydrotherapy group: Mean age = 32.1 yrs; Gender:</td>
<td>1. Both groups showed a significant decrease in</td>
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<td>Author Year Country</td>
<td>Score</td>
<td>Research Design</td>
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<tr>
<td>Downs &amp; Black score=17 Experimental</td>
<td>Non-RCT</td>
<td>N=20</td>
<td>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.</td>
<td><strong>Treatment:</strong> 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. <strong>Outcome Measures:</strong> 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.</td>
<td>Ashworth scores (hydrotherapy = p&lt;0.01 and control = p&lt;0.02) with hydrotherapy having a larger reduction in spasticity but this difference was not significant. 2. Spasticity was significantly reduced with hydrotherapy (p&lt;0.001) and with Control (p&lt;0.05) as indicated by Penn Spasm Severity. Post-treatment hydrotherapy scores were reduced vs. Controls (p&lt;0.02). 3. Oral Baclofen intake was significantly reduced for the hydrotherapy group but not for the control group (p&lt;0.002). 4. Both groups demonstrated significant increases in FIM scores (hydrotherapy = p&lt;0.0001 and control = p&lt;0.01), with a larger increase for the hydrotherapy group (p&lt;0.001).</td>
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<tr>
<td>Mirbagheri et al. 2002 Canada</td>
<td>Downs &amp; Black score=17</td>
<td>Pre-post</td>
<td>(1 unplanned control, dropout from training)</td>
<td><strong>Population:</strong> 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). <strong>Treatment:</strong> FES-assisted walking for as much time as possible during daily living (~1-3 hours/day) for 16-18 months following 4 weeks of training. <strong>Outcome Measures:</strong> 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.</td>
<td>1. Spasticity was reduced in those that did FES-assisted walking as indicated by reductions in decreased reflex (p&lt;0.001) and intrinsic (p&lt;0.001) stiffness. 2. Spasticity increased for the non-FES subject as indicated by increased reflex stiffness and no change in intrinsic stiffness. 3. The modified Ashworth score either showed no change following the training period or was not collected (this was not clearly presented by the authors).</td>
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<td>Granat et al. 1993 Scotland</td>
<td>Downs &amp; Black score=5</td>
<td>Pre-post</td>
<td>N=6</td>
<td><strong>Population:</strong> 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. <strong>Treatment:</strong> 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. <strong>Outcome Measures:</strong> Spasticity (Ashworth Scale and Pendulum Test), Manual muscle tests using Oxford Scale (MMT), maximum voluntary contraction (MVC),</td>
<td>1. Significant reductions in spasticity as indicated by increased relaxation index of pendulum test (p&lt;0.05). 2. No changes were evident with Ashworth scale. 3. Gait and muscle strength changes are elaborated in Chapter entitled “Lower Limb Rehabilitation&quot;.</td>
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<tr>
<td>Author Year</td>
<td>Country</td>
<td>Score</td>
<td>Research Design</td>
<td>Total Sample Size</td>
<td>Methods</td>
<td>Outcome</td>
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<td>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.</td>
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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 subthreshold 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

<table>
<thead>
<tr>
<th>Author Year Country Score Research Design Total Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>van der Salm et al. 2006 Netherlands Downs &amp; Black score=18 Prospective Controlled Trial N=10</td>
<td><strong>Population:</strong> 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. <strong>Treatment:</strong> 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 threshold for afferent stimulation. <strong>Outcome Measures:</strong> 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.</td>
<td>1. Only the agonist muscle stimulation differed significantly (46% reduction) from the placebo as indicated by reduced MAS (p&lt;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&lt;0.015) but the carryover effect was not significant.</td>
</tr>
<tr>
<td>Robinson et al. 1988a USA Downs &amp; Black score=15 Pre-post N=12</td>
<td><strong>Population:</strong> Age = 21-62 yrs; Level of injury: paraplegia = 6, tetraplegia = 6; Severity of injury: complete = 6, incomplete = 6. <strong>Treatment:</strong> 1, 20 minute session of electrical stimulation of quadriceps with leg maintained at 60° flexion (isometric exercise). <strong>Outcome Measures:</strong> Normalized relaxation index obtained during Pendulum test (R2n) collected prior and immediately after stimulation.</td>
<td>1. Decrease in spasticity was noted with pendulum test (average R2n increased in most cases) (p&lt;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.</td>
</tr>
<tr>
<td>Seib et al. 1994 USA</td>
<td><strong>Population:</strong> Age = 19-73yrs; Gender: males = 6, females = 4;</td>
<td>1. Spasticity was reduced in 9/10 participants (p&lt;0.05) (p&lt;0.05)</td>
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</table>
### Discussion

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.

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.

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<th>Author Year</th>
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<th>Score</th>
<th>Research Design</th>
<th>Total Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Aydin et al. 2005</td>
<td>Turkey</td>
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<td>Population: SCI (n=21): Severity of Injury: complete, incomplete; Cause</td>
<td>1. For both treatment groups a significant improvement was</td>
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<td>Author Year Country</td>
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<td>PEDro = 6</td>
<td>RCT</td>
<td>N=41</td>
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<td>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&lt;0.011 Baclofen group and p&lt;0.020 TENS group), SFS (p&lt;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&lt;0.005, TENS group p&lt;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.</td>
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<tr>
<td>Laessoe et al. 2004</td>
<td>Denmark</td>
<td>PEDro=6</td>
<td>RCT</td>
<td>N=9</td>
<td>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 Scale</td>
<td>1. There was a significant decrease in spasticity after penile stimulation as indicated by decreases in Modified Ashworth Scale (0&lt;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</td>
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<td>Walker 1985</td>
<td>USA</td>
<td>PEDro=4</td>
<td>RCT</td>
<td>N=41</td>
<td>was also collected immediately after stimulation. compared to before vibration (p&lt;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.</td>
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<td>van der Salm et al. 2006</td>
<td>The Netherlands</td>
<td>Downs &amp; Black score=18</td>
<td>Pre-post</td>
<td>N=10</td>
<td>Population: Level of injury: T12-L2; Time since injury &gt; 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.</td>
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<td>Halstead et al. 1993</td>
<td>USA</td>
<td>Downs &amp; Black score=17</td>
<td>Pre-post</td>
<td>N=9</td>
<td>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 1. Spasticity was reduced as indicated by reduced Ashworth scores assessed within 1 hour post-stimulation (p&lt;0.01). 2. Spasticity relief as indicated by</td>
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<td>Author Year</td>
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<td>Alaca et al. 2005</td>
<td>Turkey</td>
<td>Downs &amp; Black score=16</td>
<td>Pre-post</td>
<td>N=10</td>
<td>since injury = 0.5-15 yrs. <strong>Treatment</strong>: 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. <strong>Outcome Measures</strong>: 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-report 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.</td>
<td>self-report was for 7.8/9.5 hours (quad/para mean values). 3. No significant correlation of RPES effect on spasticity were 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.</td>
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<td>Goulet et al. 1996</td>
<td>Canada</td>
<td>Downs &amp; Black score=16</td>
<td>Pre-post</td>
<td>N=14</td>
<td><strong>Population</strong>: 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 mths. <strong>Treatment</strong>: TENS stimulation (i.e., low threshold afferent nerve stimulation) over the common peroneal nerve for 30 minutes. <strong>Outcome Measures</strong>: 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.</td>
<td>1. There was a significant decrease in spasticity after penile stimulation as indicated by decreases in the Ashworth Scale (p&lt;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 (nonsignificant) 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.</td>
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<td>Author Year</td>
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<tr>
<td>Downs &amp; Black</td>
<td>Canada</td>
<td>15</td>
<td>Pre- post N=17</td>
<td>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).</td>
<td>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.</td>
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<tr>
<td>Price et al. 1993</td>
<td>USA</td>
<td>12</td>
<td>Pre-post N=25</td>
<td>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 collected prior to, during and 1 hour after cryotherapy. 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 spasticity as indicated by elastic path length (p=0.0198) but only a trend was noted for total path length (p=0.058).</td>
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<td>Bajd et al. 1985</td>
<td>Yugoslavia</td>
<td>10</td>
<td>Pre-post N=6</td>
<td>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 mins. Outcome Measures: Pendulum test (relaxation index) performed just prior to and just after stimulation as well as 2 hours post-stimulation.</td>
<td>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.</td>
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Note: AIS=ASIA Impairment Scale; EMG=electromyography; FES=functional electrical stimulation; FDS=Function Disability Scale; FIM=Functional Independence Measure; MAS=modified Ashworth Scale; RPE= 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.

Other researchers have examined the effects of TENS following a single session (Bajd et al. 1985; Goulet et al. 1996; 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 plantarflexor 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. In this trial, 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 $\alpha$-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 $\alpha$-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, Laessoe 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 Laessoe 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.

Conclusions

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

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

There is level 1 evidence from a single RCT 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 1 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 and helium-neon irradiation may result in immediate spasticity reduction but require more research to examine long-term effects.

2.5 Interventions Based on Direct Spinal Cord 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;
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).”

Table 6 Studies of Spinal Cord Stimulation for Reducing Spasticity

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<th>Author Year Country</th>
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<td>Barolat et al. 1995 USA Downs &amp; Black score=15 Pre-post N=48</td>
<td>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 implantation.</td>
<td>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=0.001) and 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. 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.</td>
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<td>Pinter et al. 2000 Austria &amp; USA Downs &amp; Black score=10 Pre-post (Pilot study) N=8</td>
<td>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.</td>
<td>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 &gt; 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</td>
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<td>Author Year</td>
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<tr>
<td>Midha &amp; Schmitt 1998</td>
<td>USA</td>
<td>Downs &amp; Black score=7</td>
<td>Case Series N=29</td>
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**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 1986-1988.  
**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 - 7 years): 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**

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=0.0001) and 2 years (p=0.0012) relative to baseline. It should be noted that the positive nature of the long-term findings are somewhat muted as subjects were increasingly dropped from the analysis over time when they were lost to follow-up or discontinued due to lack of efficacy. Of 48 initial subjects, 40 provided data at 3 months, 33 at 6 months, 31 at 1 year and 18 at 2 years (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.

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.

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).

Table 7 Neurosurgical Interventions for Reducing Spasticity

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<tr>
<th>Author Year</th>
<th>Country</th>
<th>Score</th>
<th>Research Design</th>
<th>Total Sample Size</th>
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<tr>
<td>Livshits et al. 2002</td>
<td>Israel</td>
<td>PEDro=5</td>
<td>RCT</td>
<td>Initial N=40; Final N=32</td>
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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 =

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
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.

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 (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 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

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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).
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

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<th>Author</th>
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<th>Year</th>
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<th>Methods</th>
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<tr>
<td>Hinderer et al. 1990</td>
<td>USA</td>
<td>PEDro = 9</td>
<td>RCT (single subject design)</td>
<td>N=5</td>
<td>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 wks), 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 (Mon/Thu or Tue/Fri) over 9 weeks.</td>
<td>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&lt;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.</td>
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<td>Duncan et al. 1976</td>
<td>USA</td>
<td>PEDro = 8</td>
<td>RCT</td>
<td>N=22</td>
<td>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).</td>
<td>1. Number of spasms was significantly reduced with Baclofen vs. placebo (p&lt;.01) as was number of nocturnal awakenings (p&lt;.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&lt;.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.</td>
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<td>Burke et al. 1971</td>
<td>Australia</td>
<td>PEDro=7</td>
<td>RCT</td>
<td>N=6</td>
<td>Population: SCI (N=6): Level of injury: tetraplegic; Severity of injury: complete, incomplete; Cause of injury = trauma; Chronicity = chronic. 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</td>
<td>1. No group statistical results were provided. 2. All 6 subjects had a reduced EMG/velocity ratio for any given 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</td>
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<td>Author Year</td>
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<tr>
<td>Aydin et al. 2005</td>
<td>Turkey</td>
<td>PEDro=6</td>
<td>RCT</td>
<td>N=41</td>
<td>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.</td>
<td>1. For both treatment groups a significant improvement was noted post treatment in the lower limb Ashworth score (p&lt;0.011 Baclofen group and p&lt;0.020 TENS group), SFS (p&lt;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&lt;0.005, TENS group p&lt;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 (p=0.026).</td>
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<td>Dicpinigatis et al. 2000</td>
<td>USA</td>
<td>D&amp;B=21</td>
<td>Prospective controlled trial</td>
<td>N=24</td>
<td>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</td>
<td>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).</td>
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<td>Nance 1994</td>
<td>Canada</td>
<td>Downs &amp; Black score=15</td>
<td>Pre-post</td>
<td>N=25</td>
<td>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.</td>
<td>1. A significant reduction in spasticity was seen with Baclofen in all 3 outcome measures - as with the other 2 drugs tested (p&lt;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&lt;0.0007 – along w/ cyproheptadine).</td>
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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 on 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 on 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.

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 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 1 evidence that oral Baclofen improves muscle spasticity secondary to SCI. This conclusion is based on the results from three 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, rhabdomyolysis, seizures and death.

Table 9 Intrathecal Baclofen for Reducing Spasticity

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<th>Author Year</th>
<th>Country</th>
<th>Score</th>
<th>Research Design</th>
<th>Total Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
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<tr>
<td>Nance et al. 1995</td>
<td>Canada</td>
<td>PEDro=9</td>
<td>RCT for test dose</td>
<td>N=7</td>
<td>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.</td>
<td>1. Test dose: Intrathecal Baclofen 50 mcg decreased the average Ashworth score. 2. Long-term: A decrease in Ashworth score mean = 1.8 (p&lt;0.005) and spasm frequency score mean =0.8 (p&lt;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.</td>
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<tr>
<td>Penn et al. 1989; USA</td>
<td>PEDro=9</td>
<td>RCT (double blind crossover)</td>
<td>test dose; Pre-post (Open label) long term</td>
<td>N=20</td>
<td>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.</td>
<td>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&lt;0.01). Overall (all subjects combined), the Ashworth score decreased from 4.0 ± 1.0 to 1.2 ± 0.4 (p&lt;0.0001) and the spasm frequency scale decreased from 3.3 ± 1.2 to 0.4 ± 0.8 (p&lt;0.0005). 2. Long-term: For all patients combined, the Ashworth scale and spasm frequency scale decreased.</td>
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<td>Coffey et al. 1993</td>
<td>USA</td>
<td>RCT for test dose; Pre-post for long term</td>
<td>PEDro=8</td>
<td>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.</td>
<td>3. Follow-up ranged from 10-33 months (average 19).</td>
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<tr>
<td>Ordia et al. 1996</td>
<td>USA</td>
<td>RCT for trial dose</td>
<td>PEDro=6</td>
<td>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 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.</td>
<td>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).</td>
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<td>Hugenholtz et al. 1992</td>
<td>Canada</td>
<td>RCT (Cross-over)</td>
<td>PEDro = 6</td>
<td>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.</td>
<td>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&lt;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&lt;0.05). 4. Scores in the Smith Hand</td>
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<tr>
<td>Avellino &amp; Loeser 2000</td>
<td>USA</td>
<td>Downs &amp; Black score=18</td>
<td>Case series N=62</td>
<td>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</td>
<td>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&lt;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.</td>
<td></td>
</tr>
<tr>
<td>Boviatsis et al. 2005</td>
<td>Greece</td>
<td>Downs &amp; Black score=18</td>
<td>Case Series Initial N=22; Final N=21</td>
<td>Population: MS, SCI (N=7): Level of injury: C4 to T11. 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</td>
<td>1. The SCI group demonstrated a lower Ashworth score (4.57 to 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&lt;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</td>
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<td>Author Year</td>
<td>Country</td>
<td>Score</td>
<td>Research Design</td>
<td>Total Sample Size</td>
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<td>Outcome</td>
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<tr>
<td>Plassat et al. 2004</td>
<td>France</td>
<td>Downs &amp; Black score=16</td>
<td>Case series</td>
<td>Initial N=41; Final N=37</td>
<td><strong>Population:</strong> SCI (N=17), MS and cerebral spasticity. <strong>Treatment:</strong> Intrathecal Baclofen pump placement. <strong>Outcome Measures:</strong> VAS satisfaction score locomotion, pain, sleep, Ashworth.</td>
<td>revealed a limited improvement in pain (p=0.0941). 4. Follow-up ranged from 9-55 months (median 35 months).</td>
</tr>
<tr>
<td>Zahavi et al. 2004</td>
<td>Netherlands</td>
<td>Downs &amp; Black score=16</td>
<td>Case series (long-term)</td>
<td>Initial N=38; Final N=21</td>
<td><strong>Population:</strong> MS, SCI (N=6), Other spinal spasticity. <strong>Treatment:</strong> Intrathecal Baclofen pump implantation. <strong>Outcome Measures:</strong> Ashworth scale, spasm score, EDSS, AI, ISS, SIP, Hopkins symptom check list.</td>
<td>1. Improvement in Ashworth score from baseline 2.82 to final assessment 0.91 (p&lt;0.05) and spasm score from baseline 1.79 to final assessment 0.67 (p&lt;0.05). 2. Worsening in EDSS, AI and ISS (all p&lt;0.05) compared with baseline (in progressive and non-progressive groups of patient disabilities). Worsening in level of disability (EDSS and ISS p&lt;0.05) and the psychosocial aspect of the perceived health status scale (SIP) (p&lt;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.</td>
</tr>
<tr>
<td>Abel &amp; Smith 1994</td>
<td>USA</td>
<td>Downs &amp; Black score=13</td>
<td>Pre-post</td>
<td>N=23</td>
<td><strong>Population:</strong> MS, SCI (N=17): Level of injury: C4-T12; Severity of injury: AIS: A-D. <strong>Treatment:</strong> Intrathecal Baclofen pump implantation. <strong>Outcome Measures:</strong> Ashworth score and spasm score.</td>
<td>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.</td>
</tr>
<tr>
<td>Loubser et al. 1991</td>
<td>USA</td>
<td>Downs &amp; Black score=13</td>
<td>Randomized test dose; Pre-post long term follow-up</td>
<td>N=9</td>
<td><strong>Population:</strong> SCI: Gender: males = 9; Level of injury: C2-T12; Cause of injury: trauma. <strong>Treatment:</strong> 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. <strong>Outcome Measures:</strong> Ashworth scale, neurological reflex scale, evaluation of functional abilities, evaluation of personal independence and global assessment scale.</td>
<td>1. Test dose: A decrease was seen in optimal reflex score (t=7.69, p&lt;0.001) and the Ashworth score with Baclofen grade (t=6.05, p&lt;0.001), between placebo and optimal reflex score a change was noted (t=3.68, p&lt;0.01) and Ashworth grade (t=6.0, p&lt;0.001) and between placebo and control Ashworth grade (t=2.95, p&lt;0.02). At optimum intrathecal Baclofen dosage, 8/9 patients benefited in functional evaluations. 2. Long-term: Only 7 subjects participated. The Ashworth score decreased.</td>
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<td>Author Year</td>
<td>Country</td>
<td>Score</td>
<td>Research Design</td>
<td>Total Sample Size</td>
<td>Methods</td>
<td>Outcome</td>
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<tr>
<td>Penn et al. 1992</td>
<td>USA</td>
<td>13</td>
<td>Case Series</td>
<td>N=66</td>
<td>Population: MS, SCI (N=32). Treatment: Intrathecal Baclofen pump implantation. Outcome Measures: Ashworth score and spasm frequency scale.</td>
<td>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).</td>
</tr>
<tr>
<td>Korenkov et al. 2002</td>
<td>Germany</td>
<td>10</td>
<td>Pre-post</td>
<td>N=12</td>
<td>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.</td>
<td>1. Significant post-operative reduction of muscle tone and spasm (P&lt;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.</td>
</tr>
<tr>
<td>Ochs et al. 1989</td>
<td>Germany</td>
<td>10</td>
<td>Pre-post</td>
<td>N=28</td>
<td>Population: MS, SCI (N=10). Treatment: Intrathecal Baclofen pump implantation. Outcome Measures: Ashworth and spasm frequency scale, electrophysiological data.</td>
<td>1. Improvement in Ashworth and spasm frequency scale. Intrathecal Baclofen had an effect on electrophysiological data 2. Follow-up up to 2 years.</td>
</tr>
<tr>
<td>Parke et al. 1989</td>
<td>USA</td>
<td>9</td>
<td>Pre-post</td>
<td>N=8</td>
<td>Population: MS (N=4), SCI (N=4). Treatment: Intrathecal Baclofen pump implantation. Outcome Measures: Ashworth scale, muscle strength and modified PECS scale.</td>
<td>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.</td>
</tr>
<tr>
<td>Denys et al. 1998</td>
<td>France</td>
<td>5</td>
<td>Pre-Post</td>
<td></td>
<td>Population: MS, SCI (N=5); Gender: males = 9; Level of injury: C4-T11; Severity of injury: AIS: A-C. Treatment: Intrathecal Baclofen</td>
<td>1. No decrease in libido. 2. The ability of subjects to achieve reflexogenic (9/9) or psychogenic erections (3/9).</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Total Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>N=9</td>
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<tr>
<td>Author Year</td>
<td>Total Sample Size</td>
<td>Methods</td>
<td>Outcome</td>
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<tr>
<td>Coffey et al. 1993</td>
<td>N=75 (SCI=59)</td>
<td><strong>Test dose:</strong> Randomized trial test injection Baclofen versus placebo with up-titration from 50 mcg to 100 mcg. <strong>Long-term:</strong> Intrathecal Baclofen pump implantation.</td>
<td><strong>Test dose:</strong> 88 patients (94.6%) responded to the test dose with a decrease in Ashworth and spasm scale. No patients responded to placebo. <strong>Long-term:</strong> For the SCI group, the Ashworth score and spasm score decreased post-pump.</td>
</tr>
<tr>
<td>Loubser et al. 1991</td>
<td>N=9 (SCI=9)</td>
<td><strong>Test dose:</strong> 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. <strong>Long-term:</strong> Intrathecal Baclofen pump implantation.</td>
<td><strong>Test dose:</strong> At optimum intrathecal Baclofen dosage, 8/9 patients benefited in functional evaluations. <strong>Long-term:</strong> Only 7 subjects participated. The Ashworth score and mean reflex score decreased.</td>
</tr>
<tr>
<td>Penn et al. 1989</td>
<td>N=20 (SCI=10)</td>
<td><strong>Test dose:</strong> A 3 day infusion of saline or intrathecal Baclofen (100 mcg/milliliter) via programmable pump. <strong>Long-term:</strong> An open label long-term observation of intrathecal Baclofen.</td>
<td><strong>Test dose &amp; Long-term:</strong> Overall (all subjects combined), significant decreases for the Ashworth score and the spasm frequency scale decreased as a result of intrathecal Baclofen.</td>
</tr>
<tr>
<td>Ordia et al. 1996 Initial N=66; Final N=57 (SCI =27)</td>
<td></td>
<td><strong>Test dose:</strong> N=9 patients were randomized to receive normal saline or test dose intrathecal Baclofen. Subsequent test doses were not open label. <strong>Long-term:</strong> Intrathecal Baclofen pump implantation.</td>
<td><strong>Test dose:</strong> All 66 patients responded positively to test bolus dose and none of the 9 randomized patients responded to placebo. <strong>Long-term:</strong> A significant decrease in Ashworth score and spasm frequency scale at last follow-up</td>
</tr>
<tr>
<td>Nance et al. 1995 Initial N=7; Final N=6 (SCI =5)</td>
<td></td>
<td><strong>Test dose:</strong> A daily bolus of placebo or Baclofen (12.5 to 100 mcg titrated dose). <strong>Long-term:</strong> Intrathecal Baclofen pump implantation.</td>
<td><strong>Test dose:</strong> Intrathecal Baclofen 50 mcg decreased the average Ashworth score. <strong>Long-term:</strong> A significant decrease in Ashworth score and spasm frequency score and an improved leg swing in pendulum test.</td>
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</table>

**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 (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; Boviatis et al. 2005; Avellino & Loeser 2000). 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 (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). Tolerance to intrathecal Baclofen has been observed (Ochs et al. 1989; Coffey et al. 1993; Abel & Smith 1994; Ordia et al. 1996). 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 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

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Total Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
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</table>
| 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  
| 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. 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 |
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<th>Author Year</th>
<th>Total Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
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<tr>
<td>Loubser et al. 1991 N=9 (SCI =9)</td>
<td><strong>Test dose:</strong> 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. <strong>Long-term:</strong> Intrathecal Baclofen pump implantation.</td>
<td>At optimum intrathecal Baclofen dosage, 8/9 patients benefited in functional evaluations.</td>
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**Note:** ADL=Activities of Daily Living; AI=Amulatory 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 21.12 Summary Intrathecal Baclofen for Reducing Spasticity – Cost Analysis**

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<th>Author Year</th>
<th>Total Sample Size</th>
<th>Methods</th>
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<tr>
<td>Nance et al. 1995 Initial N=7; Final N=6 (SCI =5)</td>
<td><strong>Long-term:</strong> Intrathecal Baclofen pump implantation.</td>
<td>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.</td>
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<tr>
<td>Ordia et al. 1996 Initial N=66; Final N=57 (SCI =27)</td>
<td><strong>Long-term:</strong> Intrathecal Baclofen pump implantation. N=10 patients were studied for costs study comparing 1 year pre and post pump implantation.</td>
<td>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 &lt;2.5 years.</td>
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**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, rhabdomyolysis, 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**

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<th>Author Year Country</th>
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<tr>
<td>Meythaler et al. 2003 USA</td>
<td>Meythaler et al. 2003 USA</td>
<td>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</td>
<td>1. Addition of 4mg of cyproheptadine treatment resulted in a relief of itching and signs of baclofen withdrawal.</td>
</tr>
<tr>
<td>Downs &amp; Black score=11 Case series N=4</td>
<td>Crawley et al. 2004 UK Downs &amp; Black score =8 Pre-Post N=11</td>
<td>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</td>
<td>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.</td>
</tr>
</tbody>
</table>
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 1 evidence from five small-sample RCTs that bolus or test dose intrathecal Baclofen decreases spasticity.

There is level 4 evidence from thirteen 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 eleven 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 cyproheptadine 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 imidazoline-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 α2-adrenergic agonist it acts at both a spinal and supraspinal level.

**Table 13 Summary of Tizanidine Studies for Reducing Spasticity**

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Country</th>
<th>Score</th>
<th>Research Design</th>
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<th>Methods</th>
<th>Outcome</th>
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<tr>
<td>Nance et al. 1994</td>
<td>USA/Canada PEDro=10 RCT (DB) N=118</td>
<td>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.</td>
<td>1. Ashworth: Tizanidine produced significantly (p&lt;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&lt;0.0135), P2 (p&lt;0.0401) and EP (p&lt;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).</td>
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<tr>
<td>Mathias et al. 1989</td>
<td>UK Downs &amp; Black score=14 Pre-post N=10</td>
<td>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.</td>
<td>1. Ashworth: peak reduction between 1-1.5 hrs (p&lt;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&lt;0.05 after 1.5hrs) 4. Sedation: Sedation in tetras&gt;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 0.5hrs and peaked by 1 hour. At 6 hrs, level was at 85% peak and still detectable but low levels at 12 and 24 hrs. Plasma half-life was 2.7±0.06hrs. 6. Adverse Events: Sedation and dry mouth.</td>
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*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 1 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.

Conclusions

There is level 1 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 $\alpha_2$-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 14 Summary of Clonidine Studies for Reducing Spasticity

<table>
<thead>
<tr>
<th>Author Year Country Score Research Design</th>
<th>Methods</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Stewart et al. 1991 Canada PEDro=8 RCT-DBPC N=12</td>
<td><strong>Population:</strong> SCI: Cause of injury: trauma, non trauma; Chronicity = chronic. <strong>Treatment:</strong> 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). <strong>Outcome Measures:</strong> 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 (Aes).</td>
<td>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 -/+/-: 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.</td>
</tr>
<tr>
<td>Author Year Country</td>
<td>Score</td>
<td>Research Design</td>
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<td>Malinovský et al. 2003 France Downs &amp; Black score=18 Prospective controlled trial N=36</td>
<td><strong>Population:</strong> Age=21-73yrs <strong>Treatment:</strong> Patients with urinary tract surgery under spinal anaesthesia 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. <strong>Outcome Measures:</strong> Sedation, BIS</td>
<td>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 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. 4. Normal patients showed a decrease in BIS earlier than the control patients (p&lt;0.001).</td>
</tr>
<tr>
<td>Nance et al. 1989 Canada Downs &amp; Black=16 Prospective Controlled Trial (Single Blind) N=6</td>
<td><strong>Population:</strong> SCI. <strong>Treatment:</strong> Clonidine, clonidine and desipramine, diazepam, placebo. <strong>Outcome Measures:</strong> Vibratory inhibition index (VII) of the H-reflex; Achilles reflex; duration of clonus.</td>
<td>1. VII significantly reduced by clonidine (p&lt;0.001) but not the other interventions. 2. Achilles reflex not affected by any intervention. 3. Duration of clonus not affected by any intervention.</td>
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<tr>
<td>Nance 1994 Canada Downs &amp; Black score=15 Pre-post N =25</td>
<td><strong>Population:</strong> SCI with at least moderate spasticity: Severity of injury: complete, incomplete; Chronicity = chronic. <strong>Treatment:</strong> 1 wk up-titration, 1 wk target dose (0.05mg bid clonidine; 4mg qid cyproheptadine; 20 mg qid Baclofen) , 1 wk down-titration. <strong>Outcome Measures:</strong> Ashworth, Pendulum, Vibratory Inhibition Index (VII).</td>
<td>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&lt;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&lt;0.01.</td>
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<tr>
<td>Weingarden &amp; Belen 1992 USA Downs &amp; Black score=13 Case Series N=17</td>
<td><strong>Population:</strong> SCI: Cause of injury: trauma. <strong>Treatment:</strong> Transdermal clonidine. <strong>Outcome Measures:</strong> Clinically significant relief of spasticity; continuation of study drug after trial; discontinuation of other anti-spasticity medications.</td>
<td>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.</td>
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<tr>
<td>Donovan et al. 1988 USA Downs &amp; Black score=13 Case Series</td>
<td><strong>Population:</strong> SCI: Level of injury: paraplegia, tetraplegia; Severity of injury: complete, incomplete. <strong>Treatment:</strong> Oral clonidine – 0.05mg</td>
<td>1. Results indicate that quadriplegics responded to the medication better than the paraplegics. (p&lt;0.033).</td>
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<tr>
<td>Author Year Country Score Research Design Total Sample Size</td>
<td>Methods</td>
<td>Outcome</td>
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<td><strong>Remy-Neris et al. 1999</strong>&lt;br&gt; France Downs &amp; Black score=11&lt;br&gt; Non-randomized, placebo controlled trial N=11</td>
<td>bid and increased to 0.4mg bid if tolerated by the subject. <strong>Outcome Measures:</strong> Success of medication was defined as a decrease in hypertonicity.</td>
<td>2. No significant difference based on complete vs. incomplete lesions.&lt;br&gt;3. 31/55 subjects responded to clonidine.&lt;br&gt;4. Many non-responders withdrew due to AEs.</td>
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<td><strong>Yablon &amp; Sipski 1993</strong>&lt;br&gt; USA Downs &amp; Black score=10&lt;br&gt; Case Series Initial N=3; Final N=3</td>
<td>Population: SCI: Level of injury: paraplegia; Severity of injury: incomplete.&lt;br&gt;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. <strong>Outcome Measures:</strong> 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.</td>
<td>1. Significant decrease in Ashworth spasticity score (p&lt;0.0001) at all doses levels (30, 60, 90) with no consistent significant differences detected in reflexes.&lt;br&gt;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).&lt;br&gt;3. 90 and 120 μg doses did not produce significant improvement in 3 subjects able to walk after 60ug.</td>
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<tr>
<td><strong>Remy-Neris et al. 2001</strong>&lt;br&gt; France Downs &amp; Black score=6&lt;br&gt; Prospective Controlled Trial N=15</td>
<td>Population: SCI: Severity of injury: incomplete.&lt;br&gt;Treatment: Intrathecal clonidine injection (30/60/90 μg). <strong>Outcome Measures:</strong> 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.</td>
<td>1. FRR amplitude change significant (P&lt;0.02) between 30 and 90 μg IT Clonidine but not significant between 30 and 50 μg between 30 and 90, NS for 30/60).&lt;br&gt;2. FRR stimulation threshold significantly increased for each Clonidine dose compared to pre-injection. (P&lt;0.05 for dose-dependent effect; no change in placebo effects showing no effect of lumbar puncture).&lt;br&gt;3. Decrease in Ashworth score appeared a few minutes after injection, which lasted 4-6 hrs after a single 60μg dose.&lt;br&gt;4. Latencies of the quadriceps stretch showed a significant increase in the latency after clonidine in all but 1 subject.&lt;br&gt;5. Amplitudes of the quadriceps</td>
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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 lacked somewhat in scientific rigor. 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 1 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 15 Summary of 4-Aminopyridine Studies for Reducing Spasticity

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Country</th>
<th>Score</th>
<th>Research Design</th>
<th>Total Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Potter et al. 1998</td>
<td>Canada &amp; USA</td>
<td>PEDro=10</td>
<td>RCT</td>
<td>N=29</td>
<td>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</td>
<td>Significant benefit of Fampridine-SR over placebo: 1. Motor scores (adjusted to only paretic segments; p1 &lt; 0.01). 2. Sensory scores (p1 &lt; 0.01), including both pinprick and light touch (p1 = 0.059 and 0.058). 3. Ashworth (p2 &lt; 0.05). 4. Patient satisfaction and quality of life scores (McNemar’s test, p2 &lt; 0.01 and &lt;0.05). 5. No statistical significance on measures of pain, bowel/ bladder/sexual function or FIM. 6. Side effects: lightheadedness</td>
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<td>Author Year</td>
<td>Country</td>
<td>Score</td>
<td>Research Design</td>
<td>Total Sample Size</td>
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<td>Outcome</td>
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<tr>
<td>Donovan et al. 2000</td>
<td>USA</td>
<td>PEDro=9</td>
<td>RCT</td>
<td>N=12</td>
<td>Patient satisfaction questionnaire, seven point terrible delighted scale and FIM.</td>
<td>and nausea – transient/trivial relative to efficacy. 7. ~30% of patients reported a wish to continue to use.</td>
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<td>Cardenas et al. 2007</td>
<td>USA</td>
<td>PEDro = 7</td>
<td>RCT</td>
<td>Initial N= 91 ; Final N=71</td>
<td><strong>Population:</strong> SCI: Severity of injury: complete, incomplete.  <strong>Treatment:</strong> 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)  <strong>Outcome Measures:</strong> Patients were serially examined during and after infusion clinically for – Pain (McGill questionnaire); Sensorimotor function (ASIA): Hypertonicity (Ashworth scale, Reflex scale); Electrophysiologic measurements (Brain motor control assessment); Blood and CSF sampling.</td>
<td>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.</td>
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<tr>
<td>Hayes et al. 1994</td>
<td>Canada &amp; USA</td>
<td>Downs &amp; Black score=15</td>
<td>Pre-post</td>
<td>N=6</td>
<td><strong>Population:</strong> SCI: Cause of injury = trauma; Chronicity = chronic.  <strong>Treatment:</strong> 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  <strong>Outcome Measures:</strong> Neurophysiological and standard neurological examination. Adverse Event monitoring.</td>
<td>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.</td>
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<td>Author Year</td>
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<td>Potter et al. 1998</td>
<td>Canada &amp; USA</td>
<td>Downs &amp; Black score=10 Pre-post N=3</td>
<td>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.</td>
<td>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).</td>
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<td>A. Physical Exam:</td>
<td>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 &quot;renewed vigour&quot; (N=2).</td>
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<td>B. Neurophysiological Results:</td>
<td>9. MEPs increased in amplitude (N=1), 10. Ankle hypertonicity reduced (N=1).</td>
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<td>C. Pharmacokinetics and Adverse Events:</td>
<td>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.</td>
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**Note:** AIS=ASIA Impairement Scale; BP=blood pressure; CSF=cerebrospinal fluid; FIM=Functional Independence Scale; IV=intravenous; 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 b.i.d. treatment vs. placebo. A post hoc subgroup analysis of subjects with more marked spasticity at baseline resulted in a significant treatment (25 mg b.i.d.) related improvement in spasticity (p<0.25) compared to placebo.
treatment. The 3 group comparison (40 vs. mg b.i.d. 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 1 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.

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

Cyproheptadine

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

Table 16 Summary of Cyproheptadine Studies for Reducing Spasticity

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Country</th>
<th>Score</th>
<th>Research Design</th>
<th>Total Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
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<tr>
<td>Wainberg et al. 1990</td>
<td>Canada</td>
<td>PEDro=7</td>
<td>RCT</td>
<td>N=8</td>
<td>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</td>
<td>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</td>
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<tr>
<th>Author Year Country</th>
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<th>Score</th>
<th>Research Design</th>
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<th>Outcome</th>
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<tr>
<td>Barbeau et al. 1982 Canada</td>
<td>Downs &amp; Black score=12</td>
<td>Case series – Pre-post N=6</td>
<td>walking without overhead harness BWS when possible or 40% BWS - Temporal distance, surface EMG, Joint angular displacement, spasm severity in 2 positions, spasticity diary.</td>
<td>associated decrease in the % double support duration.</td>
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<tr>
<td>Meythaler et al. 2003 USA</td>
<td>D&amp;B=11</td>
<td>Case series N=4</td>
<td>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</td>
<td>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.</td>
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Note: BWS=body weight supported; EMG=electromyography; ITB=Intrathecal Baclofen; 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 and 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 1 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 cyproheptadine (along with baclofen and diazepam) as an adjunct treatment of acute intrathecal baclofen withdrawal syndrome.

<table>
<thead>
<tr>
<th>Author Year Country Score Research Design Total Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gruenthal et al. 1997 USA PEDro=7 RCT N=28</td>
<td>Population: SCI: Chronicity = subacute 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</td>
<td>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.</td>
</tr>
</tbody>
</table>

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).
Discusssion

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 1 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.

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 18 Summary of Orphenadrine Citrate Studies for Reducing Spasticity

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<thead>
<tr>
<th>Author Year</th>
<th>Country</th>
<th>Score</th>
<th>Research Design</th>
<th>Total Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casale et al. 1995</td>
<td>England</td>
<td>Downs &amp; Black score= 14</td>
<td>Prospective Controlled Study</td>
<td>N=11</td>
<td>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; @ baseline, initial injection, 10, 20, 30 &amp; 60 minutes post injection.</td>
<td>1. A significant difference was observed when comparing the use of orphenadrine and placebo (p&lt;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&lt;0.0001), as compared to no effect for the placebo.</td>
</tr>
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</table>

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 1 evidence from a single RCT supporting the anti-spastic action of intravenous orphenadrine citrate. Further 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).

Table 19 Effect of Other Potential Anti-Spasmodics for Reducing Spasticity

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Country</th>
<th>Score</th>
<th>Research Design</th>
<th>Total Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>L-Threonine</td>
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</table>
| 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/day or 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 | 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 glycerine. 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
**Author Year Country Score Research Design Total Sample Size**

<table>
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<tr>
<th>Methods</th>
<th>Outcome</th>
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<tr>
<td>concentrations. Measurements pre and post treatment. All measures conducted by a single investigator.</td>
<td>and 2 for non-medical reasons.</td>
</tr>
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</table>

**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>
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<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Score</th>
<th>Research Design</th>
<th>Total Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Hagenbach et al 2007</td>
<td>Switzerland</td>
<td>PEDro score= 6</td>
<td>RCT with preliminary Pre-post</td>
<td>N= 22 (RCT Phase 3 N=15)</td>
<td>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 dronabinol 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; @ baseline, day 1, 8 &amp; 43 for each phase of study.</td>
<td>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&gt;0.05). 5. There were no significant differences on mood or psychological testing in</td>
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<tr>
<td>Author Year</td>
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<td>Research Design</td>
<td>Total Sample Size</td>
<td>Methods</td>
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<tr>
<td>Maurer et al 1990</td>
<td>Switzerland</td>
<td>PEDro = 3</td>
<td>Single Subject RCT</td>
<td>N=1</td>
<td>Treatment vs. placebo groups.</td>
<td>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.</td>
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<tr>
<td>Malec et al. 1982</td>
<td>USA</td>
<td>Downs &amp; Black score=12</td>
<td>Observational</td>
<td>N=43</td>
<td>Population: SCI from patient database: Age &lt;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.</td>
<td>SCI persons reported decreased spasticity with marijuana use; Present use of marijuana correlated positively with past use; and 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&lt;0.001; n=43; agrees with other studies). Also correlated with degree of use in present social reference group (r=0.32, p&lt;0.05, n=38) and prior social reference group (r=0.30, p&lt;0.05, n=37). Age was negatively correlated with current use (r=0.56, p&lt;0.001, n=43). Reduction in spasticity via use was reported in 88% (21/24) while 12% reported no change. No correlation between Spasticity Change Index and any variable (if significant correlation, then perhaps placebo effect). Education moderately</td>
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</table>
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. 
Treatmen: Open label design: Oral dronabinol (initial dosage = 5mg BID, increased to 20mg TID) + current spasticity regimen. 
Outcome Measures: Pendulum Drop Test; Weschler Memory Scale (WMS); Profile of Moods Scales (POMS). 

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. 
3. There was no worsening in psychological parameters and two subjects had improvements in memory testing. 

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 has been only one placebo controlled trial (Hagenbach et al. 2007) 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 (N= 13) in persons with SCI related spasticity in order to evaluate the efficacy and side effects of orally and rectally delivered delta 9 THC (dronabinol) for the treatment of spasticity. The main outcomes were the spasticity sum score (SSS) using the modified Ashworth score (MAS) as well as self rating of spasticity. A flexible dosing titration was used. The average oral dose of THC was 31mg (range 20mg to 60mg/day). 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 on mood or psychological testing in treatment vs. placebo groups. 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. 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.

Maurer et al (1990) studied one patient with pain and spasticity due to spinal cord injury. Although this single subject study did not meet the inclusion criteria for inclusion in SCIRE, 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. 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 Wesler 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.

Although these various trials provided modest support for the use of dronabinol in the treatment of spasticity in SCI and confirmed the safety of its use, a well-designed and well-implemented RCT is needed to provide a less equivocal picture of the effectiveness of cannabinoids for the management of spasticity.

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.*

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

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 (Francisco 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 to relieve 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 no studies have 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). Therefore, we present the results of three studies which examined the effect of BTX-A on spasticity secondary to SCI but had either insufficient n (i.e., individual case studies) (Richardson et al. 1997; Al-Khodairy et al. 1998) or a subject pool comprised of only a small subset of subjects with spasticity secondary to SCI (Richardson et al. 2000). 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 21 Botulinum Neurotoxin for Reducing Spasticity

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<thead>
<tr>
<th>Author Year</th>
<th>Country</th>
<th>Score</th>
<th>Research Design</th>
<th>Total Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Richardson et al. 2000</td>
<td>England</td>
<td>PEDro=9 RCT N=52 (6 with SCI)</td>
<td>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 @ 3, 6, 9 &amp; 12 weeks.</td>
<td>1. Spasticity was significantly reduced for active Tx vs. placebo (as shown by modified Ashworth aggregate scores) (p&lt;.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&lt;.03). As with modified Ashworth most marked changes were between baselines - 3 weeks. 3. In general, the various functional measures showed no systematic improvement.</td>
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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).
<table>
<thead>
<tr>
<th>Author Year</th>
<th>Country</th>
<th>Score</th>
<th>Research Design</th>
<th>Total Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Richardson et al. 1997</td>
<td>England</td>
<td>Downs &amp; Black score=10</td>
<td>Case Study</td>
<td>N=1</td>
<td>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. Outcome Measures: Ashworth Scale, grip strength (Jamar dynamometer), passive ROM, Jebsen Hand Function Test, Rivermead Motor Assessment Scale @ 3, 6, 9 &amp; 12 weeks.</td>
<td>significant differences other than Subjective Rating of Problem Severity with aggregate outcome scores significantly better for active Tx vs. placebo (p&lt;.025).</td>
</tr>
<tr>
<td>Hecht et al. 2008; Germany</td>
<td>Downs &amp; Black score=10</td>
<td>Case Series</td>
<td>Initial N=19; Final N=11</td>
<td>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.</td>
<td>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) &amp; CK elevation (n=1).</td>
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<tr>
<td>Al-Khodairy et al. 1998</td>
<td>Switzerland</td>
<td>Downs &amp; Black score=7</td>
<td>Case StudyN=1</td>
<td>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.</td>
<td>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.</td>
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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 a case series of 19 chronic hereditary spastic paraplegics (Hecht et al 2007) reporting 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 1 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.*

<table>
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<tr>
<th>Author Year</th>
<th>Country Score</th>
<th>Methods</th>
<th>Outcome</th>
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**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 a result can cause sensory nerve damage and complications such as painful neuropathy as a complication of treatment (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 one study was identified that met our criteria for the treatment of spasticity in spinal cord injury.

**Table 22 Phenol Neuorlysis for Reducing Spasticity**
Research Design
Total Sample Size

| Population: | Spinal cord injury with C5 level tetraplegia with varying degrees of completeness; age mean 55.8 yrs; Gender: males = 7, females = 0; Time since injury >/= 5mo. |
| Treatment: | subscapular nerve block with phenol. |
| 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). |

Note: ROM=range of motion

Discussion:

Uchikawa et. 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).

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.

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.

5.0 Summary

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

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

There is level 1 evidence from a single RCT 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 1 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 short periods of massage (e.g., 3 minutes) of the triceps surae results in reduced H-reflexes with the effect lasting no longer than a few minutes.

There is level 4 evidence 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 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 1 evidence that oral baclofen improves muscle spasticity secondary to SCI. This conclusion is based on the results from three 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 1 evidence from five small-sample RCTs that bolus or test dose intrathecal baclofen decreases spasticity.

There is level 4 evidence from thirteen 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 eleven 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 benzodiazipenes may be useful for the treatment of intrathecal baclofen withdrawal.

There is level 1 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 1 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 and less than robust study designs.

Limited level 1 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 1 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 1 evidence from a single RCT (n=28) 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 1 evidence from a single RCT that evidence for 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.

Based on 2 case studies and 1 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 for the use of phenol neurolysis in the treatment of focal spasticity involving the shoulder in tetraplegia due to SCI.

There use of alcohol neurolysis in the treatment of spasticity in SCI has not been studied.
References


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


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.


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


