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REVIEW

Chemodenervation for treatment of limb spasticity following spinal cord injury: a systematic review

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Study design: Systematic review.
Objectives: To systematically review the literature on chemodenervation with botulinum toxin (BoNT) or phenol/alcohol for treatment of limb spasticity following spinal cord injury (SCI).
Setting: British Columbia, Canada.
Methods: EMBASE, MEDLINE, CINAHL, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials were searched for English language studies published up until March 2014. Studies were assessed for eligibility and quality by two independent reviewers.
Results: No controlled trials were identified. A total of 19 studies were included: 9 involving BoNT and 10 involving phenol/alcohol. Owing to the clinically diverse nature of the studies, meta-analysis was deemed inappropriate. The studies produced level 4 and level 5 evidence that chemodenervation with BoNT or alcohol/phenol can lead to improvement in outcome measurements classified in the body structure and function, as well as activity domains of the International Classification of Functioning, Disability and Health framework. The Modified Ashworth Scale (MAS) was the most commonly used outcome measure. All six studies on BoNT and three of the four studies on phenol/alcohol measuring MAS reported a decrease in at least one point. An improvement in MAS was not always associated with improvement in function. The effect of phenol/alcohol has the potential to last beyond 6 months; study follow-up did not occur beyond this time point.
Conclusion Chemodenervation with BoNT or phenol/alcohol may improve spasticity and function in individuals with SCI. However, there is a lack of high-quality evidence and further research is needed to confirm the efficacy of these interventions.
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INTRODUCTION

Although precise definitions vary, spasticity is commonly cited as 'a motor disorder characterized by a velocity dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflexes, as one component of the upper motor neuron syndrome'.[1] Spasticity frequently occurs following damage to the central nervous system, such as spinal cord injury (SCI). Literature has shown that 53–78% of individuals with chronic SCI experience symptoms of spasticity.[2,3] Importantly, 27–40% of affected individuals consider spasticity to be problematic and associated with significant functional impairments.[4,5] The negative impacts of limb spasticity include restricted ability to carry out activities of daily living, inhibition of functional ambulation, pain, fatigue, increased risk of developing contractures and pressure sores and difficulties with self-hygiene.[2] Spasticity can be a major barrier to participation and employment[6] and is negatively associated with quality of life[7] following SCI.

Generally, limb spasticity is managed through a multimodal approach, which may include physical interventions (for example, stretching, bracing and muscle strengthening), anti-spasticity medications (for example, delivered orally, via injection to the muscles/nerves, or intrathecally) and surgery. Oral antispasticity medications are often prescribed to SCI patients; however, the effectiveness of these medications varies and may be limited by systemic side effects including sedation, confusion, hallucinations, nausea, generalized muscle weakness, hypotension and potential liver toxicity.[8] It is estimated that up to 40% of patients with spasticity are unable to tolerate the side effects of oral antispasticity agents.[9] Chemodenervation is an attractive option for the management of limb spasticity, as it is a local injection technique that may be used to manage focal muscle overactivity while minimizing systemic side effects. Commonly used chemodenervation agents include botulinum toxin (BoNT), phenol and alcohol.[10] The utility of phenol has been reported in the literature for over 5 decades,[11] whereas the utility of alcohol and BoNT has been demonstrated more recently.

Various systematic reviews have examined the safety and efficacy of chemodenervation for managing spasticity in stroke[12,13] and cerebral palsy.[14,15] However, no such review exists for SCI. Although studies on stroke and cerebral palsy have consistently shown that BoNT can reduce muscle tone and spasticity, its effect on functional outcomes is

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less certain.[16] Furthermore, spasticity patterns may differ according to whether a lesion occurs in the brain or at the level of the spinal cord.[17] For example, muscle synergy and spasticity induce distinctive and complex movement patterns in individuals with stroke primarily characterized by spastic hemiplegic posturing'[18] whereas extensor spasms, flexor withdrawal spasms and clonus are frequently reported in SCI.[19] Different patterns can impact the functional sequelae of the spasticity,[19] and consideration of these patterns may improve the dosing, goal setting and outcome measures selected to examine the effects of spasticity treatment. Therefore, it is important to consider population-specific outcomes when examining the benefit of an intervention such as chemodenervation.

The objective of this systematic review is to provide clinicians with evidence regarding the efficacy of chemodenervation with either BoNT or phenol/alcohol for the management of limb spasticity in SCI. In addition, identifying gaps in the evidence will allow researchers to direct future efforts to areas of priority.

PATIENTS AND METHODS

Literature search

A systematic literature search was conducted in EMBASE, MEDLINE, CINAHL, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials electronic databases up to March 2014. Librarians at the Royal College of Physicians and Surgeons of British Columbia developed search strategies. The search strategy for MEDLINE is described in the Appendix. Reference lists of reviews and relevant studies were retrieved and scanned for citations to expand the data set.

Selection criteria

Inclusion criteria for studies were as follows: (1) study population of adults (⩾18 years) with SCI and limb spasticity; (2) if the study involved participants with spasticity from different etiologies, at least 50% must have SCI; (3) intervention of chemodenervation with either BoNT, phenol or alcohol injected into one or more limbs; and (4) English language and available as a full-text article. Studies were excluded if chemodenervation was used to treat conditions other than upper or lower limb spasticity.

Study selection

Two independent reviewers (JL and MS) screened study titles and abstracts for eligibility. If eligibility remained unclear, the full article was reviewed. Any disagreement was resolved by consulting a third reviewer (PM).

Risk of bias assessment

It was determined *a priori* that quality assessment would be performed using the Physiotherapy Evidence Database (PEDro)[20] scoring system for randomized controlled trials (RCTs) and the Downs and Black[21] tool for non-RCTs. All other study designs would be deemed low quality, with levels of evidence described by Sackett *et al.*[22] used to draw conclusions about the level of evidence for the identified studies. As previously described in the literature, Sackett's[22] levels of evidence were collapsed into five categories, whereby evidence was rated level 1 if derived from good to excellent RCTs with PEDro scores of ⩾6, level 2 if derived from RCTs with PEDro scores of ⩽5 or from nonrandomized prospective controlled and cohort studies, level 3 if derived from case–control studies, level 4 if derived from either pre-test/post studies or case series, and level 5 if obtained from an observational report or case report involving a single subject or from clinical consensus.[23]

Data extraction

A customized excel spreadsheet was developed with a template adapted from the Cochrane Collaboration.[24] Data were extracted by two reviewers (JL and MS) and reviewed in duplicate by another (PM). Data extracted included sample size, subject characteristics, injection details, outcome measures used and results, as well as adverse events. If study data were missing, or if subject level data were desired, two attempts separated by two weeks were made to contact the corresponding authors.

The International Classification of Functioning, Disability and Health[25] (ICF) was published by the World Health Organization in May 2001 to provide a common international language for describing health and disability in clinical and research settings. The ICF framework classifies function in four domains: body structure and function, activity, participation and environmental/personal factors domains. Outcome measures from the studies included in this review were listed and classified according to ICF domains. Outcome measures that did not fit within a domain were classified as 'other'.

Statistical analyses

Because of a large variation in participant characteristics (for example, site of spasticity and degree of spasticity) and study methods (for example, dosing, injection techniques, follow-up periods and outcome measurements) among the included studies, a formal meta-analysis was not feasible. Therefore, the results of this review are presented in a narrative form. Description of outcome measures is presented in Table 1. The effectiveness of each intervention is outlined in Tables 2 and 3.

RESULTS

Search strategy

The electronic database search yielded 415 articles, 58 of which were duplicates (Figure 1). An additional 13 articles were added with scanning of reference lists. Upon review of titles and abstracts, 58 articles remained for detailed examination. A total of 19 articles were included in this review after inclusion criteria were applied.

Studies

Nine studies investigated the use of BoNT,[26–34] and 10 studies investigated phenol/alcohol[35–44] for management of spasticity in SCI with chemodenervation. The literature search did not identify any randomized or non-RCTs looking at management of spasticity in a sample population with ⩾50% SCI participants, precluding the use of PEDro and Downs and Black Scale for quality assessment. One RCT by Richardson *et al.*[45] had 6 out of 52 participants with SCI; however, we were unable to obtain participant level data; therefore, this study was excluded. All included studies were non-blinded; risk of bias was therefore high for all included studies. None of the studies were adequately powered.

Description of outcome measures

A total of 43 distinctive outcome measures were used within the studies (Table 1). In all, 25 measurements were classified in the ICF body structure and function domain, 15 in the activity domain, none in the participation and environmental/personal factors domain and three did not fit within one of the four domains. No studies used an outcome measurement that measured quality of life. The most commonly used outcome measure was the MAS ($n=10$).

Chemodenervation with BoNT

BoNT is injected into spastic muscles to cause weakness via blockade of the neuromuscular junction. The toxin is internalized by the presynaptic motor neuron, where it inhibits the release of acetylcholine by disrupting the function of the SNARE complex, which is required for the exocytosis of presynaptic vesicles.[2] Two serotypes of BoNT exist for use in spasticity management: Type A (for example, Botox, Dysport, Xeomin) and Type B (Myobloc). Mechanistically, these differ in terms of where they bind on the SNARE complex.[46] However, the end result is the same—acetylcholine is not released, neuromuscular transmission is inhibited and muscle paresis occurs. Clinically, the effect of BoNT can last 2–6 months. With time,

Table 1 Description of outcome measures

Outcome measure	*BoNT studies*	*Phenol/alcohol studies*
Structure/function		
MAS	6	4
Pain VAS	3	3
Spasm frequency score	3	1
MRC for strength	1	1
AS	1	1
Quadriceps peak voluntary isokinetic torque	1	—
Stretch-reflex angle at peak torque	1	—
MTS grade+angle	1	—
Peak knee flexion	1	—
Muscle balance score	1	—
Toe clawing VAS	1	—
EPUAP	1	—
ROM scale of passive abduction of hip joint	—	1
Passive ROM of shoulder joint	—	1
Active ROM of shoulder joint	—	1
Muscle spasm score: degree of adductor tone	—	1
Buttock seat interface pressure	—	1
ROM of hip joint	—	1
Hip extension angle-prone	—	1
Hip extension angle with mundale technique	—	1
Activity		
Gait analysis (velocity; stride length; cadence; swing phase%)	6	—
% functional improvement (participant report)	2	—
Hygiene score	—	2
Timed stair climbing test	1	—
6-min walk test	1	—
VRS-Gait Function discomfort with walking	1	—
Modified rivermead mobility index	1	—
Repty functional index	1	—
Functional ambulatory category	1	—
Hospital de Sagunto Gait Scale	1	—
Timed walking over 20 m	1	—
Gait scale	—	1
Eating item of functional independence measure	—	1
Hygiene score	—	1
ADL (self reported improvement)	—	1
Other		
Modified FACES scale for satisfaction	1	—
Antispasticity medication dose	1	—
Subjective spasticity evaluation	1	—

Abbreviations: ADL, activities of daily living; EPUAP, European Pressure Ulcer Advisory Panel Classification system; MRC, Medical Research Council Scale; MTS, Modified Tardieu Scale; ROM, range of motion; VRS, Verbal Rating Scale.

collateral sprouting and regrowth of nerve endings will reverse the effects of BoNT.[9]

The effects of BoNT on individuals with SCI were reported in three level 4 pre–post studies[26–28] and six level 5 studies (one retrospective chart review,[29] five case series/studies[30–34]). Results from the included studies are summarized in Table 2. All studies examined BoNT serotype A. Total doses were variable, ranging from 50 to 400 U (Botox) or 400 to 2360 U (Dysport). Follow-up post injection varied from 14 days to 6 months between studies. Two of the pre–post studies had only a portion of participants with SCI: Opara *et al.*[27] also included multiple sclerosis participants, and Beseler *et al.*[28] included stroke and brain injury participants. One case series[31] also included stroke patients. Only results that pertained to the participants with SCI are described in this review.

All studies[27,28,30–33] measuring MAS reported a decrease in at least one point in response to BoNT. Most studies[26–29,31,33] also reported an improvement in functional outcome measures in the ICF activity domain. However, an improvement in MAS was not always associated with improvement in function; 8 of the 19 participants in the case series by Hecht *et al.*[30] discontinued BoNT injections for this reason. A majority of the participants perceived noticeable reduction in spasticity. However, only participants with a relevant global subjective improvement decided to continue the injections.

The small ($n=28$) retrospective chart review by Marciniak *et al.*[29] reported no differences in improvement between the AISA Impairment Scale (AIS) A versus B,C or D (40% versus 70%, $P=0.315$), injection within $\leqslant 1$ year of SCI versus >1 year (60% versus 65%, $P=1.000$) or injection to upper versus lower limb (65% versus 64%, $P=1.000$).

Adverse events with BoNT injections

Four[28,29,33,34] of the nine studies did not report on adverse events. Bernuz *et al.*[26] reported that 3/15 participants had subsequent hip flexion weakness after injection of rectus femoris, despite no weakness in the knee extensors. Whether the weakness affected walking ability was not reported, and there was no subanalysis for whether outcomes were worse for these affected individuals. Duration of weakness was not reported. Hecht *et al.*[30] reported 3/19 cases of transient lower extremity muscle weakness but also did not report duration of weakness or impact on functional abilities. Hecht *et al.*[30] also reported 1/19 cases of localized muscle pain post injection with elevated CK, with subsequent investigations demonstrating peripheral neuropathy and myopathy. The authors felt these findings were independent of the injection.

Levels of evidence, BoNT

There is level 4 and level 5 evidence, based on three pre–post studies,[26–28] one retrospective chart review[29] and five case series/studies,[30–34] that BoNT has variable effects on lower limb spasticity in SCI. Generally, there were improvements in outcomes measures that looked at body structure and function (for example, MAS), as well as activities (for example, gait). However, an improvement in MAS of at least one point did not necessarily translate to an improvement in activities or subjective global improvement. There is level 5 evidence that BoNT may improve upper limb function in individuals with spasticity from SCI[29] and that there is no difference in outcomes between individuals with AIS A versus AIS B-D, whether injections are performed $\leqslant 1$ year versus $\geqslant 1$ year post injury, or to the upper versus lower limbs.[29] However, small sample sizes and high risk of bias limit firm conclusions, and it is clear that further research is required to confirm the benefits of BoNT as a treatment for spasticity in individuals with SCI.

Chemodenervation with phenol/alcohol

Phenol and ethanol mediate their effect through direct neurolysis of the nerves that supply spastic muscles. Injection of these agents into the area of a nerve causes denaturation and fibrosis, which disrupts neural transmission and therefore may diminish reflex arcs that are responsible for muscle hypereflexivity.[2] The duration of effect is highly variable, but it is thought that a degree of permanent denervation occurs with every injection. The effects of phenol/alcohol on

Table 2 Characteristics and results of the studies on BoNT injections to the spastic limb

Author[ref.] *country; research design; sample size;*	*Population*	*Intervention*	*Results*
Bernuz *et al.*[26]; France; NB pre–post; $N=15$	Age: 43 ± 15 years; 14M:1F; cervical ($n=7$), thoracic ($n=7$), lumbar ($n=1$); AIS D; DOI: 10 years ± 10 months; no previous BoNT; rectus femoris spasticity during gait (confirmed using the Duncan Ely test, MTS and 3D motion analysis of peak knee flexion during the swing phase of gait)	1 BoNT-A (Botox) treatment Dosing: 200 U (total) Dilution: NA Localization: EMG+electrostimulation Muscles injected and dose: Rectus femoris (200 U per 2sites)	4–6 weeks post injection: ↓Quadriceps peak voluntary isokinetic torque (–16%; $P<0.001$) ↑Stretch-reflex angle at peak torque (+5°, $P<0.05$) ↓MTS grade (2.7 ± 0.7–1.9 ± 1, $P<0.05$) ↑MTS angle (50 ± 30°–93 ± 44°, $P<0.01$) ↑Peak knee flexion (34.7 ± 10°–38.7 ± 10°; $P<0.05$) ↑Timed stair climbing test (39.6 ± 38–30.1 ± 14s, $P<0.05$) Unchanged 6-min walk test (331 ± 146–332 ± 143 m, $P>0.05$) ↑Gait velocity (56.8 ± 31.2–67.5 ± 34.3 m s^{-1}, $P<0.01$) ↑Stride length (88.9 ± 25.6–97.72 ± 26.4 m, $P<0.01$) ↑Swing phase (%) (31.1 ± 8.33–32.7 ± 8, $P<0.01$) ↓Walking discomfort VRS (6.3 ± 1.2–4.1 ± 1.7; $P=0.001$) Adverse events: three participants reported hip flexion weakness
Opara *et al.*[27] Poland NB pre-post $N=8$ SCI/20[a]	Age: 23–62 years (mean = 40.25 years); 8M:0F; cervical ($n=6$), dorsal ($n=2$); DOI: 0.25–32 years (mean = 5.3 years); no previous BoNT; lower extremity spasticity	1 BoNT-A (Botox) treatment Dosing: 100–400 U (range) Dilution: 100 U ml^{-1} 0.9% saline Localization: Surface anatomy+palpation Muscles injected: Hip adductors (4 sites) Knee flexors (4 sites) Foot flexors (4 sites)	3 weeks post injection: ↓MAS (3.1–1.9, $t=5.35$, $P<0.001$) ↓Pain VAS (64.4–14, $t=2.86$, $P<0.02$) ↑MRMI (23.7–24.5, $t=-4.0$, $P<0.003$) ↑RFI (59–63.9, $t=-4.16$, $P<0.003$) Adverse events: none
Beseler *et al.*[28] Spain NB pre-post $N=2$ SCI/10[a]	Participant 1: Age: 44 years; F; T6 AIS D; DOI: 4 months Participant 2: Age 30 years; M; T7 AIS D; DOI: 3 years; lower extremity spasticity	1 BoNT-A (Botox) treatment Dosing: 50–200 U (range) Dilution: 100 U per 2 ml 0.9% saline Localization: EMG Muscles injected and dose: Participant 1 Adductor magnus (200 U) Hamstring (100 U) Biceps femoris (50 U) Participant 2 Gastrocnemius-medial head (50 U) Gastrocnemius-lateral head (50 U) Bilateral adductor magnus (100 U each)	3 weeks post injection: Participant 1: ↓MAS (2–1) ↑Muscle balance score (6–8) ↓SFS (1–0) ↑HSGS (1–2) ↑FAC (2–3) FACES satisfaction: 6/10 Participant 2: ↓MAS (1–0) No change in muscle balance score: (15–15) No change in SFS (0–0) No change in HSGS (2–2) No change in FAC (3–3) FACES satisfaction: 10/10 Adverse events: not reported
Marciniak *et al.*[29] USA Retrospective	Age: 20–76 years (mean = 46 years); AIS A ($N=5$), AIS B,C,D ($N=23$); DOI: < 1 year ($n=5$), > 1 year ($n=23$); no previous BoNT; upper and lower extremity spasticity	1 BoNT-A (Botox) treatment Dosing: 50–400 U (range per person); 10–119 U (range per muscle) Dilution: NA Localization: EMG	After first injection, follow-up duration not specified: Ambulation ($n=9$): 56% reported improvement Upper-limb function ($n=7$): 78% reported improvement Hygiene: ($n=3$): 67% reported improvement

Table 2 (Continued)

Author[ref.] country; research design; sample size;	*Population*	*Intervention*	*Results*
chart review *N*=28		Muscles injected and dose (mean): gastrocnemius-medial head, 75–200 U (118 U), lateral head, 75–200 U (111 U); soleus, 40–100 U (68 U); adductor longus, 50–400 U (170 U); adductor magnus, 50–100 U (67 U); anterior tibialis, 100 U; extensor hallucis longus, 50 U; posterior tibialis, 50–60 U (55 U); adductor brevis, 50 U; vastus medialis, 30 U; vastus lateralis, 30 U; medial hamstring, 100 U; flexor hallucis longus, 80 U; flexor hallucis brevis, 10 U; flexor digitorum superficialis, 30–60 U (41 U); flexor carpi radialis, 20–60 U (43 U); flexor carpi ulnaris, 20–50 U (36 U); triceps (*n*=4), 60–100 U (83 U); pectoralis (*n*=4), 60–80 U (70 U); flexor digitorum profundus, 30–70 U (50 U); biceps, 30–90 U (70 U); brachioradialis, 20–40 U (30 U); pronator teres, 10–90 U (53U); flexor pollicis longus, 20–30 U (23 U); infraspinatus, 60 U; trapezius, 60 U; teres major, 40 U; brachialis, 60 U; lumbricals, 30 U; extensor carpi radialis, 50 U	Pain (*n*=6): 83% reported improvement Positioning (*n*=7): 71% reported improvement Adverse events: not reported
Hecht *et al*.[30] Germany NB case series *N*=19	Age: 41.6±18.6 years; 14M:5F; hereditary spastic paraplegia; DOI: 18.5±10.9 years (range 5–49 years); lower extremity spasticity	Multiple BoNT-A (Botox or Dysport) treatments Dosing: 120–400 U (range; Botox); 400–1500 U (range; Dysport) Dilution: NA Localization: NA Muscles injected: Hip adductors (*n*=12); Iliopsoas (*n*=2); Rectus femoris (*n*=2); Gastrocnemius (*n*=13); Tibialis posterior (*n*=6); Ischiocrural (*n*=1)	6 weeks post injection: ↓MAS by 1 point (*n*=17), by 3 points (*n*=1), not scored (*n*=1) Global subjective improvement: good or very good in 11/19 participants Only participants with good or very good subjective improvement chose to continue with BoNT treatment Adverse events: three participants had reversible increase in muscle weakness; one participant experienced calf pain during walking and elevated creatine kinase for several weeks. A muscle biopsy 9 months post injection revealed peripheral neuropathy thought to be unrelated to BoNT treatment.
Lim *et al*.[31] Singapore NB case series *N*=1 SCI/7[a]	Age: 38 years; M; C5–6 (traumatic); DOI: 9 years; toe-clawing and ankle inversion	1 BoNT-A (Botox) treatment Dosing: 70 U (total) Dilution: 100 U per 2 ml 0.9% saline Localization: EMG+electrostimulation Muscles injected and dose: Flexor digitorum longus (20 U) Flexor digitorum brevis (20 U) Tibialis posterior (30 U)	6 weeks post injection: ↓MAS (2–0) Unchanged pain VAS (0) ↓Timed walking over 20 m (21–20s) % functional improvement: 75% ↓VAS for toe clawing (2–0) Duration of benefit: 3 months Adverse events: none
Al-Khodairy *et al*.[32] Switzerland	Age: 50 years; M; T12 AIS C (traumatic); DOI:18 years; no previous BoNT; bilateral lower extremities spasticity	8 treatments of BoNT-A (Botox; q3-12 weeks, escalating dose) Dosing: 100–400 U (range) Dilution: NA Localization: EMG+electrostimulation	14 days post first injection: ↓MAS (2–3 to 1) ↓Pain VAS (8–1) ↓SFS (4–2)

Table 2 (Continued)

Author[ref.] *country; research design; sample size;*	*Population*	*Intervention*	*Results*
NB case study *N*=1		Muscles injected and dose: Gastrocnemius (50 U per 4 sites) Tibialis anterior (50 U per 2 sites) Peroneus tertius (50 U per 2 sites) Extensor digitorum longus (50 U) Extensor hallucis longus (50 U) Soleus (30 U per 2 sites) Peroneus longus (30 U per 2 sites)	↓Medication dose Subjective evaluation: good to moderate effect after first 7 injections, no effect after last (8th) injection Adverse events: none
Gross *et al.*[33] France NB case study *N*=1	Age: 53 years; M; C7 AIS D (traumatic); DOI: 18 months; no previous BoNT; lower extremity spasticity	1 BoNT-A (Botox) treatment Dosing: 100 U (total) Dilution: NA Localization: electrostimulation Muscles injected and dose: Rectus femoris (100 U)	6 weeks post injection: ↓MAS (3–2) MRC: no change ↑Max gait speed (0.51–0.71; +39%) ↑Step length (0.73–1.02; +40%) Unchanged cadence (42.1–41.9; 0%) Adverse events: not reported
Intiso *et al.*[34] Italy NB case study *N*=1	Age: 27 years; M; T-level SCI (traumatic); DOI: 5 years; left gluteal pressure ulcer secondary to severe lower limb spasticity	1 BoNT-A (Dysport) treatment Dosing: 2360 U (total) Dilution: NA Localization: EMG Muscles injected and dose: Bilateral hip adductors and hamstrings (1700 U total) Left gluteus maximus (660 U total)	6 months post injection: ↓AS (3–2) SFS: change not reported (preinjection=4) Ulcer healed in 6 months; change in EPUAP not reported Adverse events: not reported

Abbreviations: DOI, duration of injury; EPUAP, European Pressure Ulcer Advisory Panel Classification system; FAC, Functional Ambulatory Category; HSGS, Hospital de Sagunto Gait Scale; MRC, Medical Research Council scale; MRMI, Modified Rivermead Mobility Index; MTS, Modified Tardieu Scale; NA, not available; NB, non-blinded; RFI, Repty Functional Index; SFS, Spasm Frequency Score; VRS, Verbal Rating Scale.
[a]only SCI participant data reported

Table 3 Characteristics and results of the studies on phenol/alcohol injections to the spastic limb

Author[ref.] country research design sample size	*Population*	*Intervention*	*Results*
Ghai *et al.*[35] India NB pre–post *N*=18 SCI/20[a]	Age: 36.7±9.8 years; 17M:3F, DOI: 10.6±12.2 months; hip adductor spasticity	Dosing: 8–10 ml 6% phenol Localization: Electrostimulation+diagnostic block (0.5% bupivacaine) Nerve(s) injected: Obturator	1 h, 1 day, 1 week, 1 month, 2 month, 3 month post injection: ↓MAS at all time intervals, except ↑between 2nd and 3rd month: 3.0±0.4–2.7±0.5 (1 h), 2.1±0.4 (1 day), 1.9±0.4 (1 week), 1.8±0.7 (1 month), 2.0±0.7 (2 months), 2.1±0.7 (3 momths); $P<0.000$ ↓ROM scale scores at all time intervals: 2.8±0.37–2.7±0.5 (1 h), 2.1±0.7 (1 day), 1.8±0.5 (1 week), 1.7±0.9 (1 month), 1.8±0.8 (2 months), 2.2±0.9 (3 months), $P<0.000$ ↓Pain VAS at all time intervals: 7.0±2.6–3.3±2.1 (1 h), 3.4±1.5 (1 day), 2.1±1.4 (1 week), 2.8±2.4 (1 month), 3.3±2.6 (2 months), 4.1±2.5 (3 months), $P<0.000$ ↓SFS at all time intervals: 3.5±0.7–0.2±0.6 (1 h), 2.1±0.9 (1 day), 1.5±0.8 (1 week), 1.4±1.2 (1 month), 1.7±1.2 (2 months), 2.0±1.2 (3 months), $P<0.000$ ↓Difficulty of hygiene at all time intervals: 2.4±0.6–2.2±0.6 (1 h), 1.8±0.4 (1 day), 1.4±0.6 (1 week), 1.4±0.7 (1 month), 1.5±0.7 (2 months), 1.7±0.7 (3 months) ↓Gait Scale score after 1 day: 2.8 ±0.4–2.8±0.6 (1 day), 2.7±0.8 (1 week), 2.7±0.8 (1 month), 2.7±0.8 (2 months), 2.7±0.7 (3 months) Adverse events: 2 participants developed dysesthesia lasting for 7–10 days; 1 participant developed fibrosis at the injection 20 days post injection; no participants developed neuritis or secondary deafferentation pain
Gunduz *et al.*[36] Turkey NB pre–post *N*=36	Age: 29±8.2 years; 31M:5F; cervical (*n*=14), thoracic (*n*=18), lumbar (*n*=4), all traumatic; lower body spasticity	Dosing: 2–3 ml 5% phenol Localization: electrostimulation Nerve(s) injected: Obturator (*n*=34) Sciatic (*n*=11) Femoral (*n*=5)	1 week, 1 month, 2 months post injection: ↓AS: 4.72±0.095–2.72±0.137 (1 week), 3.06±0.155 (1 months), 3.54±0.154 (2 months); $P<0.01$ Adverse events: 1 participant developed cutaneous anesthesia lasting 19 days
Uchikawa *et al.*[37] Japan NB pre–post *N*=7	Age: 55.8±4 years; C5 (*n*=7), AIS: A (*n*=2), C (*n*=1), D (*n*=4); DOI: >5 months; marked limitation of shoulder ROM due to spasticity	Dosing: 0.2–0.3 ml 5% phenol Localization: electrostimulation Muscle injected: Subscapularis muscle motor points	24 h post injection: ↑Passive ROM of shoulder joint: flexion (23.7°), abduction (19.4°), external rotation (16.3°); $P<0.05$ No significant change in active ROM of shoulder joint No significant change in MAS ↓Pain VAS (6.0–3.4, $P<0.05$) No significant change in MRC for strength ↑ 'Eating item' score of Functional Independence Measure (2.3–5.4, $P<0.05$) Adverse events: None
Wassef *et al.*[38] USA	Group A (*n*=7 SCI/10): interadductor technique; Age: 53.1±2.9 years; 3M:7F; DOI: 16.1±1.7 years	Dosing: 5 ml 6% phenol Localization: electrostimulation, diagnostic block 1 (5 ml 2% lidocaine), diagnostic block 2, 3 (5 ml	Unknown time post injection: ↓Muscle spasm score: Group A (3.3±0.1–1.3±0.1), Group B (3.2±0.1–1.7±0.1); $P<0.01$

Table 3 (Continued)

Author[ref.] *country research design sample size*	*Population*	*Intervention*	*Results*
NB pre-post *N*= 14 SCI/20[a]	Group B (*n*=7 SCI/10): traditional technique; Age: 59.1±2.3 years; 3M:7F; DOI: 17.6±1.0 years	0.5% bupivacaine+1:200 000 epinephrine) Nerve(s) injected: obturator	↓Hygiene score: Group A (3.3±0.2–1.1±0.1), Group B (3.3±0.2–1.8±0.2); $P<0.01$ Adverse events: None
Yasar *et al.*[39] Turkey Retrospective chart review *N*=20	Age: 42.85±13.24 years; 19M:1 F; cervical (*n*=3), thoracic (*n*=17), AIS: A=13, B=7; DOI: 41.8±47.2 months; hip adductor spasticity	Dosing: 10 ml 5% phenol Localization: electrostimulation Nerve(s) injected: obturator	2 weeks post injection: ↓Buttock seat interface pressure: proportion of participants ⩽37 mm Hg (62.91–71.16%, $P<0.001$) proportion of participants >37 mm Hg (37.08–28.85%, $P<0.001$) ↓MAS (2.35±0.48–1.35±0.41, $P<0.001$) No significant differences between AIS A and AIS B participants Adverse events: None
Ghai *et al.*[40] India NB case series *N*=3	Case 1: Age: 18 years; M; T4-6 (nontraumatic), AIS D; bilateral spasticity of leg adductors (MAS=3/3) Case 2: Age: 16 years; M; T4 (traumatic); bilateral spasticity of leg adductors (MAS=3/2) Case 3: Age: 21 years; M; C4-5; bilateral spasticity of leg adductors (MAS=4/4)	Dosing: 8–10 ml 65% alcohol Localization: surface anatomy+diagnostic block (0.5% bupivacaine) Nerve(s) injected: obturator	1 week post injection: Case 1: 'Drastic' improvements in hip joint ROM, VAS, MAS, hygiene Duration of improvements: 3 months for ROM, MAS, hygiene; 4 months for VAS Case 2: 'There was significant improvement in pain, spasticity, range of motion of hip joint, hygiene scores and the number of muscle spasms. It has been 6 months now, and the effect of alcohol is still persisting' Case 3: 'Though the VAS score decreased significantly but spasticity and numbers of spasms were not much alleviated, and the participant was quite unsatisfied with the block' Adverse events: none in case 1; not reported in cases 2 and 3
Koyama *et al.*[41] Japan Case series *N*=3 SCI/12[b]	Case 1: Age: 17 years; M; hip flexor spasticity Case 2: Age: 58 years; M; hip flexor spasticity Case 3: Age: 67 years; F; hip flexor spasticity	Dosing: ⩽3.5 ml 5% phenol per muscle Localization: electrostimulation+ultrasound Nerve(s) injected: lumbar nerves at motor points of psoas major and minor muscles	Immediately post injection: Case 1: ↑Prone hip extension (right and left.: 155°–165°) ↑Hip extension with Mundale technique (right and left.: 155°–165°) ADL: improved sitting posture Case 2: ↑Prone hip extension (140°–155°) ↑Hip extension with Mundale technique (145°–155°) ADL: improved sitting posture,↓pain Case 3: ↑Prone hip extension (140°–155°) ↑Hip extension with Mundale technique (140°–155°) ADL: improved sitting posture,↓pain Adverse events: None

Table 3 (Continued)

Author[ref.] *country research design sample size*	*Population*	*Intervention*	*Results*
Singler[42] USA NB case study *N*=1	Age: 44 years; M; T10–T12 (traumatic); large pressure ulcer on right greater trochanter secondary to uncontrolled spastic flexion of knee and hip, recovery complicated by inability to lie prone	Dosing: 7.5 ml 100% alcohol+2.5 ml 0.75% bupivacaine Localization: electrostimulation+diagnostic block (10 ml 0.75% bupivacaine with 1:200 000 epinephrine) Nerve(s) injected: femoral and sciatic	24 h post injection: Spastic activity persisted to a minimal degree Less spasticity of the hip flexors elicited with noxious stimuli Participant able to achieve prone position to facilitate pressure ulcer healing ↓spastic activity lasted for 6 months post injection Adverse events: None
Takenaka *et al.*[43] Japan NB case study *N*=1	Age: 32 years; M; C6 complete (traumatic); DOI: 6 years; severe bilateral spasticity of hip flexors, adductors, knee extensors	First intervention: 3 injections over 3 days Dosing: 2 ml 7% phenol (second intervention: psoas compartment block—results not reported in this paper) Localization: electrostimulation, diagnostic block (2 ml 2% lidocaine) Nerve(s) injected: femoral, obturator, sciatic	3 weeks post injection: Spasticity completely ceased but returned 6 months later; could not achieve peripheral nerve block again due to the absence of evoked twitches from nerve degeneration Adverse events: none
Wilkes *et al.*[44] USA Case study *N*=1	Age: 41 years; M; T7 (traumatic); DOI: 10 years; chronic pressure sores and osteomyelitis secondary to bilateral lower limb spasticity	Dosing: 7.5 ml 98% ethanol+5 ml 0.5% bupivacaine Localization: electrostimulation+diagnostic block (2 ml 0.5% bupivacaine) Nerve(s) injected: sciatic, femoral	1 day post injection: Straightening participant's leg was possible Participant experienced prolonged pain relief Skin grafts were able to stay in place; facilitated ulcer healing Participant discharged and not readmitted for 16 months Adverse events: None

Abbreviations: ADL, activities of daily living; DOI, duration of injury; F, female; M, male; MRC, Medical Research Council scale; NA, not available; NB, non-blinded; SFS, Spasm Frequency Score.
[a]All data reported as SCI participants were ⩾50%.
[b]Only SCI participant data reported.

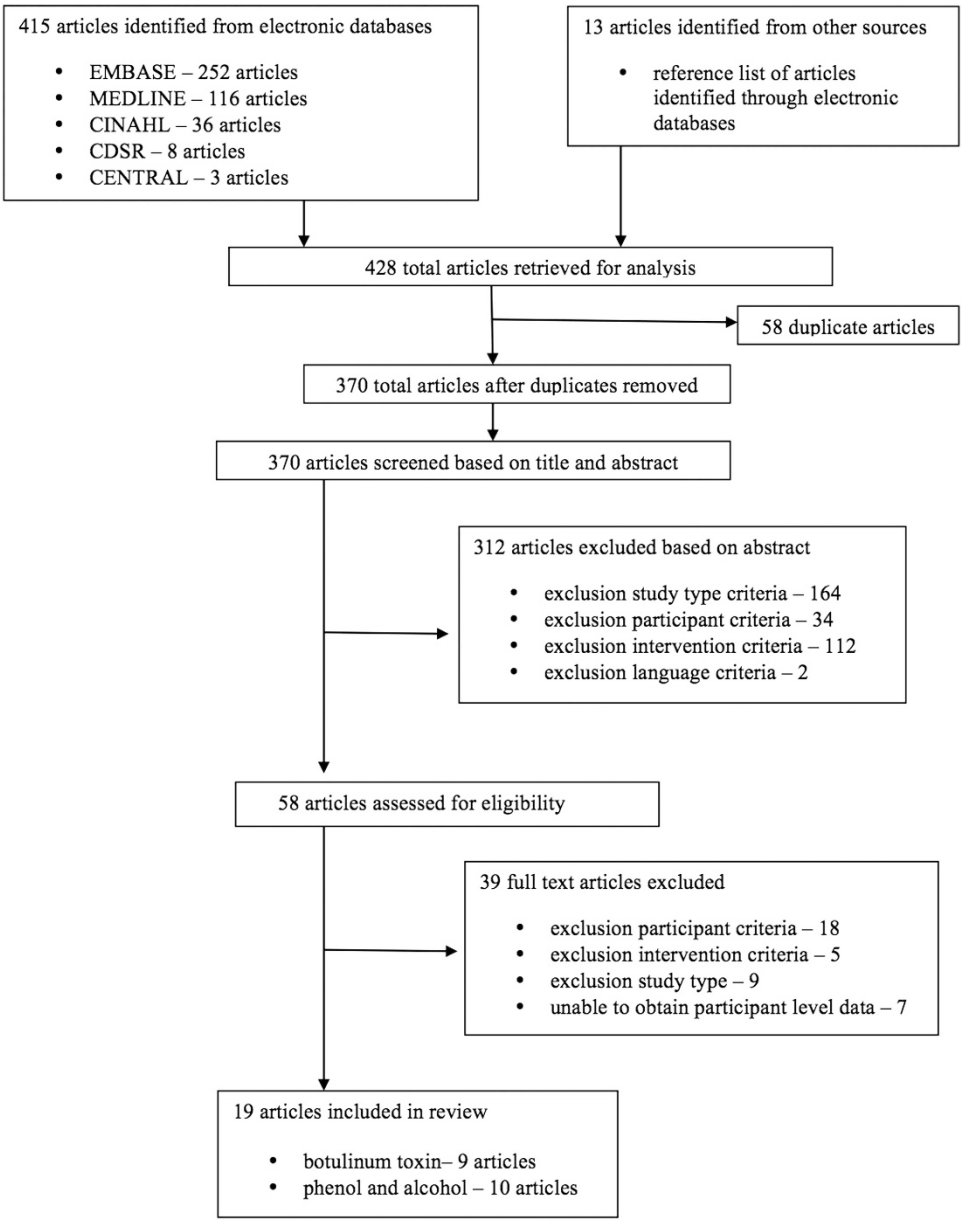

Figure 1 Studies selection flowchart. CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials.

individuals with SCI have been reported in four level 4 pre–post studies[35–38] and six level 5 studies (5 case series/studies,[40–44] one retrospective chart review[39]). Results from these studies are summarized in Table 3.

Seven[35–39,41,43] of the 10 studies involved phenol injections ranging from 0.3 to 10 ml and 5 to 6% concentration. Alcohol concentration used in three case series/studies[40,42,44] ranged from 68 to 100%, with volumes between 7.5 and 10 ml. Uchikawa *et al.*[37] injected subscapularis motor points and Koyama *et al.*[41] injected motor points of the psoas muscle. All other studies targeted peripheral nerves in the lower extremities for neurolysis.

Studies by Ghai *et al.*[35] and Wassef *et al.*[38] included participants with non-SCI spasticity. As SCI participants comprised $\geqslant 50\%$ of the samples, and we were unable to obtain patient level data, data pertaining to the entire subject group were included.

Ghai *et al.*,[35] Yasar *et al.*[39] and Uchikawa *et al.*[37] used MAS as a primary outcome measure, otherwise selection of outcome measures was variable between studies. The three case studies[42–44] did not report formal outcome measures and instead provided qualitative descriptions.

Timing of assessments post injection varied from 1 h to 3 months between studies. Duration of improvement lasted 6 months in the study by Takenaka *et al.*,[43] 3–4 months in Singler *et al.*,[42] and 6 months in Ghai *et al.*,[40] depending on the outcome measure. All other studies did not comment on the duration of improvement, although benefits were still present at 2 months in Gunduz *et al.*[36] and 3 months in Ghai *et al.*[35] Wassef *et al.*[38] used two different techniques to target the obturator nerve (interadductor versus traditional technique) and found no differences between the two approaches.

Overall there were improvements in outcome measurements of body structure and function such as MAS and pain visual analogue scale (VAS) in trials of injections to the lower extremities. The only study looking at spasticity of the upper extremity by Uchikawa *et al.* found improvements in passive range of motion and pain VAS without an improvement in MAS following phenol to subscapularis motor points. Studies looking at outcome measurements of activity consistently found improvements. Ghai *et al.*[35,40] and Wassef *et al.*[38] reported improved hygiene score, which measured the ability of nursing staff to access the perineal area. Ghai *et al.*[35] also reported an improved gait score after neurolysis as measured by the gait scale (0 = able to walk without difficulty, 3 = unable to walk) in three ambulatory participants, although whether these participants had SCI was not reported. Inspection of gait after the injection revealed decreased scissoring of hips, improved balance and gait speed. All of them, however, still needed assistive devices for ambulation. Uchikawa *et al.*[37] measured shoulder function with the 'eating item' of the Functional Independence Measure and reported a significant improvement following phenol injection.

Adverse events with phenol/alcohol injections

In Ghai *et al.*,[35] 2/20 participants developed cutaneous dysesthesia, which lasted seven to ten days after the injection. One participant also developed fibrosis at the site of the injection 20 days post injection. It was reported that no participants developed neuritis or secondary deafferentation pain. Gunduz *et al.*[36] reported that 1/36 participant developed cutaneous dysesthesia lasting 19 days. Ghai *et al.*[40] did not report adverse events for two of the three participants.

Levels of evidence, phenol/alcohol

There is level 4 and 5 evidence from four pre–post studies,[35–38] one retrospective chart review[39] and four case series/studies[40,41,43,44] that chemodenervation with phenol/alcohol improves limb spasticity as measured by outcomes of body structure and function (for example, MAS, AS, pain visual analogue scale and range of motion). There is level 5 evidence from a retrospective chart review[39] that phenol neurolysis of obturator nerves improves buttock seat interface pressures, which would presumably decrease the risk of pressure ulcers, in individuals with hip adductor spasticity from SCI. There is level 4 evidence (two pre–post studies[35,38]) and level 5 evidence (one case series[40]) of decreased difficulty with hygiene performed in the perineal area after phenol neurolysis of the obturator nerves in individuals with adductor spasticity from SCI. There is level 4 evidence from one pre–post study[35] of improved gait after phenol injection into the obturator nerves, although it is not known whether the three ambulatory participants had SCI versus multiple sclerosis or Koch's spine. There is level 4 evidence from one pre–post study[37] with $\geqslant 50\%$ participants with SCI that phenol into the subscapularis motor points improves the 'eating item' score as measured by the Functional Independence Measure. Given the limited number of studies, the small sample sizes and the fact that two out of the four pre–post studies included subjects with etiologies other than SCI, further research is required to determine whether chemodenervation with phenol/alcohol is a safe and effective intervention for the management of spasticity in SCI.

DISCUSSION

Our systematic review of the literature on chemodenervation for the management of spasticity in SCI found nine studies on BoNT and 10 studies on alcohol/phenol. These were of low quality, with small sample sizes. The existing literature on BoNT is also limited by incomplete descriptions of the intervention, such as dilution used and a lack of reporting of adverse of events. Currently, both BoNT and alcohol/phenol are used clinically in the SCI population to manage limb spasticity; however, these interventions have not been rigorously studied in individuals with SCI.

Chemodenervation has the potential to be a useful tool in treating focal limb spasticity after SCI, but there may also be significant side effects with both BoNT and phenol/alcohol, including the potential to worsen functional abilities. The pre–post studies by Ghai *et al.*[35] (phenol injection) and Bernuz *et al.*[26] (BoNT injection) examined chemodenervation of proximal muscles in the leg (hip adductors and knee extensors, respectively) in ambulatory participants. This represents a challenging clinical scenario, as it is difficult to compensate for excessive weakening of these more proximal muscles, unlike the use of an ankle–foot orthosis to compensate for weakness of the ankle dorsi/plantar flexors post injection. Therefore, there is a concern that chemodenervation of hip and knee stabilizers could lead to a worsening of gait, which can significantly impact the individual's functioning and quality of life for what could be a prolonged period of time. The study by Bernuz *et al.*[26] injected 200 U of BoNT into the rectus femoris, an important muscle for stabilizing the knee during stance phase. A mean improvement in gait parameters and stair climbing was reported, despite subsequent hip flexion but not knee extension weakness in three participants. However, there was no subanalysis on whether outcomes were worse in these affected participants. The authors' recommendation was to avoid injections into the rectus femoris in individuals with hip flexion strength $\leqslant 2$ on the Medical Research Council scale. Given that these results are based on a small number of participants, further research into this area is necessary to establish whether and in what scenarios the benefits of BoNT injection into the rectus femoris for stiff-knee gait outweigh the risk of negatively impacting ambulation.

The study by Ghai *et al.*[35] also had only three participants who were ambulatory, and they found an improved gait scale score after obturator neurolysis with phenol for adductor spasticity. Their population of 20 included two participants with multiple sclerosis and two with Koch's spine in addition to the 16 with SCI, but they did not describe the etiology of spasticity for the three ambulatory participants. Therefore, it is difficult to determine whether the improved gait scale score is relevant to the SCI population. Further research is also required to determine whether obturator neurolysis is a safe and effective intervention in ambulatory individuals with adductor spasticity from SCI, especially as the effects of phenol have the potential to last beyond 6 months.

Recommendations for future research

Currently, there is great variability in the choice of outcome measures used in limb spasticity research. The MAS was the outcome measure most commonly used across studies in this review ($n = 10$). The reduction in spasticity of MAS of at least one point did not necessarily translate to an improvement in activities or participant's global subjective improvement,[30] suggesting that MAS changes without functional changes may not be sufficiently important to continue with chemodenervation. Also, the minimally clinically important difference for the MAS has not been established in the literature. Given that spasticity is known to affect participation and employment[6] as well as quality of life[7] in individuals with SCI, researchers should attempt to capture these outcomes in future studies. There is evidence that clinical assessment of spasticity has poor correlation with the general spasticity experience in SCI;[30,47] therefore, subjective, self-reported measures should also be evaluated. Detailed information on

adverse events, including the duration and impact of muscle weakness on functional abilities, should also be collected, as these results are crucial for clinicians and patients deciding on whether the benefits of chemodenervation outweigh the risks.

Studies should describe in detail the characteristics of the SCI participants including level, completeness and duration of injury. Marciniak *et al.*[29] did not find a difference in response between individuals with AIS A versus AIS B-D, nor differences between participants with $\leqslant 1$ versus >1 year duration of injury; however, this was a small retrospective chart review. Further research may clarify whether these factors affect outcomes in spasticity management in SCI. In addition, complete description of the intervention including concentration, dosing, muscle selection, muscle or nerve method of localization is crucial, so as to enable comparisons across studies. There is evidence from at least one RCT that BoNT dilution[48] can affect outcomes. Also, the sole use of anatomical landmarks has been shown to be inferior to electromyography plus anatomy for muscle localization,[49] therefore should be avoided when possible both in the research and clinical setting.

Finally, there are questions regarding the cost-effectiveness of using BoNT in chemodenervation. A recent Health Technology Assessment report suggested that BoNT treatment of upper limb spasticity in stroke is not cost-effective given the high cost of the drug and limited functional improvements observed.[50] Future studies should include a similar economic evaluation on BoNT and SCI spasticity. Given the large difference in cost between BoNT and phenol/alcohol, a cost-effectiveness analysis between the agents may be warranted.

Study limitations

The strength of our findings is limited by the inclusion of small, low-quality studies and the inability to meta-analyze results due to heterogeneity of study methods. This paper has tried to take these factors into account by assessing risk of bias and assignation of levels of evidence. Articles reviewed were limited to English and, although the search strategy to identify studies for this review was comprehensive, given the broad nature of the topic reviewed, it is possible that some studies may have been missed.

CONCLUSION

A small number of studies with low levels of evidence were found examining the use of chemodenervation with BoNT or phenol/alcohol for management of limb spasticity in SCI. These results highlight the need for additional evaluations and more complete reporting of interventions and outcomes including adverse events to help guide clinicians treating individuals with limb spasticity from SCI. As the patterns of spasticity seen in SCI can differ compared with those with other etiologies of spasticity, there is a need for research specific to the SCI population. Areas of priority include establishing a consensus on what outcome measures should be used and exploration of potential factors (for example, type and duration of injury) that can affect outcomes with spasticity management in SCI.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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APPENDIX

MEDLINE search strategy

1. Spinal cord injuries/
2. Paraplegia/
3. Brown sequard syndrome/
4. Quadriplegia/
5. Central Cord Syndrome/
6. (spinal cord adj5 (trauma or transection or laceration or contusion)).mp.
7. (traumatic adj3 myelopathy).mp.
8. (spinal cord adj5 injur$).mp.
9. (paralysis adj3 (lower extremit$ or leg$ or lower limb$)).mp.
10. (quadripleg$ or tetrapleg$ or parapleg$).mp.
11. (paraplegia adj3 (spinal or spastic)).mp.
12. or/1–11
13. Exp Muscle Spasticity/
14. ((muscle* or muscular) adj3 (spasm* or cramp* or spastic* or clonus)).ab,ti.
15. spasticit*.mp.
16. or/13–15
17. exp Phenols/
18. exp Denervation/
19. exp Alcohols/
20. exp Ethanol/
21. exp Botulinum Toxins/
22. or/17–21
23. 12 and 16 and 22
24. Limit 23 to humans
25. Limit 24 to English language