Spasticity After Spinal Cord Injury: An Evidence-Based Review of Current Interventions

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Purpose: To provide an overview of evidence for spinal cord injury (SCI) spasticity interventions in peer-reviewed, published literature. **Method:** Structured review and synthesis of spasticity treatments in the literature. Each publication was rated according to the Downs and Black methodology for assessing nonrandomized studies and according to the Physiotherapy Evidence Database (PEDro) scale for assessing randomized controlled trials. **Results:** Level 1 evidence supports the use of transcutaneous electrical nerve stimulation (TENS), penile vibration, baclofen, tizanidine, clonidine, cyproheptadine, gabapentin, and L-threonine to reduce spasticity in SCI. **Conclusion:** Although spasticity is a common complication following SCI, there is relatively little evidence for the treatment of spasticity and even less evidence that has been confirmed by independent replication. TENS is the only routine nonpharmacological treatment for spasticity that is supported by adequate level 1 evidence. Several pharmacological treatments, including baclofen, tizanidine, and clonidine, are supported by level 1 evidence. There is level 1 evidence to support test doses of intrathecal baclofen for the short-term reduction of spasticity in SCI but not for its long-term use. The lack of level 1 evidence for spasticity interventions does not necessarily reflect a lack of effective treatments, but it does emphasize the need for further studies. All other interventions reviewed would benefit from further study. **Key words:** *clonus, hyperreflexia, hypertonia, intervention, paraplegia, quadriplegia, SCI, spasticity, spinal cord injury, tetraplegia, treatment*

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Spasticity has been reported in an estimated 53% to 78%[1,2] of individuals with spinal cord injury (SCI) and has been identified as having a significant impact on quality of life by restricting activities of daily life and limiting workplace reintegration.[1,3] Classically, Lance has described spasticity as being "characterised by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex."[4(p485)] Pandyan et al.[5] described spasticity as "disordered sensorimotor control, resulting from an upper motor neurone lesion, presenting as intermittent or sustained involuntary activation of muscle."[5(p5)] The tonic component of increased muscle tone (i.e., changes of viscoelastic muscle properties and/or tonic muscle activation inducing increased passive resistance) and the phasic component of the stretch reflex (i.e., tendon hyperreflexia) outlined in the Lance definition are measureable using the original and modified Ashworth scale (AS,[6] MAS[7]) and the Wartenberg Pendulum Test (WPT[7]). Other aspects of spasticity characterized in the Pandyan definition such as clonus or other involuntary limb movements are reflected in outcome measures such as the Penn Spasm Frequency Scale (PSFS[8]) and the Spinal Cord Assessment Tool for Spastic reflexes (SCATS[9]). Other spasticity assessment tools include patient self-report with a visual analogue scale (VAS[10]) or less clinically accessible measures such as electrophysiological measures (e.g., H-reflexes[11,12]) or torque resistance in response to sinusoidal angular displacements.[13]

Rehabilitation therapies, surgery, pharmacotherapy, and neurolysis are the most common treatment options currently employed to manage spasticity in SCI. The present article is intended as a broad overview for clinicians and summarizes the evidence for each of these approaches as part of SCIRE, which is an evidence-based review of interventions associated with SCI rehabilitation. Although salient conclusions are noted in this article, further details may be referenced at http://www.icord.org/SCIRE/.

Method

A systematic review of all relevant literature published from 1980 to 2006 using multiple databases was conducted using SCIRE methodology as outlined separately in this issue (see Eng et al.,"Spinal Cord Injury Rehabilitation Evidence: Method of the SCIRE Systematic Review"). A quality assessment of each investigation was conducted using the Physiotherapy Evidence Database (PEDro) scale[14] for all randomized controlled trials (RCTs). Higher scores indicate better methodological quality (9–10, *excellent*; 6–8, *good*; 4–5, *fair*; <4, *poor*). The Downs and Black tool[15] was used for all non-RCTs (maximum score of 28). Following each individual study assessment, conclusions were drawn about the accumulated evidence for specific interventions aimed at reducing spasticity using a modification of Sackett's level of evidence.[16] Sackett's levels of evidence were collapsed into five categories where level 1 evidence came from "good" to "excellent" RCTs with a PEDro score greater than or equal to 6 and level 2 evidence corresponded to RCTs with PEDro scores less than 6 or nonrandomized prospective controlled or cohort studies. Evidence from case-control studies was assigned to level 3. Levels 4 and 5 corresponded to evidence from pre-post/posttest/case series and observational/

case report studies, respectively (see Eng et al., in this issue). Note that because there were no sample size restrictions, level 1 evidence could be based on single studies with small group sizes, however these studies would have been rated highly according to the standardized PEDro scale.

Results

A summary of the results of the evidence for nonpharmacological and pharmacological interventions is presented in **Table 1**. This table lists each of the interventions, the associated level of evidence, and a brief concluding statement.

Nonpharmacological interventions for spasticity

Interventions based on passive movement or stretching

Stretching and other passive movement modalities are commonly considered as the conservative first step to the treatment of spasticity prior to the use of antispasticity medication and surgical procedures.[17,18] Three small sample investigations (i.e., $n \leq 12$) employing pre-post study designs (level 4 evidence) support rhythmic passive movements[10,19] or prolonged assisted standing[20] as a means of providing short-term spasticity reduction. These trials used a variety of spasticity outcome measurement tools including MAS,[10] VAS,[10] patient self-report,[19] and torque resistance to passive sinusoidal movement.[19,20] In all cases, objective outcome assessment was limited to times immediately after the treatment session, although Skold[10] noted at least partial maintenance of reductions in spasticity with a VAS question asking participants to rate spasticity from "none" to "worst imaginable" 4 days following the last treatment session.

Interventions based on active movement (including FES-assisted movement)

Active movement approaches use a variety of exercise forms that may provide benefits beyond spasticity reduction (e.g., strength, endurance, and gait retraining). The studies reviewed included hydrotherapy exercises,[21] locomotor training programs using functional electrical stimulation (FES),[22,23] and FES-powered orthoses.[24]

There was a single prospective nonrandomized controlled trial ($n = 20$) suggesting an enhanced effect of adding hydrotherapy to other conventional spasticity therapies (i.e., oral baclofen, range of motion exercises)[21] to produce short-term reductions in spasticity as measured by AS and PSFS. The use of a prospective nonrandomized controlled study design permits the assignment of level 2 evidence for the provision of hydrotherapy in association with other conventional therapies, albeit further study is required.

Three small sample studies ($n = 6$–21) demonstrated short-term reductions in spasticity with FES-assisted walking,[22–24] although these findings were limited by lower quality pre-post study designs and inconsistent results depending on the particular outcome measurement tools employed. Therefore, FES-assisted walking programs for spasticity reduction are supported only by level 4 evidence.

Interventions based on neuromuscular electrical stimulation

Electrical stimulation applied directly to the muscle or motor nerve to produce muscle contractions has been used to reduce spasticity. Two prospective controlled trials,[13,25]

Table 1. Levels of evidence (LOE) and conclusions for various interventions

Intervention	LOE	Conclusion
Nonpharmacological treatment of spasticity		
10.1 Passive movement or stretching		
Rhythmic, passive movement	4	*Short-term reduction in spasticity.*[10,19]
Externally applied forces (e.g., assisted standing)	4	*Short-term reduction in spasticity.*[20]
Active movement (including FES-assisted movement)		
Hydrotherapy	2	*Short-term reduction in spasticity.*[21]
Program of FES-assisted walking	4	*Short-term reduction in ankle spasticity (i.e., ≤24 hours).*[22–24]
	—	*No evidence for length and time course of spasticity effect for hydrotherapy or FES-assisted walking.*
10.2 Direct muscle electrical stimulation		
Surface muscle stimulation (single bout)	2	*Reduces local muscle spasticity (agonist stimulation more effective than antagonist stimulation) although conflicting evidence for effect duration (i.e.,~ ≤ 6 hours).*[13,25]
Surface muscle stimulation (ongoing program)	—	*No evidence that reduces muscle spasticity (may even increase local muscle spasticity)*[27]
10.3 Various forms of afferent stimulation		
TENS (ongoing program)	1	*Reduces spasticity for up to 24 hours.*[11]
TENS (single bout)	4	*Reduces spasticity (to a lesser degree than with ongoing TENS) with nerve stimulation*[12,37] *but null result with dermatomal stimulation (level 2).*[25]
Penile vibration (single bout)	1	*Reduces spasticity (3 to 6 hours).*[30,31]
Rectal probe stimulation	4	*Several sessions reduce lower limb muscle spasticity for up to 8 hours.*[32]
Muscle massage	4	*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.*[33]
Hippotherapy	4	*May reduce lower limb muscle spasticity immediately following an individual session.*[35]
Cryotherapy	4	*May reduce muscle spasticity for up to 1 hour after removal of the cold stimulus.*[34]
Helium-neon irradiation of sensory nerves	2	*May suppress ankle clonus for up to 60 minutes following 40 seconds of stimulation.*[36]
10.4 Direct spinal cord stimulation		
Spinal cord stimulation (ongoing)	4	*May provide some relief in otherwise intractable spasticity for some time (i.e., months to years)*[38,39] *but is not generally effective (cost-benefit) long-term.*[40]

10.5 Neuro-surgical		
Dorsal T-myelotomy	2	*May result in reduced spasticity initially refractory to conservative approaches-may not be maintained over several years.*[41,43]
	2	*Pourpre's technique is more effective than Bischof II in maintaining reduced spasticity.*[41]
Pharmacological treatment of spasticity		
10.6 Oral baclofen		
Oral baclofen	1	*Improves muscle spasticity secondary to SCI.*[11,46–48]
10.7 Intrathecal baclofen		
Intrathecal baclofen (bolus or test dose)	1	*Decreases spasticity.*[50–54]
Intrathecal baclofen (long-term)	4	*Decreases spasticity.*[50–54,56,58–60,62–64]
	4	*May improve functional outcomes.*[52,53,55–59]
	4	*Low complication rates with the long-term use.*[50–53,57,60,62,64,100]
	4	*Is a cost-effective intervention.*[52,53]
10.8 Medications other than baclofen on spasticity after SCI		
Tizanidine	1	*Effective for SCI spasticity.*[65] *Note: non-ITT analysis.*
Clonidine	1	*Effective for SCI spasticity.*[71]
4-Aminopyridine (4-AP)	C	*Conflicting evidence for the anti-spasmodic effects of 4-AP.*[74–77]
Cyproheptadine	1	*Effective for treating SCI spasticity (n = 8).*[78]
Gabapentin	1	*Modest improvements in spasticity. No confidence intervals reported and small sample size (n = 28).*[80]
L-threonine	1	*An RCT investigating L-threonine for the treatment of SCI spasticity showed only minimal effects on spasticity based on very weak correlations between PSFS, AS, and plasma [L-threonine].*[82]
Diazepam, dantrolene	—	*No current evidence supports the use of diazepam or dantrolene for the treatment of spasticity secondary to SCI.* [92]
Cannabis (THC)	4	*Based on 1 prospective pre-post study, THC reduces spasticity secondary to SCI.*[83]
Botulinum neurotoxin	4	*Based on 2 case studies, botulinum neurotoxin improves focal muscle spasticity secondary to SCI.*[90,91] *This is cautiously supported by an RCT where only 6/52 subjects had spasticity due to SCI.*[92]
	4	*Long-term administration of botulinum neurotoxin effective for treatment of focal spasticity (single case study: 8 treatments over 2 years). Tolerance to BTX-A may have occurred with final treatment.*[91]

(continued)

Table 1. Continued

Intervention	LOE	Conclusion
Pharmacological treatment of spasticity		
10.9 Spasticity outcome measures		
Spasticity outcome measures	N/A	*Total of 66 spasticity outcome measures used in literature surveyed with only a small subset of these partially validated (AS, MAS, PSFS, SCATS, VAS).*[101]

Note: Level 1 = RCT with PEDro ≥6; 2 = RCT with PEDro <6, prospective controlled (nonrandomized), cohort; 3 = case control; 4 = pre-post, posttest, case series; 5 = clinical consensus, case report. C = conflicting; — = no evidence; N/A = not applicable. AS = Ashworth Scale; FES = functional electrical stimulation; ITT = intent to treat; MAS = modified Ashworth Scale; PSFS = Penn Spasm Frequency Scale; RCT = randomized controlled trial; SCATS = Spinal Cord Assessment Tool for Spastic reflexes; SCI = spinal cord injury; TENS = transcutaneous electrical nerve stimulation; VAS = visual analogue scale; WPT = Wartenberg Pendulum Test.

each with 10 subjects, and a single pre-post trial ($n = 12$)[26] using neuromuscular electrical stimulation demonstrated immediate spasticity reduction, although these effects waned and were mostly absent by the next day.[13,25,26] Across these studies, spasticity reduction was evident by examining torque resistance to sinusoidal ankle movement,[13] pendulum test,[26] and MAS but not clonus scores or H-reflexes.[25] These findings provide level 2 evidence for the role of neuromuscular electrical stimulation in reducing spasticity.

In the only study of the repeated application of neuromuscular stimulation, Robinson et al.[27] obtained mixed results with increased spasticity after 4 weeks and little change in mean spasticity at 8 weeks. Despite severe subject retention issues, this null result provides conflicting evidence and begs further study of the effects of repeated applications of neuromuscular stimulation given the beneficial results obtained with single applications.[28,29]

Interventions based on various forms of afferent stimulation

A variety of forms of afferent stimulation have been assessed as a means of reducing spasticity in SCI including the following modalities: transcutaneous electrical nerve stimulation (TENS),[11,12] penile vibration[30,31] rectal probe stimulation,[32] massage,[33] cryotherapy,[34] hippotherapy,[35] and helium-neon irradiation.[36]

A single RCT (n = 21 SCI, 20 healthy controls) examining TENS demonstrated reductions in spasticity lasting for up to 24 hours and more profound effects with repeated applications.[11] This study demonstrated similar significant benefits for TENS as those seen with baclofen treatment over a variety of outcome measures including AS, PSFS, deep tendon reflexes, H-reflexes, and the FIM™* and to a lesser extent in plantar stimulus response and clonus scores.[11] Corroboratory evidence for TENS was provided by a pre-post study (n = 14) that demonstrated short-term reductions in spasticity with various clinical measures but not with electrophysiological measures.[12] Although

*FIM™ is a trademark of Uniform Data System for Medical Rehabilitation, a division of UB Foundation Activities, Inc.

reflecting only a single RCT with support from a single pre-post study, these results provide level 1 evidence for the use of TENS in reducing SCI spasticity. Null or less significant results have been demonstrated when TENS involved dermatomal stimulation, associated with stimulation over cutaneous skin receptors supplying the sensory nerve,[25,37] as opposed to the positive findings obtained with stimulation being applied directly over the sensory nerve.[11,12]

Although clinical applicability may be limited, the antispastic effects of penile vibration[30,31] and rectal probe stimulation[32] have been investigated following anecdotal reports of spasticity reduction associated with these procedures during sperm retrieval in fertility clinics. Similar findings were obtained in a small sample RCT ($n = 9$)[31] and a small sample pre-post trial ($n = 10$)[30] of penile vibration, each of which demonstrated significant reductions in AS/MAS but only smaller nonsignificant reductions in the PSFS. Similarly, a small sample pre-post trial ($n = 9$) of rectal probe stimulation produced significant reductions in AS and a measure of self-report of spasticity interference of function.[32] These reports indicate that penile vibration and rectal probe stimulation may be effective at reducing lower limb muscle spasticity for several hours achieving evidence of levels 1 and 4, respectively.

Other forms of afferent stimulation including massage,[33] cryotherapy,[34] and hippotherapy[35] have only been examined with single investigations involving pre-post study designs. Each of these studies used different single outcome measurement tools including H-reflexes,[33] torque resistance to sinusoidal ankle movement,[34] and AS,[35] respectively. Spasticity reductions were seen for each study indicative of level 4 evidence for each of these modalities. An investigation of the antispastic effect of helium-neon irradiation[36] involved a poor quality RCT (i.e., PEDro score <6, $n = 41$) with reliance on a single measure of reduced clonus count to reflect reductions in spasticity and no documentation of statistical comparisons. Despite these serious methodological issues, this was assigned an evidence level of 2 in accordance with SCIRE methodology (see Eng et al., in this issue).

Interventions based on spinal cord stimulation

Spinal cord stimulation involves surgical implantation of an electrode and control system placed over the dorsal columns of the spinal cord. Pinter et al.[38(p524)] noted a declining interest with this approach in the 1990s because of technical concerns and "the realization that spinal cord stimulation was less effective in patients with severe spasms of the lower limbs." A pre-post pilot trial ($n = 8$) showed spasticity reductions as indicated by significant reductions in AS as well as various observations associated with the pendulum test, clinical rating scale, EMG responses, and spasticity medication reductions.[38] Two case series reports ($n = 48$, $n = 29$) demonstrated that over several years the number of individuals receiving benefits gradually waned with others encountering equipment failures or other problems.[39,40] Thus, there is level 4 evidence that spinal cord stimulation may provide spasticity relief over a few months[38,39] but long-term effectiveness and cost-effectiveness are less certain.[39,40]

Neuro-surgical interventions

Surgical approaches have been considered as a treatment option for those individuals with severe spasticity refractory to conservative approaches and with no potential func-

tion below the level of the lesion.[41] The primary and most commonly investigated technique is that of longitudinal myelotomy, and this approach has been applied to pain management as well as spasticity reduction in other etiologies in addition to those with SCI.[42,43] A single study using an RCT design (n =32) favored Poupre over the Bischof II technique of dorsal longitudinal T-myelotomy in producing reduced spasticity, although the duration of the antispastic effect was not always maintained over the course of several years.[41] This report was limited by imprecise documentation of results. Subjects were simply classified as having "good" or "bad" effects with respect to spasticity reduction; although these were based on AS and PSFS scores, mean values or levels of significance for these measures were not provided. This RCT was supported by a single case study,[43] also with inadequate data analysis and reporting, in accordance with SCIRE methodology (see Eng et al., in this issue). This intervention was assigned a rating of level 2 evidence due to a PEDro scoring of <6 for the RCT.

Pharmacological interventions for spasticity

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.[17,44] Despite the general acceptance and clinical experience of using oral baclofen to reduce spasticity in people with SCI, at least two systematic reviews have noted a relative paucity of high-quality studies (i.e., RCTs) demonstrating specific or comparative efficacy.[44,45] Considering the widespread use of oral baclofen, studies older than our review inclusion criteria (i.e., 1980–2006) were included in lieu of more recent studies. The only recent RCT[11] investigating the use of oral baclofen for the treatment of SCI spasticity (n = 21) demonstrated a significant reduction in spasticity as measured by a variety of outcome measurement tools (PSFS, AS, flexion reflexes, deep tendon reflexes, H-reflexes, etc.).

This level 1 evidence that oral baclofen improves muscle spasticity secondary to SCI is based on the results from three positive RCTs[11,46,47] and an additional pre-post study[48] but is muted somewhat by a negative finding from a small (n = 5) single-subject design RCT.[49] It should be noted that this latter negative study evaluated baclofen's effect on viscous and elastic stiffness as assessed by monitoring ankle torque after sinusoidal ankle perturbations, a measure less available in clinical settings.

Intrathecal baclofen for reducing spasticity

As with oral baclofen, there is a relative paucity of high-quality studies demonstrating specific or comparative efficacy of intrathecal baclofen usage in the treatment of spasticity in persons with SCI. The present review includes five small, mixed population studies using RCT designs, all using AS and all but one[50] using PSFS, to evaluate the effects of test doses of intrathecal baclofen.[50–54] These trials provide a body of level 1 evidence to support the use of intrathecal baclofen test doses to decrease spasticity similar to that reported in a recent Cochrane review by Taricco et al.[44]

Ten pre-post studies, all using the AS and all except two[55,56] using PSFS, provided level 4 evidence supporting the long-term use of intrathecal baclofen to decrease spasticity.[50,52,53,55–61] The effects of intrathecal baclofen were found to be more pronounced

in the lower extremities than the upper extremities.[60] In addition to reductions in spasticity, some studies examined outcomes such as functional improvements[50,52,53,55–59,61] and cost-effectiveness.[52,53] It should be noted that not all of these studies met the SCIRE criteria of >50% of the study sample being comprised of individuals with SCI. Given that functional improvements were measured using a wide variety of validated scales (e.g., FIM™, Kurtzke Expanded Disability Status Scale [EDSS]) or subjective notations in a mixed subject population, caution should be taken for the assignment of level 4 evidence on improvements in SCI dysfunction mediated through the use of intrathecal baclofen.[50,52,53,55–59,61] Similarily, there were two pre-post studies providing level 4 evidence of cost-effectivness (i.e., per day/patient savings or overall savings[52,53]) with intrathecal baclofen in the same mixture of populations.

Effect of medications other than baclofen on spasticity after SCI

Of the 20 baclofen studies included in the SCIRE review to date, 5 oral formulation studies[11,46–49] included a total of 68 combined subjects while the remaining 15 intrathecal baclofen studies[50–64] included a total of 250 combined subjects. However, the largest single study (n = 118)[65] undertaken to address pharmacological treatment of spasticity secondary to SCI was an RCT for tizanidine (an α_2-adrenergic agonist) where significance was achieved for reductions in spasticity (level 1 evidence). It is noteworthy that 34% of treated subjects who discontinued prematurely due to adverse events, lack of efficacy, and other reasons not specified were not included in the study analysis, representing a serious methodological limitation. However, a small (n = 10) single-dose, pre-post study of tizanidine did present evidence to corroborate the reduction of SCI spasticity and further revealed that muscle power was not affected at any stage in the study.[66]

Collectively, clonidine as an antispasmodic has been studied in 144 SCI patients across eight studies.[48,67–73] This constitutes level 1 evidence for the antispasmodic property of clonidine based on one RCT[71] and seven other studies of less rigorous design,[48,67–70,72,73] where reductions in multiple dimensions of spasticity were demonstrated regardless of formulation (i.e., oral,[67] transdermal,[72,73] or intrathecal[48,69,70]) or outcome measure used (i.e., AS/MAS, PSFS, VAS, H-reflex, WPT, etc). Of note is the presence of head-to-head comparison studies[48,68] with clonidine, diazepam, cyproheptadine, and baclofen. Clonidine was superior to a clonidine-desipramine combination, diazepam, and placebo[68] but inferior to cyproheptadine and baclofen[48] in significantly reducing spasticity as measured by the H-reflex and Vibration Inhibition Index.

Despite the fact that 4-aminopyridine (4-AP) has not yet received regulatory approval for clinical use, this potassium channel blocking agent has been studied as a potential therapy to treat spasticity, dysfunctional ambulation, and lower extremity weakness in SCI and multiple sclerosis (MS). Included in this review are four published studies involving 49 SCI subjects.[74–77] The largest of these studies (n = 29) was an RCT design[76] and provided significant AS reductions accompanied by significant patient satisfaction and quality of life scores for a sustained-release tablet. This was not supported in an RCT of intravenous 4-AP versus placebo (n = 12).[74] Despite differing formulations, maximum plasma concentrations were comparable and the AS was used in both studies. The remain-

ing two case series studies did report some findings of spasticity reduction but the results were anecdotal. Therefore, the evidence for 4-AP as an antispastic therapy is currently conflicting.

Cyproheptadine is a nonselective serotonergic antagonist and antihistamine that has been reported to improve spasticity in SCI. Although level 1 evidence based on a single small ($n = 8$) RCT[78] favoring cyproheptadine in reducing PSFS and spasm severity scale scores versus placebo is a generous assignment, it was supported by level 4 evidence based on the previously noted comparison study[48] and a pre-post case series study showing improved ankle clonus and PSFS.[79]

The antiepileptic drug, gabapentin, has also been used for the treatment of neurogenic pain and spasticity in multiple indications including SCI. Level 1 evidence for gabapentin as a pharmacological intervention for spasticity is provided by an RCT[80] where gabapentin ($n = 28$) resulted in statistically significant reductions in spasticity compared to placebo as measured by the AS and patient self-report (Likert scale). Another RCT ($n = 6$)[81] using a surface EMG-based quantitative assessment technique only yielded positive anecdotal findings in the open extension portion of the trial, which suggested the need for larger scale controlled trials at higher doses.

L-threonine, an amino acid supplement that is important for the formation of collagen, has been studied for the treatment of spasticity secondary to SCI. Level 1 evidence for the use of L-threonine as an antispasmodic is represented by a single RCT[82] with a sample of 33, but the reader should be cautioned that only very weak correlations were reported between PSFS, AS, and plasma threonine levels.

Cannabis or THC (tetrahydrocannabinol) is another agent that has been studied for the treatment of spasticity secondary to SCI and other indications. A small sample, open-label, dose escalation study[83] provided level 4 evidence that spasticity secondary to SCI resulted in significant MAS reductions after THC administration. However, limitations of the study included a high side effect–related dropout rate, the use of high dosages (i.e., average daily oral dose of 31 mg), and insufficient attention to the effects of overall functioning considering the known psychogenic and sedative properties of this substance.[84]

No current evidence (1980 to date) could be found to support the use of dantrolene and diazepam[68] in the treatment of spasticity secondary to SCI.

Neurolysis with botulinum neurotoxin

Clinicians and researchers have advocated the use of botulinum neurotoxin for relieving focal muscle spasticity in individuals with SCI,[17,85,86] and the Spasticity Study Group purport that the decision to use botulinum neurotoxin "is independent of the etiology of the spasticity, depending rather on the presence of an increase in muscle tone that interferes with function."[85(pS208)] Two case studies involving botulinum neurotoxin for treatment of focal SCI spasticity are reviewed in lieu of studies that meet the criteria established for the present review. (Three non–English-language articles have been identified that examine the effects of botulinum neurotoxin on muscle spasticity in SCI.[87–89])

Individual case studies using EMG-guided BTX-A injections in SCI have been conducted by Richardson et al.[90] and Al-Khodairy et al.[91] demonstrating positive benefits, although there was a possibility of drug tolerance (i.e., reduced effect).[91] Richardson

et al.[92] also investigated the effects of BTX-A on focal disability in a group of 52 subjects with various etiologies using a randomized, double-blind, placebo-controlled, parallel group design, although the sample included only six SCI subjects. Reduced spasticity was demonstrated with both active treatment and placebo; there was a significantly greater reduction with BTX-A.

Based on two case studies (level 4 evidence), botulinum neurotoxin improves focal muscle spasticity secondary to SCI.[90,91] As noted previously, studies that did not meet the SCIRE criteria were included as supplemental information when available literature was scarce or absent. Given this qualification, the use of botulinum neurotoxin for the improvement of focal spasticity secondary to SCI is cautiously supported by an RCT where only 6/52 subjects had spasticity due to SCI.[92]

Discussion

Although many of the interventions assessed in this review are current therapeutic practices, the quality of the evidence supporting each intervention is highly varied. One of the most obvious findings of this review is the paucity of large, randomized clinical studies involving SCI subjects. Crossover studies, which contribute scientific rigor in the absence of large patient populations, may provide a better study design alternative in the SCI literature. Generalizability of the results can be enhanced with study replication and confirmation.

Another significant finding is the wide range of outcome measures of which the majority are only partly validated for individuals with SCI. The studies reviewed included 66 outcome measures that have been subjectively summarized into four categories: (1) known clinical measures ($N = 28$), (2) other measures ($N = 25$); (3) electrophysiological measures ($N = 11$), and (4) quality of life measures ($N = 3$). Among the known measures, very few are validated for SCI and only a subset of those are clinically practical, such as the AS[93] and MAS[7] and the PSFS.[8,94] Focusing on one or two outcome measures may cause authors to erroneously over- or underrepresent the magnitude of treatment effects, because spasticity is multidimensional and no single outcome measure can capture this.[94] Priebe et al.[94] identified that spasticity is best measured by a battery of tests that recognize not only the many physical aspects (i.e., velocity dependency, frequency, severity, etc.) but also the influence of other clinical or subclinical conditions such as concurrent infections, bladder status, and emotional status. In a recent review of spasticity outcome measurement tools, Priebe[95] noted the importance of careful attention to technical, training, and environmental factors of testing; the need to further validate current SCI spasticity measures; and the need to incorporate functional and quality of life aspects of SCI spasticity in a comprehensive battery of tests.

Only one commonly used, clinically practical, nonpharmacological approach to treating spasticity in SCI (TENS) is supported by level 1 evidence.[11] In addition, short-term (i.e., 3–6 hours) antispasticity benefits of a single treatment of penile vibration is also supported by level 1 evidence, although this procedure is currently not in practice as a treatment option for SCI spasticity.[31] The role of oral baclofen as a typical first choice for pharmacological treatment is consistent with the available level 1 evidence that supports the use of baclofen (oral and intrathe-

cal), even though rigorous studies involving samples of subjects with predominantly SCI etiology are few. In contrast, only level 4 evidence supports the use of intrathecal baclofen for long-term maintainance of spasticity, improved functional outcomes, low complications rates, and cost-effectiveness. It is interesting that the only large-scale pharmacological RCT (n = 118) of spasticity specifically in SCI supports the use of tizanidine.[65] However, it is important to note that the tizanidine study did not undergo intent-to-treat analysis (34% of patients were not included in the analysis). Considering tizanidine is reported to not reduce muscle strength,[66] a comparison study of baclofen versus tizanidine could be helpful to assist clinicians in making better decisions for treatment of spasticity in SCI.

The evidence that oral baclofen improves muscle spasticity secondary to SCI is based on the results from three positive small-scale RCTs, but it is muted somewhat by a null finding from a small sample (n = 5) single-subject design RCT.[49] These null findings were obtained by Hinderer et al.,[49] who used measurements of viscous and elastic stiffness in response to sinusoidal passive ankle movements to assess spasticity. Aydin et al.[11] also reported nonsignificant differences for electrophysiological variables (i.e., H-reflex amplitude, latency, and H-reflex/maximum motor amplitude [H/M] ratio) in an otherwise positive RCT (i.e., significant improvement of AS and PSFS) favoring baclofen for the treatment of spasticity secondary to SCI. The remaining positive results (significant when statistical data were available) were derived from common clinical measures (i.e., AS, PSFS, etc.). These contradictory findings emphasize the need to understand the multiple dimensions of spasticity measured through different outcome measures.[87]

There is a lack of available evidence to support diazepam use as an adjunctive treatment to baclofen in persons with SCI, despite its widespread use.[96] Considering the known addictive, tolerance, and sedative characteristics of diazepam,[97] a long-term investigation of diazepam[98] as a secondary adjunct treatment to baclofen (oral or intrathecal) is surprisingly absent from the literature. Clonidine was superior to diazepam in a single-blind, nonrandomized controlled trial of six persons with SCI.[68]

After baclofen, the pharmacological agent most frequently studied specifically in the SCI population is clonidine, with eight studies (N = 154) meeting the review criteria. All studies indicated that clonidine was an effective antispasmodic regardless of formulation or outcome measure used. The presence of head-to-head comparison studies comparing clonidine against other antispasmodics showed that clonidine was superior to a clonidine-desipramine combination, diazepam, and placebo but inferior to cyproheptadine and baclofen.[48,68] Comparison studies among other antispasmodics would be helpful to clinicians treating SCI spasticity with attention given to potential side effects of medications, such as hypotension with the use of clonidine.

In summary, level 1 evidence supports the use of ongoing TENS[11] and penile vibration[31] for short-term reduction of spasticity (24 hours and 3–6 hours, respectively) as measured by a variety of outcome measures. Similarly level 1 evidence supports the ongoing use of baclofen (oral[11,46,47] and intrathecal[50–54]), tizanidine,[65] and clonidine[71] for reductions in multiple dimensions of SCI spasticity. Although level 1 evidence is also found for the ongoing use of cyproheptadine[78], gabapentin,[80] and L-threo-

nine[82] for spasticity treatment secondary to SCI, reported therapeutic benefit was limited. Unique to 4-AP was the presence of conflicting level 1 evidence,[74,76] a finding that can only be clarified with further study. No recent evidence could be found to support the use of diazepam and dantrolene for the treatment of SCI spasticity, despite reported use.[99]

Level 2 evidence supports the use of single but not multiple applications of electrical surface neuromuscular stimulation,[13,25] helium-neon irradiation of sensory nerves,[36] and hydrotherapy.[21] Studies of electrical or other forms of stimulation would be highly adaptable to an RCT design to improve the strength of this evidence. In addition, intractable spasticity refractive to conservative approaches can be treated by dorsal T-myelotomy (Poupre's technique is more effective than the Bischof II) as supported by level 2 evidence.[41,43] Due to the invasive nature and the relatively rare need for this type of procedure, the accumulation of more robust evidence is unlikely.

Level 4 evidence provides limited rationale for the use of rhythmic-passive movement, [10,19] assisted standing,[20] FES-assisted walking,[22–24] single bout of TENS,[12,37] rectal probe stimulation,[32] muscle massage,[33] hippotherapy,[35] cryotherapy,[34] ongoing spinal cord stimulation,[38,39] and cannabis.[83] Confirmatory studies of rigorous study design are needed for these potential antispasmodic therapies.

Conclusion

Although spasticity is one of the most common complications in SCI, there is little evidence-based treatment of spasticity in SCI that has been confirmed by independent replication. Only one current nonpharmacological SCI antispasticity treatment that would be useful in routine clinical practice (TENS[11]) is supported by level 1 evidence. Convincing reductions in SCI spasticity for pharmacological treatments, such as baclofen,[11,46,47,50–54] tizanidine,[65] and clonidine[71] for short (hours) and medium (days to weeks) term, are supported by level 1 evidence. There are no data for treatment regimes over years, which is a typical requirement in chronic SCI. Given that the rate of intrathecal baclofen related long-term maintenance of antispastic effects,[50–54] low complications,[52,53] functional improvement,[50,52,53,55–59,61] and cost-effectiveness[52,53] are only supported by level 4 evidence, head-to-head treatment comparisons among these three agents would be beneficial to practitioners in guiding treatment decisions. All other interventions reviewed would benefit from further study.

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