Evidence of treating spasticity before it develops: a systematic review of spasticity outcomes in acute spinal cord injury interventional trials

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Abstract

Introduction: Spasticity is a common consequence of spinal cord injury (SCI), estimated to affect up to 93% of people living with SCI in the community. Problematic spasticity affects around 35% people with SCI spasticity. The early period after injury is believed to be the most opportune time for neural plasticity after SCI. We hypothesize that clinical interventions in the early period could reduce the incidence of spasticity. To address this, we evaluated the spasticity outcomes of clinical trials with interventions early after SCI.

Methods: We performed a systematic review of the literature between January 2000 and May 2021 to identify control trials, in humans and animals, that were performed early after SCI that included measures of spasticity in accordance with PRISMA guidelines.

Results: Our search yielded 1,463 records of which we reviewed 852 abstracts and included 8 human trial peer-reviewed publications and 9 animal studies. The 9 animal trials largely supported the hypothesis that early intervention can reduce spasticity, including evidence from electrophysiological, behavioral, and histologic measures. Of the 8 human trials, only one study measured spasticity as a primary outcome with a sample size sufficient to test the hypothesis. In this study, neuromodulation of the spinal cord using electric stimulation of the common peroneal nerve reduced spasticity in the lower extremities compared to controls.

Conclusion: Given the prevalence of problematic spasticity, there is surprisingly little research being performed in the early period of SCI that includes spasticity measures, and even fewer studies that directly address spasticity. More research on the potential for early interventions to mitigate spasticity is needed.

Keywords: neuromodulation, outcomes, rehabilitation, spasticity, spinal cord injuries

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Introduction

Spasticity is a common consequence of spinal cord injury (SCI) and is estimated to affect around 65% of patients with SCI discharged from acute rehabilitation and up to 93% of people living in the community.[1,2] Spasticity has been defined as a sensorimotor control disorder resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activations of muscles, and resulting in a number of impairments including hyperreflexia, hypertonia, dyssynergia, and clonus, to name a few.[3] Problematic spasticity, defined as

one that either limits function and/or requires anti-spasticity medications, has been estimated to affect around 35% of people living with SCI in the chronic stage, with 11–14% considered as moderate to severe problematic spasticity.[1,4,5]

Spasticity after an acute SCI develops gradually. There is usually an initial phase of areflexia following an acute SCI with flaccid tone below the level of injury.[6] This period is known as spinal shock.[6,7] This phase may last from days to weeks and sometimes even months.[6,7] As a patient starts

emerging from spinal shock, various reflexes return.[6,7] Incomplete injuries with spared sensation and motor activity below the level of injury are prone to develop severe spasticity.[1] Following the return of reflexes, various pathophysiological changes result in hyperreflexia, spasms, and clonus.[8] In a recent retrospective study, emergence of spasticity in the first month after SCI was found to be associated with significantly decreased mobility and function.[9] Poorly treated spasticity interferes with activities of daily living, transfers, gait, and quality of sleep and can cause joint contractures, skin breakdown, and ultimately decreases the potential of neurologic recovery.[2,7]

Despite the potentially negative impact of spasticity, clinicians are left to treat spasticity after it has developed, rather than implementing preventive strategies. Although there are anecdotal spasticity management successes, overall treatment options are suboptimal based on systematic reviews. Beginning with physiotherapy and pharmacologic interventions, as is often the initial treatment, there is no high-quality evidence to support either to decrease spasticity.[10,11] Next steps in management often involve chemodenervation for treatment of limb spasticity, which has shown some evidence for reduction of spasticity, without improvement in function.[12] Intrathecal baclofen showed a significant effect in reducing spasticity and improving activity performance, but there are risks of surgical complications, infections, pump failure, and life-threatening mismanagement.[11,13] Even some of the latest advances, like robot-assisted gait training in SCI, have not shown clinically meaningful reductions in spasticity in a meta-analysis.[14] Finally, barriers to treatment exist, including inadequate funding, lack of access to providers skilled at managing spasticity, and limited access to treatment options such as intrathecal baclofen pumps, alcohol/ phenol neurolysis, and botulinum toxin injections.[15] Thus, treatment of spasticity after it has developed has not been an overall successful approach.

The objective of this systematic review is to identify control trials, in humans and animals, that were performed during the acute phase of SCI that may have an impact on mitigating the development of spasticity in SCI.

Methods
A systematic literature review was performed in accordance with PRISMA (2020) guidelines (Figure 1). The initial search was performed in July 2020 to identify relevant abstracts published between January 2000 and July 2020. After screening, the search was updated to include publications up to May 2021. Combinations of search terms including 'spinal cord injuries', 'spasticity', 'acute', 'early', and 'recent' were queried in PubMed, Scopus, Embase, CINAHL, Cochrane, and ClinicalTrials.gov databases (Supplemental Appendix 1). Abstracts and manuscripts were screened independently by at least two authors (LJ, MK, EP, MH, and AS) and differences were resolved by unanimous agreement. Abstracts included in this systematic review were (1) human and animal studies, (2) that included SCI, and (3) mentioned spasticity outcome measures. Abstracts were excluded if (1) the manuscripts were not written in English, (2) duration of injury exceeded 6 months in humans and 4 weeks in animals, and (3) if the intervention lacked an active control group (i.e. not a historical control group). Manuscripts were evaluated for numbers of subjects, diagnoses, duration of SCI, intervention, primary outcome, sample size justification, secondary outcomes, spasticity measures, and spasticity treatment effects (Supplemental Appendix 2). Complications related to the interventions were also included. Risk of bias was performed using RoB 2 (2019) for human studies.[16] For animal studies, the SYRCLE's risk of bias tool was used.[17] Risk of bias was assessed by at least two authors independently, for human and animal studies, and discrepancies were resolved after discussion with unanimous agreement.

Data from the manuscripts are presented in narrative form. Whenever possible, means and ranges are presented for continuous variables and numbers with percentages for categorical variables. For the instances where group means and standard deviations were published, they were combined using the calculation recommended in the Cochrane Handbook.[18] This systematic review has been registered with PROSPERO (CRD42021250836).

Results
Our search yielded 1463 records of which we reviewed 852 abstracts (Figure 1). After screening based on exclusion criteria, 61 manuscripts met eligibility; 36 studies were conducted in humans and 25 in animals. After reviewing the manuscripts with human participants, eight publications described controlled interventions in
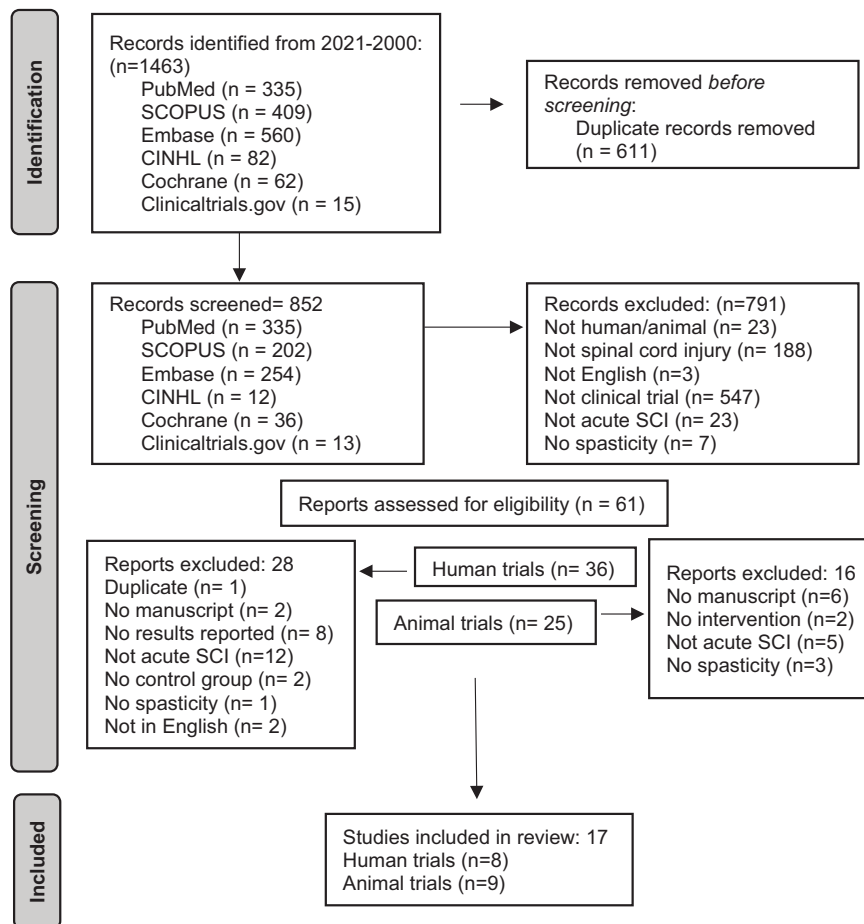
Figure 1. PRISMA flow diagram.
SCI, spinal cord injury.

people with SCI between 0 and 6 months of injury with an assessment of spasticity outcomes. Of the 25 eligible abstracts involving animal studies, nine publications described control trials with interventions performed within 4 weeks of SCI with spasticity measurements.

Demographics

Animal trials. With the exception of one mouse study,[19] all trials used the rat model (Table 1). Samples ranged from 21 to 71 animals, and age ranges, when provided, were from 8 to 16 weeks old. Interventions were performed within 3 days of SCI in six trials, at day 8 in two trials, and at 14 days after SCI in one trial. The three earliest trials used thoracic transection models at levels 4 and 6. Only the Marcantoni *et al.*[19] trial used transection in the mouse at the S2 level. Otherwise, moderate contusions models were used at

T8 and T9, and two studies at C6/7, and both Hou *et al.*[20] and van Gorp *et al.*[21] utilized an L3 compression as their model. Five studies used female rats, three studies used male rats, and the mouse study used both sexes.

Human trials. There were 195 patients enrolled in interventional trials that included people within 6 months of injury, with only three participants greater than 6 months of injury. An additional three patients were excluded from Kumru *et al.*[28] study, due to infections and severe spasticity, leaving a total of 189 patients (Table 2). Sample sizes ranged from 7 to 54 patients, and age ranges, when provided, were from 18 to 70 years old. The duration of injury, when provided, ranged from 15 to 195 days at enrollment. All studies reported on SCI phenotypes of complete *versus* incomplete and tetraplegia *versus* paraplegia. Many provided information about etiology of SCI, traumatic *versus* nontraumatic.

Table 1. Description of animals, injury model, and intervention.

Manuscript	Species	n	Age, weeks	Sex	Injury	Time of intervention[a]	Assessment duration[a]
Ryu et al.[22]	Rat	27	Adult	F	Moderate T8 contusion	1 day	4 weeks
Hou et al.[23]	Rat	30	Young adult	F	C6/7 moderate contusion	Day 8 (treadmill training) Day 14 (magnetic stimulation)	8 weeks
Marcantoni et al.[19]	Mouse	40	8–16	B	S2 transection	1 or 42 days	15 weeks
Hou et al.[20]	Rat	38	Adult	F	C6/7 moderate contusion	Day 8 (treadmill training)	7 weeks
van Gorp et al.[21]	Rat	42	12	F	L3 compression (15 min)	3 days	8 weeks
Avila-Martin et al.[24]	Rat	54	10	M	Moderate T9 contusion	0–28 days	4 weeks
Rabchevsky et al.[25]	Rat	21	Adult	F	T4 transection	14–21 days	3 weeks
Advokat[26]	Rat	71	Adult	M	T6 transection	1 or 31 days	1 or 31 days
Duke & Advokat[27]	Rat	33	Adult	M	T6 transection	2 or 41 days	2 or 41 days

B, both sexes; C6/7, cervical levels 6/7; F, female; L3, lumbar level 3; M, male; S2- sacral level 2; T(4,6,8,9), thoracic levels.
[a]Post-injury.

Study designs, interventions, and outcome measures

Animal trials. Six of the nine trials described randomization of treatment allocation, and no studies used crossover designs (Table 3). Five of the studies investigated a single medication administered early after SCI to reduce spasticity: pentobarbital,[27] clonidine,[26] gabapentin,[25] nimodipine, and escitalopram.[22] One pharmacologic study investigated several medications: albumin (Alb), oleic acid (OA), Alb-OA, and Alb-elaidic acid.[24] Hou et al. incorporated treadmill training in both of his studies, with the addition of early spinal cord magnetic stimulation in the 2020 publication.[23] van Gorp et al.[21] performed instraspinal grafting of clinical grade human fetal spinal cord-derived neural stem cells (HSSC) 3 days after SCI.

In most of the studies (7/9), spasticity was not present at baseline. Spasticity outcome indices included behavioral measures, electrophysiologic measures, and measures of torque during joint movement. Behavioral measures included (number of studies) tail flick responses during stimulation (3) and evidence of spasms or clonus during swimming (1). Electrophysiologic measures included H-reflex (3) and electromyogram (EMG) recordings of limb/tail (7). The two studies by Hou et al. utilized velocity-dependent ankle torque and van Gorp et al.[21] measured gastrocnemius muscle resistance.

Human trials. All of the studies used randomization for treatment allocation (Table 4). Most studies used parallel groups, while two studies used crossover designs.[31,35] Five studies evaluated the effects of neuromodulation techniques in conjunction with therapy: repetitive transcranial magnetic stimulation (rTMS) in two, functional electric stimulation (FES) in one, transcutaneous spinal stimulation (TSS) in one, and transcutaneous electrical nerve stimulation (TENS) in one. One study evaluated a progressive resistance strength training program. The remaining two studies utilized biological interventions: autologous bone marrow cell transplant (BMCT) and granulocyte-colony stimulating factor (G-CSF).

Only two of the eight studies reviewed evaluated spasticity as a primary outcome measure.[29,34] The remainder of the studies evaluated spasticity as a secondary outcome, except for one which measured spasticity as a possible adverse event.[30] Sample size calculations were described in three studies, in which one used a secondary outcome measure to determine the sample size.[30] Three of the studies justified the lack of a sample size calculation because they were pilot trials, while two

Table 2. Demographics of participants in the assessed human studies.

Manuscript	n	Age, years	Duration of injury, days	Male	Tetraplegia	Complete	Traumatic
		Mean (range)	Mean (range)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Estes *et al.*[29]	16	44.4 (18–65)	100.3 (36–195)	14 (78%)	15 (94%)	0 (0%)	Unknown
Derakhshanrad *et al.*[30] [a]	54	33.9 (12)[b]	113.9 (55.9)[b]	49 (91%)	23 (43%)	0 (0%)	54 (100%)
Gharooni *et al.*[31]	7	46.6 (29–70)	107.1 (90–150)	5 (71%)	7 (100%)	0 (0%)	5 (71%)
Bye *et al.* [32]	30	46 (25–65)[c]	60 (42–93)[c]	24 (80%)	24 (80%)	8 (27%)	Unknown
Chhabra *et al.*[33]	21	27.7 (18–40)	9.5 (1–15)	18 (86%)	0 (0%)	21 (100%)	21 (100%)
Kumru *et al.*[28]	31	47.6 (19–69)	84.7 (15–180)	24 (77%)	14 (45%)	0 (0%)	14 (45%)
Oo[34] [a]	16	37 (13.7)[b]	95.7 (53.9)[b]	15 (94%)	8 (50%)	6 (38%)	16 (100%)
Ralston *et al.*[35]	14	25 (22–32)[c]	118 (64–135)[c]	11 (79%)	8 (57%)	13 (93%)	Unknown

n, subjects in the trial.
[a]Calculation used to combine means and SD.
[b]Mean and SD.
[c]Median and interquartile range.

did not provide any information on sample size. Seven of the eight trials included people with SCI that already had spasticity as baseline, and one of the studies did not provide information on baseline spasticity.

Spasticity outcome measures, both objective and subjective, varied across studies. For the objective measures, seven of the eight trials used some form of the Ashworth Scale (AS), or Modified Ashworth Scale (MAS). Gharooni *et al.*[31] combined the scores of the MAS of the bilateral elbow and wrist extensors. Ralston *et al.*[35] combined the AS of the quadriceps, hamstrings, calves, and hip adductors to generate one score. Kumru *et al.*[28] measured the MAS at both knees, while Chhabra *et al.*[33] used a decrease in the MAS by one grade or more to indicate successful treatment. As noted previously, the MAS was also used to measure spasticity as an adverse event in one study. Win Min Oo[34] utilized the composite spasticity score (CSS) which includes a modified double-weighted five-point AS, ranging from 0 to 8. The CSS also includes an ankle jerk score and ankle clonus score. Estes *et al.*[29] also measured ankle clonus with the ankle clonus drop test. For their primary outcome of spasticity, however, Estes *et al.* utilized the Wartenberg pendulum test.[36] They also used the Spinal Cord Assessment Tool for Spastic reflexes (SCATS). Three studies incorporated subjective measures

of spasticity. Estes *et al.* used the modified SCI-spasticity evaluation test (mSCI-SET). Gharooni *et al.* used the Leeds Adult Spasticity Impact Scale (LASIS) and the Visual Analog Scale for spasticity (VAS-S). Ralston *et al.* used the Patient-Reported Impact of Spasticity Measure (PRISM).

Outcomes and spasticity treatment effect
Animal trials. None of the animal studies provided sample size justification or anticipated treatment effect of the intervention. Although primary/secondary objectives were not explicitly mentioned, the titles and study design elements all would suggest that spasticity outcomes were the primary objectives. Thus, we assessed the risk of bias of all included animal manuscripts using the SYRCLE's risk of bias tool (Table 5).[17] We found all of the included animal studies to have a high risk of bias, largely based on the lack of blinding animal researchers, caregivers, and outcome assessors. Description of attrition and the reporting of outcomes had a low risk of bias in all the studies.

Nonpharmacologic interventions. Hou *et al.* investigated early treadmill training (Tm; 2014) and early Tm plus spinal cord magnetic stimulation (TMSCS; 2020). They demonstrated that early Tm initiated 8 days after SCI, 5 days weekly

Table 3. Description of study design and outcomes in animal trials.

Manuscript	Design	Intervention[a]	Baseline spasticity	Primary outcome	Spasticity measure(s)	Treatment effect
Ryu et al.[22]	Randomized control trial (RCT), intervention v placebo in injured controls.	Escitalopram (selective serotonin reuptake inhibitor) daily for 28 days after SCI.	No	Spasticity Locomotor recovery (BBB scale)	Swimming test (evidence of spasm or clonus during swimming) at 3- and 4 weeks post-injury. RDD of H-reflex	Escitalopram administration in the acute phase of SCI reduced occurrence of spastic behaviors during the swimming test, at 3–4 weeks post-SCI No effect of treatment on H-reflex after SCI No effect of treatment on locomotor recovery
Hou et al.[23]	RCT, intervention v injured controls.	Treadmill training with spinal cord magnetic stimulation (TMSCS)	No	Spasticity Gait impairment (3D kinematics and CatWalk) Forelimb grip strength	Transcutaneous EMG recording during velocity-dependent ankle torque (VDAT) RDD of H-reflex	Relative to SCI controls, TMSCS showed significantly decreased EMG and VDAT recordings at 4- and 8- weeks. RDD in the TMSCS was similar to non-SCI controls at 10-weeks. CatWalk gait analysis was not significantly different in the intervention group compared with non-SCI controls at 4- and 8- weeks. Grip strength improved in the intervention group compared with the SCI no-treatment group.
Marcantoni et al.[19]	Randomized block design, 3 groups: early intervention, late intervention, early vehicle control	Nimodipine (early Day1), late (week 6) for 6 weeks.	No	Spasticity	EMG recording from tail Severity index based on the angles of tail segments	Early (Day 1) treatment with nimodipine prevented the development of tonic muscle contraction and muscle spasms after SCI. Early treatment showed a greater reduction in spasticity than late treatment.
Hou et al.[20]	RCT with 4-groups (treadmill alone, treadmill and magnetic stimulation)	Bodyweight-supported treadmill training (Tm)	Yes	Gait analysis (CatWalk, three-dimensional kinematics) Spasticity	Velocity-dependent ankle torque (VDAT) Electromyograms (EMGs) during 12-degree dorsiflexion ankle rotation.	Tm initiated 8days after SCI reduced spasticity based on VDAT and EMGs at 4- and 7- weeks compared with controls. At week 7, the Tm group showed improved gait parameters compared with controls, and walking speeds similar to baseline
van Gorp et al.[21]	RCT with 3 groups: vehicle, no-injection, and intervention	Intraspinal grafting of clinical grade human fetal spinal cord-derived neural stem cells (HSSC) 3 days post-injury	No	Gait analysis Spasticity Pain	Gastrocnemius muscle resistance EMG during motor-driven ankle dorsiflexion.	In those with the most spasticity as measured by muscle resistance and EMG, HSSC-injection reduced spasticity compared with controls at 8- weeks post-injury

(Continued)

Table 3. (Continued)

Manuscript	Design	Intervention[a]	Baseline spasticity	Primary outcome	Spasticity measure(s)	Treatment effect
Avila-Martin et al.[24]	RCT with 5 groups, including a saline control.	Albumin (Alb), Oleic Acid (OA), Alb-OA, Alb-Elaidic Acid, intrathecal immediately after SCI and then every 3 days for 28 days	No	Motor recovery (rotarod) Pain Spasticity	EMG recordings of tibialis anterior (TA) activity during mid-thoracic electrical stimulation	Albumin, oleic acid, and Alb-OA reduced spasticity based on nociceptive reflex response of the TA at 28 days post-SCI compared with controls
Rabchevsky et al.[25]	Control trial, intervention v saline	One-time injections of gabapentin *versus* saline at 2 or 3 weeks post-SCI, 1 h before outcome measures	Yes	Autonomic dysreflexia Spasticity	5-point behavioral scale of tail responses to stimulation	Gabapentin reduced spasticity and AD compared with controls when administered at 2- and 3- weeks post-SCI
Advokat[26]	Control trial with 4 groups: acute, acute control group, chronic, and intact	Intrathecal clonidine, intrathecal saline control	No	Spasticity Pain (tail flick)	Tail flick response elicited by noxious stimulation. Hindlimb flexion reflex via electric stimulation	Intrathecal clonidine did not affect the tail flick response or hindlimb flexion reflex of acute spinal rats compared with intact rats
Duke and Advokat[27]	Control trial with 5 groups, three of which are acute: intact/pentobarbital(pento), SCI/pento, and SCI/saline	Single-dose of intraperitoneal pento, intraperitoneal saline 2 days after SCI.	No	Spasticity	30 min after injections: H-reflex and RDD Hindlimb flexion reflex via electric stimulation	No differences were seen in the H-reflex or flexion reflex in acute SCI with intraperitoneal pentobarbital. The RDD of the H-reflex in the pentobarbital group showed decreased amplitude and increased latency compared with controls

Alb, albumin; BBB, Basso, Beattie and Bresnahan; EMG, electromyogram; HSSC, human fetal spinal cord-derived neural stem cells; OA, oleic acid; RCT, Randomized control trial; RDD, rate-dependent depression; SCI, spinal cord injury; TA, tibialis anterior; TMSCS, treadmill training with spinal cord magnetic stimulation; VDAT, velocity-dependent ankle torque.
[a]Intervention performed within 4 weeks of SCI.

Table 4. Study design and outcomes of human trials reviewed.

Manuscript	Study design	Intervention	Primary outcome measure	Spasticity outcome measures	Spasticity required	Baseline spasticity	Primary outcome	Spasticity treatment effect	Power analysis for sample size?
Estes et al.[29]	4 week RCT	Lokomotor training (LT) ± transcutaneous spinal simulation (TSS)	10MWT, pendulum test	pendulum test, ankle clonus drop test, modified SCI-spasticity evaluation test (mSCI-SET), SCATS	Yes	pendulum degrees at baseline 60.22 [18]	improved walking speed and distance in LT + TSS through 4 weeks, not seen in sham group.	No significant changes in spasticity measures of quadriceps or ankle clonus. Effect sizes for all spasticity measures were small to medium	No, pilot trial
Derakhshanrad et al.[30]	double-blind RCT	7 daily subcutaneous administrations of 300 µg/day of granulocyte-colony stimulating factor (G-CSF)	ISNCSCI score change between groups	modified Ashworth Scale (MAS) to detect adverse events	No	not provided	Change in ISNCSCI motor score in the G-CSF group was 14.9 ± 2.6, which was significantly higher than that in the placebo group (1.4 ± 0.34, $p < 0.001$).	Two patients in each group showed increased spasticity. Two patients showed decreased spasticity in the experimental group	Sample size calculated to detect 5-point difference in the SCIM-III between two groups
Gharooni et al.[31]	Single-blind crossover RCT	rTMS iTBS	Feasibility measures for full-scale trial	Combined MAS of bilateral elbow and wrist extensors, LASIS, VAS-S of upper extremities	Yes	Combined MAS mean 11.7, range: 7.5–16.5	Authors consider full-scale trial feasible	Combined MAS decreased by 2.7 (–5.2 to –0.2)	No, pilot trial
Bye et al.[32]	Assessor blinded within-subject (right versus left limb) RCT	progressive resistance strength training	maximum voluntary isometric strength of trained limb	Ashworth Scale (AS) of trained limb	No	baseline AS mean (SD) 0.57 (0.97)	strength increased 4.3 Nm (95% CI, 1.9–6.8) but spans clinically meaningful 2.7 Nm	AS between-group difference 0.03 (–0.25 to 0.32)	Yes
Chhabra et al.[33]	Single-blind three-arm RCT	Intrathecal autologous bone marrow cell therapy (BMCT) versus BMCT at lesion versus control	1-year AIS change or change in total motor score (TMS) ≥10 points from baseline	MAS	No	Some, unclear	No change in AIS or TMS	MAS decreased by two grades in three subjects and by one grade in two subjects; Increased by one in two subjects	No pilot trial
Kumru et al.[28]	Double-blind RCT	Lokomat® plus rTMS v sham TMS	Not indicated, but 10MWT per clinicaltrials.gov	MAS at both knees	No	mean MAS 1.1 ± 0.8 at baseline	No significant change in 10MWT	No significant change in MAS seen from baseline in real or sham rTMS groups	No
Oo[34]	Single-blind RCT	Inpatient rehabilitaiton ± TENS at bilateral common peroneal nerve for 60 min weekdays × 3 weeks	Composite spasticity score (CSS): ankle jerk score, muscle tone score, ankle clonus score	CSS	Yes	CCS 11.8 ± 0.89	Reduced score of 2.13 in the CSS score between experimental versus placebo group ($p = 0.001$)	Primary outcome	Yes, based on CSS reduction of 29.5% and between-group difference of 0.71
Ralston et al.[35]	2-week crossover 1-week washout	Routine inpatient PT/OT ± FES cycling	Urine output	AS of quadriceps, hamstrings, calves, and hip adductors, totaled as one overall measure; PRISM	No	5.6 (4.6) 0–32 range	No significant change in urine output.	No significant group difference in AS and PRISM	No

AIS, ASIA impairment scale; BMCT, bone marrow cell transplant; CSS, composite spasticity score; FES, functional electric stimulation; G-CSF, granulocyte-colony stimulating factor; ISNCSCI, international standards for neurologic classification of SCI; iTBS, intermittent theta-burst stimulation; LASIS, Leeds Adult Spasticity Impact Scale; LT, Lokomotor training; MAS, Modified Ashworth Scale; 10MWT, 10 m walk test; PRISM, Patient Reported Impact of Spasticity Measure; RCT, randomized control trial; rTMS, repetitive transcranial magnetic stimulation; SCATS, spinal cord assessment tool for spastic reflexes; SCI, spinal cord injury; SCIM-III, spinal cord independence measure version 3; SD, standard deviation; TENS, transcutaneous electric nerve stimulation; TSS, transcutaneous spinal stimulation; VAS-S, visual analog scale of spasticity.

Table 5. Risk of bias in animal and human studies reviewed.

Animal manuscript[a]	Selection	Performance	Detection	Attrition	Reporting	Overall
Ryu *et al.*[22]	High	High	High	Low	Low	High
Hou *et al.*[23]	Low	High	High	Low	Low	High
Marcantoni *et al.*[19]	High	High	High	Low	Low	High
Hou *et al.*[20]	Low	High	High	Low	Low	High
van Gorp *et al.*[21]	Low	High	High	Low	Low	High
Avila-Martin *et al.*[24]	Low	High	High	Low	Low	High
Rabchevsky *et al.*[25]	High	High	High	Low	Low	High
Advokat[26]	High	High	High	Low	Low	High
Duke and Advokat[27]	High	High	High	Low	Low	High

Human manuscript	Randomization	Deviation from protocol	Outcome Measurement	Missing Data	Reporting	Overall
Estes *et al.*[29]	Low	Low	Low	Some	Some	Some
Derakhshanrad *et al.*[30]	Low	Low	Low	Low	Some	Low
Gharooni *et al.*[31]	Low	Some	Some	Some	Some	Some
Bye *et al.*[32]	Low	Low	Low	Low	Low	Low
Chhabra *et al.*[33]	Low	Some	Low	Some	Some	Some
Kumru *et al.*[28]	Some	Some	Low	Some	Some	Some
Oo[34]	Low	Low	Low	Low	Low	Low
Ralston *et al.*[35]	Low	Low	Low	Low	Low	Low

[a]If the manuscript did not report measures to decrease bias (for example, blinding of outcome assessors), we assumed these measures were not taken.

for two 20-min sessions, reduced spasticity based on velocity-dependent ankle torque (VDAT) measurements and EMG recording during ankle dorsiflexion at 4 and 7 weeks compared with controls. At week 7, the Tm group demonstrated improved gait parameters compared with injured, untrained controls, and gait speeds similar to their baseline pre-SCI measures. Using the same Tm protocol, Hou *et al.*[23] added magnetic spinal cord stimulation across the injury site along with Tm, beginning on week 2 post-injury every other day for 6 weeks. They were able to replicate the findings of their previous studies, demonstrating reduced spasticity in the TMSCS group at 4- and 8-weeks, as well as rate-dependent depression of the H-reflex in the TMSCS group appearing similar to noninjured controls at 10-weeks. In both studies, immunohistochemistry of the lumbar spinal cord showed increased expression of signal markers known to be involved in (1) regulation of excitability [gamma-aminobutyric acid (GABA)/GABAβ, glutamate decarboxylase (GAD67), and dopamine beta-hydroxylase (DβH)] and (2) neuroplasticity [brain-derived neurotrophic factor (BDNF)], compared with untreated injured controls.

van Gorp *et al.*[21] studied the effect of intraspinal grafting of human fetal spinal cord-derived neural stem cells 3 days post-injury in a rat L3 spinal compression model. In those with the most spasticity as measured by gastrocnemius muscle resistance and EMG during motor-driven ankle dorsiflexion, the interventional group had reduced

spasticity compared with both vehicle-controls and no-injection controls at 8 weeks post-injury.

Pharmacologic interventions. Ryu et al.[22] injected intraperitoneal escitalopram (selective serotonin reuptake inhibitor) *versus* saline for 28 days starting on Day 1 after SCI and measured outcomes at 3- and 4- weeks post-injury. They found a reduction of spastic behaviors during the swimming test, without significant electrophysiologic changes of the H-reflex or improved locomotor recovery. They also evaluated the expression of serotonin (5-hydroxytryptamine; 5-HT) and potassium-chloride cotransporter (KCC2) in spinal motor neurons in the lumbar spinal cords. Consistent with other studies,[37–39] the expression of 5-HT receptors was significantly higher in SCI compared with uninjured control animals, while KCC2 was reduced. The 5-HT upregulation was mitigated in the escitalopram group compared with the SCI vehicle control group. Escitalopram did not increase the expression of KCC2.

In the mouse model of SCI, Marcantoni et al.[19] administered nimodipine (L-type calcium channel blocker) or vehicle, subcutaneously daily for 6-weeks starting on Day 1 (early) or at Week 6 (late) after SCI. Early treatment with nimodipine prevented the development of tonic muscle contractions and muscle spasms in the mouse tail, compared with controls and the late treatment group. Spinal cord tissue histology of the early treatment group was not provided.

Avila-Martin et al.[24] evaluated the intrathecal administration of several medications immediately after SCI and then every third day for 28 days. Intrathecal administration of albumin (Alb), oleic acid (OA), and Alb-OA reduced spasticity based on nociceptive reflex response via EMG of the tibialis anterior at 28 days after SCI, compared with controls. Immunohistochemical analysis revealed an increase in 5-HT innervation density in the lumbar cord in the Alb-OA group compared with saline controls. This increased 5-HT expression, associated with reduced spasticity, seems to be opposite to the findings of Hou et al. As the authors note, however, there are many 5-HT receptor subtypes with mixed inhibitory and facilitatory neuronal effects. OA is an allosteric factor for the $5\text{-}HT7_A$ receptor, which is present in the dorsal horn and may play a role in analgesia. Thus, spasticity generated from noxious stimulus could be mediated by $5\text{-}HT7_A$ receptor activation.

Rabchevsky et al.[25] injected intraperitoneal gabapentin *versus* saline vehicle 2- and 3- weeks after SCI at 1 hr prior to outcome measurements. Gabapentin reduced spasticity as measured by a 5-point behavioral scale of tail responses to stimulation compared with controls at both 2- and 3-weeks after SCI. No spinal cord tissue histology was provided.

Advokat[26] administered intrathecal clonidine *versus* saline to rats 1 day after a complete transection SCI and tested their tail flick response and hind limb flexion reflex at 30, 60, and 90 min after injections. Early administration of intrathecal clonidine did not affect the spasticity outcome measures compared with saline controls. However, clonidine did reduce the hindlimb flexion response when administered in a more chronic stage of SCI (on average 31 days post-injury), commensurate with other studies. Finally, Duke and Advokat[27] injected intraperitoneal pentobarbital *versus* saline to rats 2 days after SCI and tested H-reflex and hindlimb flexion reflex 30 min after injection. They found mixed results, with no differences in the H-reflex or flexion reflex between groups, but the rate-dependent depression of the H-reflex showed decreased amplitudes and increased latency compared with the control group. No spinal cord tissue histology was reported for these studies.

Human trials. The human studies overall had 'low' to 'some concerns' for risk of bias (Table 5). Low concern was seen in the randomization and the outcome measurements. Some concerns for risk of bias were found in deviations from protocol, missing data, and the reporting of the findings. Only two of the studies had sufficient sample sizes based on power calculations to evaluate a treatment effect of the intervention, and only one measured spasticity as the primary outcome. First, Bye et al.[32] evaluated a progressive resistance strength training program in subacute SCI for the primary objective of improving maximum voluntary isometric strength of the trained limb, compared with the contralateral limb. The study was powered for the primary aim. They found a significant strength increase with this program, but the 95% confidence interval spanned the clinically meaningful treatment effect. Spasticity was measured using the AS as a secondary outcome comparing the trained *versus* contralateral

muscle. The mean AS at baseline of 0.57 (0.97) suggests that spasticity was present in many of the participants. They found no significant between-group differences in the AS after the trial.

The sample size in the study by Win Min Oo was calculated using the composite spasticity score (CSS) as the primary outcome measure, with the effect size estimated as a reduction of 29.5% from baseline and a between-group difference of 0.71.[40] They tested the effects of TENS applied to the bilateral common peroneal nerves for 60 min, 5 days weekly, for 3 weeks during inpatient rehabilitation, to reduce spasticity based on the CSS. After 3 weeks, the TENS group had reduced spasticity by 2.75 (99% CI: 1.31–4.19), about a 23.4% reduction from baseline. The between-group CSS difference was 2.13 (99% CI: 0.59–3.66). No significant changes in CSS were seen in the control group. Overall, the study was found to have a low risk of bias (Table 5).

Human pilot trials. Several pilot trials measured spasticity as a secondary outcome measure. Findings from these studies must be considered with an abundance of caution considering that the sample sizes used may not be able to determine a true treatment effect.

Neuromodulation. There were four studies that evaluated various neuromodulation techniques to improve SCI outcomes. The study by Ralston *et al.*[35] evaluated the effects of FES cycling on urine output in 14 subjects. They found no significant difference in the primary measure of urine output, nor a change in spasticity. The AS of the lower extremities was measured at the quadriceps, hamstrings, calves, and hip adductors, and summed up as one overall measure. The baseline AS was 5.6 (4.6) with a range of 0–32, indicating some spasticity in many of the patients. They also assessed spasticity with PRISM.

The study by Kumru *et al.*[28] assessed rTMS to improve the 10-m walk test (10MWT) in 31 subjects. They found no significant change between rTMS and sham TMS. Spasticity was measured by the MAS at both knees. At baseline, the mean MAS was 1.1 ± 0.8, and no significant change was seen after the trial. Gharooni *et al.*[31] also evaluated rTMS in a feasibility trial in 7 patients, with secondary outcomes of spasticity. They combined the MAS of the elbow and wrist extensors

(possible range 0–40) and had a baseline mean of 11.7 with a range of 7.5–16.5. They found that rTMS reduced the MAS by 2.67 (95% CI: −5.17 to −0.17). The LASIS and VAS-S, as well as their other outcome measures (motor, sensory, and functional), had 95% confidence intervals that spanned zero.

Finally, the study by Estes *et al.*[29] piloted transcutaneous spinal stimulation (TSS) in 16 subjects using several outcome measures, none of which achieved significance. At baseline, the pendulum test indicated that spasticity occurred at the quadriceps at a mean (SD) angle of about 60° (18) of first swing excursion angle. They did not detect a difference in spasticity with the use of TSS plus locomotor training compared with the controls. No other spasticity outcome measures detected a difference (ankle clonus drop test, mSCI-SET, SCATS). Interestingly, they did detect a difference in the 10MWT, with improved walking speed in the experimental group throughout the 4 weeks, an effect not seen in controls.

Biologics. Chhabra *et al.*[33] performed a three-armed RCT in 21 subjects of autologous bone marrow cell transplant in complete SCI and assessed the AIS and total motor score changes from baseline to 1 year. They did not find any significant changes in either outcome measures. Spasticity was measured using the MAS in unspecified areas of the body. They found that the MAS decreased in five subjects and increased in two subjects, none of which was considered significant.

Derakhshanrad *et al.*[30] performed an RCT in 54 subjects testing granulocyte-colony-stimulating factor (G-CSF) to detect ISNSCI score changes between groups. Changes in the motor scores were significantly greater in the G-CSF group (14.9 ± 2.6) compared with the placebo group (1.4 ± 034, $p < 0.001$). Spasticity was measured by the MAS in unspecified body areas. In each group, two patients showed increased spasticity. In the experimental group, two patients showed decreased spasticity.

Discussion

Given the prevalence of problematic spasticity, there is surprisingly little research being performed in the early period of SCI to identify ways

to prevent the development of this condition. In the past 20 years, our systematic review was able to identify only 17 control trials conducted in animals or humans early after SCI that included spasticity outcomes. Surprisingly, common clinical treatment options for spasticity were not studied as an early intervention in both animal and human studies, such as oral medications (baclofen, Tizanidine), injections (BoNT and phenol neurolysis), and intrathecal baclofen therapy. We offer several possible explanations: for the human studies, most studies did not focus on spasticity; concerns for negative effects on neurologic recovery; low prevalence of problematic spasticity during the early phase of SCI; and the perception that treatment should be reserved for when spasticity becomes problematic.[41] More well-designed clinical trials are needed to not only inform on the progression of spasticity and efficacy of early interventions, but to address concerns about possible harmful effects.

The underlying mechanisms of spasticity are not well understood. This imposes challenges to develop mechanism-targeted interventions and appropriate assessment. It is generally accepted that neurally mediated paresis after CNS damage (e.g. SCI) causes relative immobility, which in turn potentiates development of peripheral muscular adaptive changes, contracture, and development of spasticity. Muscle contracture and spasticity further aggravates paresis. Such vicious cycles evolve over time and greatly worsen motor function of spastic-paretic muscles.[42,43] The early period after injury is believed to be the most opportune time for neural plasticity after SCI.[44] Thus, intervention in the early period could potentially reduce the incidence of spasticity. Indeed, the literature on post-stroke spasticity supports this idea. Botulinum toxin (BoNT) therapy in the early period post-stroke with a mean injection time of 18 days reduced the development of spasticity and contracture.[45] Our real-world clinical data have also revealed that early BoNT injection leads to a much longer interval to repeat BoNT injection.[46]

There was great inconsistency among the outcome measures used to assess changes in spasticity in the human trials. In the eight human trials reviewed for this systematic review, there were eight different objective measures and four different subjective tools utilized. Similar to findings from other reviews on SCI spasticity, we found that the Ashworth Scale or Modified Ashworth Scale were most frequently used (seven of eight clinical trials, (88%)).[47,48] However, there was tremendous variability in their use. Variations in the muscles selected (i.e. elbows and wrist extensors *versus* quadriceps, hamstrings, calves, and hip adductors *versus* quadriceps and hamstrings), the comparisons varied (i.e. baseline *versus* contralateral control limb), and its use in the scoring of spasticity (i.e. combined scores of muscles tested *versus* change in individual muscles *versus* a calculation of the AS). Given that the MAS has only satisfactory inter- and intra-rater agreement, and is more reliable in the upper extremities, its varied use in these trials greatly limits the ability to group and compare results.[49] In the animal trials, eight of the nine trials (89%) utilized electrophysiologic outcome measures to describe changes that impact spasticity. Surprisingly, electrophysiologic measures were not used as measures impacting spasticity in the human trials, often found in the studies of spasticity in chronic SCI.[50–52] The lack of electrophysiologic measures in the human trials may represent the challenges to perform standardized electromyography and nerve conduction studies during early SCI.

We included animal studies in this systematic review to identify promising early interventions that may be translated to clinical application. Yet even though the majority of the animal studies reviewed support the notion that early interventions can mitigate the development of spasticity, only eight human SCI early interventional control trials included spasticity as an outcome measure. It would stand to reason that early interventional trials in human SCI, regardless of the primary objective, should include spasticity as an outcome measure that has the potential to be affected.

However, there is little evidence of direct translation based on these studies. This may be due to the delay in translation from animal to human studies.[53] It could also reflect the challenges in translation to human clinical trials. For example, many medications that were studied have unwanted side effects which could cause adverse events during early SCI, including unwanted decreases in blood pressure, fatigue, somnolence, and exacerbation of depression, which could negatively impact efforts to recover neurologic function in rehabilitation.[54] Invasive approaches, like the intrathecal route of administration, could reduce side effects, but peri-operative complications in the early period after SCI, like

surgical infections, could compromise recovery.[55] Improved partnership between animal researchers and clinician researchers is needed to expedite translation efforts in SCI research.

The only early SCI human trial addressing SCI spasticity as a primary outcome with an appropriate sample size to evaluate treatment effects was the Win Min Oo study. In this 3-week clinical trial, bilateral common peroneal nerve stimulation was performed for 60 min prior to usual care inpatient physical therapy in patients with new, traumatic SCI, 5 days weekly for 3 weeks. They found reduced spasticity in the lower extremities based on the CSS (also found to be called the composite spasticity index) in the TENS group compared with baseline as well as between the TENS group and the control group. There were several limitations in this study. It is unclear if the changes found in the CSS, around 3 points, is clinically meaningful. Based on the scoring of CSS (1–5 normal; 6–9 mild; 10–12 moderate; 13–16 severe), a 3-point CSS reduction may be clinically important. Also, the control group lacked sham-TENS, but relying on objective measures reduces concerns for a placebo effect. Finally, the study lacked sufficient outcome measures to determine sustained effects.

The presumed mechanism of TENS in spasticity reduction includes synaptic reorganization through afferent sensory inputs, in this case the common peroneal nerve (L4-S2).[56] Utilizing sub-motor current via TENS, the large type Ia sensory fibers of the common peroneal nerve were stimulated to modulate the interneurons at the level of the spinal cord and reduce spasticity. Indeed, a similar mechanism is proposed in TSS. The effects seen in TSS are presumably from the activation of the large-diameter afferent fibers of the peripheral nerve roots.[57] Our own work in neuromodulation in acute SCI using transcutaneous tibial nerve stimulation of the sensory fibers has provided similar evidence of decreasing spasticity, in this case, of the detrusor muscle.[58,59] An important aspect of our research has been to intervene prior to the development of problems. This effort has not been a focus with the development of spasticity in human SCI.

There were several limitations with this systematic review. First, we limited our search to publications after the year 1999, potentially missing earlier trials. We think this is unlikely considering the manuscripts we reviewed did not cite earlier publications as evidence, for or against, early intervention impacting spasticity in SCI. Also, only manuscripts written in English were reviewed, therefore it is possible we may have missed publications of trials written in other languages. It is also possible we missed animal studies that may have strong evidence to support early intervention to reduce the development of spasticity. Because we were specifically interested in treatment effect, rather than mechanism, we only reviewed manuscripts in which the abstract noted comparisons to active control groups. Given the clinical heterogeneity of interventions and outcome measures used in these studies, a metanalysis was not performed.[60] Finally, with only two of the eight human studies measuring spasticity as a primary outcome, the only conclusion that can be made is that translation of promising early interventions, identified in preclinical studies, for spasticity to human trials is lagging behind.

Conclusion

There is a paucity of clinical trials studying early interventions for prevention and treatment of post-SCI spasticity. Animal studies suggest that early interventions can mitigate the neurologic changes responsible for the development of spasticity. TENS appears to be a promising intervention to prevent the development of lower extremity spasticity in SCI. Considering the challenges in treatments after spasticity has developed, more research is needed to study early interventions to mitigate spasticity development and progression and the effects of these interventions on neurologic recovery.

Author contributions

Argyrios Stampas: Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Supervision; Validation; Writing – original draft; Writing – review & editing.

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Sheng Li: Writing – original draft; Writing – review & editing.

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Supplemental material
Supplemental material for this article is available online.

References
1. Holtz KA, Lipson R Noonan VK *et al.* Prevalence and effect of problematic spasticity after traumatic spinal cord injury. *Arch Phys Med Rehabil* 2017; 98: 1132–1138.

2. Adams MM and Hicks AL. Spasticity after spinal cord injury. *Spinal Cord* 2005; 43: 577–586.

3. Pandyan AD, Gregoric M, Barnes MP, *et al.* Spasticity: clinical perceptions, neurological realities and meaningful measurement. *Disabil Rehabil* 2005; 27: 2–6.

4. Anson CA and Shepherd C. Incidence of secondary complications in spinal cord injury. *Int J Rehabil Res* 1996; 19: 55–66.

5. Maynard FM, Karunas RS and Waring WP 3rd. Epidemiology of spasticity following traumatic spinal cord injury. *Arch Phys Med Rehabil* 1990; 71: 566–569.

6. Ko H-Y. Revisit spinal shock: pattern of reflex evolution during spinal shock. *Korean J Neurotrauma* 2018; 14: 47–54.

7. Atkinson PP and Atkinson JL. Spinal shock. *Mayo Clin Proc* 1996; 71: 384–389.

8. Elbasiouny SM, Moroz D, Bakr MM, *et al.* Management of spasticity after spinal cord injury: current techniques and future directions. *Neurorehabil Neural Repair* 2010; 24: 23–33.

9. Levasseur A, Mac-Thiong JM and Richard-Denis A. Are early clinical manifestations of spasticity associated with long-term functional outcome following spinal cord injury? A retrospective study. *Spinal Cord* 2021; 59: 910–916.

10. Barbosa P, Glinsky JV Fachin-Martins E *et al.* Physiotherapy interventions for the treatment of spasticity in people with spinal cord injury: a systematic review. *Spinal Cord* 2021; 59: 236–247.

11. Taricco M, Pagliacci MC Telaro E *et al.* Pharmacological interventions for spasticity following spinal cord injury: results of a Cochrane systematic review. *Eura Medicophys* 2006; 42: 5–15.

12. Lui J, Sarai M and Mills PB. Chemodenervation for treatment of limb spasticity following spinal cord injury: a systematic review. *Spinal Cord* 2015; 53: 252–264.

13. McIntyre A, Mays R, Mehta S, *et al.* Examining the effectiveness of intrathecal baclofen on spasticity in individuals with chronic spinal cord injury: a systematic review. *J Spinal Cord Med* 2014; 37: 11–18.

14. Fang CY, Tsai JL, Li GS, *et al.* Effects of robot-assisted gait training in individuals with spinal cord injury: a meta-analysis. *Biomed Res Int* 2020; 2020: 2102785.

15. Christofi G, Bch BM, Ashford S, *et al.* Improving the management of post-stroke spasticity: time for action. *J Rehabil Med Clin Commun* 2018; 1: 1000004.

16. Sterne JAC, Savović J Page MJ, *et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366: l4898.

17. Hooijmans CR, Rovers MM, de Vries RB, *et al.* SYRCLE's risk of bias tool for animal studies. *BMC Med Res Methodol* 2014; 14: 43.

18. Selecting studies and collecting data. In: Higgins JPT and Deeks JJ (eds) *Cochrane handbook for systematic reviews of interventions: The Cochrane Collaboration*, 2011, https://handbook-5-1.cochrane.org/chapter_7/7_selecting_studies_and_collecting_data.htm

19. Marcantoni M, Fuchs A, Löw P, *et al.* Early delivery and prolonged treatment with nimodipine prevents the development of

spasticity after spinal cord injury in mice. *Sci Transl Med* 2020; 12: eaay0167.

20. Hou J, Nelson R, Nissim N, *et al.* Effect of combined treadmill training and magnetic stimulation on spasticity and gait impairments after cervical spinal cord injury. *J Neurotrauma* 2014; 31: 1088–1106.

21. van Gorp S, Leerink M, Kakinohana O, *et al.* Amelioration of motor/sensory dysfunction and spasticity in a rat model of acute lumbar spinal cord injury by human neural stem cell transplantation. *Stem Cell Res Ther* 2013; 4: 57.

22. Ryu Y, Ogata T, Nagao M, *et al.* Early escitalopram administration as a preemptive treatment strategy against spasticity after contusive spinal cord injury in rats. *Sci Rep* 2021; 11: 7120.

23. Hou J, Nelson R, Mohammad N, *et al.* Effect of simultaneous combined treadmill training and magnetic stimulation on spasticity and gait impairments after cervical spinal cord injury. *J Neurotrauma* 2020; 37: 1999–2013.

24. Avila-Martin G, Galan-Arriero I, Gómez-Soriano J, *et al.* Treatment of rat spinal cord injury with the neurotrophic factor albumin-oleic acid: translational application for paralysis, spasticity and pain. *PLoS ONE* 2011; 6: e26107.

25. Rabchevsky AG, Patel SP, Duale H, *et al.* Gabapentin for spasticity and autonomic dysreflexia after severe spinal cord injury. *Spinal Cord* 2011; 49: 99–105.

26. Advokat C. Spinal transection increases the potency of clonidine on the tail-flick and hindlimb flexion reflexes. *Eur J Pharmacol* 2002; 437: 63–67.

27. Duke M and Advokat C. Pentobarbital-induced modulation of flexor and H-reflexes in spinal rats. *Brain Res* 2000; 881: 217–221.

28. Kumru H, Benito-Penalva J, Valls-Sole J, *et al.* Placebo-controlled study of rTMS combined with Lokomat(®) gait training for treatment in subjects with motor incomplete spinal cord injury. *Exp Brain Res* 2016; 234: 3447–3455.

29. Estes S, Zarkou A, Hope JM, *et al.* Combined transcutaneous spinal stimulation and locomotor training to improve walking function and reduce spasticity in subacute spinal cord injury: a randomized study of clinical feasibility and efficacy. *J Clin Med* 2021; 10: 1167.

30. Derakhshanrad N, Saberi H, Yekaninejad MS, *et al.* Subcutaneous granulocyte colony-stimulating factor administration for subacute traumatic spinal cord injuries, report of neurological and functional outcomes: a double-blind randomized controlled clinical trial. *J Neurosurg Spine* 2018; 30: 19–30.

31. Gharooni AA, Nair KPS, Hawkins D, *et al.* Intermittent theta-burst stimulation for upper-limb dysfunction and spasticity in spinal cord injury: a single-blind randomized feasibility study. *Spinal Cord* 2018; 56: 762–768.

32. Bye EA, Harvey LA, Gambhir A, *et al.* Strength training for partially paralysed muscles in people with recent spinal cord injury: a within-participant randomised controlled trial. *Spinal Cord* 2017; 55: 460–465.

33. Chhabra HS, Sarda K, Arora M, *et al.* Autologous bone marrow cell transplantation in acute spinal cord injury – an Indian pilot study. *Spinal Cord* 2016; 54: 57–64.

34. Oo WM. Efficacy of addition of transcutaneous electrical nerve stimulation to standardized physical therapy in subacute spinal spasticity: a randomized controlled trial. *Arch Phys Med Rehabil* 2014; 95: 2013–2020.

35. Ralston KE, Harvey L, Batty J, *et al.* Functional electrical stimulation cycling has no clear effect on urine output, lower limb swelling, and spasticity in people with spinal cord injury: a randomised cross-over trial. *J Physiother* 2013; 59: 237–243.

36. Wartenberg R. Pendulousness of the legs as a diagnostic test. *Neurology* 1951; 1: 18–24.

37. Kong XY, Wienecke J, Chen M, *et al.* The time course of serotonin 2A receptor expression after spinal transection of rats: an immunohistochemical study. *Neuroscience* 2011; 177: 114–126.

38. Ren LQ, Wienecke J, Chen M, *et al.* The time course of serotonin 2C receptor expression after spinal transection of rats: an immunohistochemical study. *Neuroscience* 2013; 236: 31–46.

39. Ryu Y, Ogata T, Nagao M, *et al.* The swimming test is effective for evaluating spasticity after contusive spinal cord injury. *PLoS ONE* 2017; 12: e0171937.

40. Ping Ho, Chung B and Kam Kwan Cheng B. Immediate effect of transcutaneous electrical nerve stimulation on spasticity in patients with spinal cord injury. *Clin Rehabil* 2010; 24: 202–210.

41. Lanig IS, New PW, Burns AS, *et al.* Optimizing the management of spasticity in people with spinal cord damage: a clinical care pathway for assessment and treatment decision making from the ability network, an international initiative. *Arch Phys Med Rehabil* 2018; 99: 1681–1687.

42. Gracies JM. Pathophysiology of spastic paresis. I: paresis and soft tissue changes. *Muscle Nerve* 2005; 31: 535–551.

43. Gracies JM. Pathophysiology of spastic paresis. II: emergence of muscle overactivity. *Muscle Nerve* 2005; 31: 552–571.

44. Fouad K, Krajacic A and Tetzlaff W. Spinal cord injury and plasticity: opportunities and challenges. *Brain Res Bull* 2011; 84: 337–342.

45. Lindsay C, Ispoglou S, Helliwell B, *et al.* Can the early use of botulinum toxin in post stroke spasticity reduce contracture development? A randomised controlled trial. *Clin Rehabil* 2021; 35: 399–409.

46. Woo J, Mas MF, Zhang J, *et al.* Real-world analysis of botulinum toxin (BoNT) injections in post-stroke spasticity: higher doses of BoNT and longer intervals in the early-start group. *J Neurol Sci* 2021; 425: 117449.

47. Biering-Sørensen F, Nielsen JB and Klinge K. Spasticity-assessment: a review. *Spinal Cord* 2006; 44: 708–722.

48. Hsieh JT, Wolfe DL, Miller WC, *et al.* Spasticity outcome measures in spinal cord injury: psychometric properties and clinical utility. *Spinal Cord* 2008; 46: 86–95.

49. Meseguer-Henarejos AB, Sánchez-Meca J, López-Pina JA, *et al.* Inter- and intra-rater reliability of the Modified Ashworth Scale: a systematic review and meta-analysis. *Eur J Phys Rehabil Med* 2018; 54: 576–590.

50. Murillo N, Kumru H, Vidal-Samso J, *et al.* Decrease of spasticity with muscle vibration in patients with spinal cord injury. *Clin Neurophysiol* 2011; 122: 1183–1189.

51. Manella KJ, Roach KE and Field-Fote EC. Temporal indices of ankle clonus and relationship to electrophysiologic and clinical measures in persons with spinal cord injury. *J Neurol Phys Ther* 2017; 41: 229–238.

52. Mori F, Koch G, Foti C, *et al.* The use of repetitive transcranial magnetic stimulation (rTMS) for the treatment of spasticity. *Prog Brain Res* 2009; 175: 429–439.

53. Moon LDF and Bradbury EJ. 'Chase': in dogged pursuit of a therapy for spinal cord injury. *Brain* 2018; 141: 941–943.

54. Wilkerson C and Dailey AT. Spinal cord injury management on the front line: ABCs of spinal cord injury treatment based on American Association of Neurological Surgeons/Congress of Neurological Surgeons Guidelines and Common Sense. *Neurosurg Clin N Am* 2021; 32: 341–351.

55. Kopp MA, Watzlawick R, Martus P, *et al.* Long-term functional outcome in patients with acquired infections after acute spinal cord injury. *Neurology* 2017; 88: 892–900.

56. Joodaki MR, Olyaei GR and Bagheri H. The effects of electrical nerve stimulation of the lower extremity on H-reflex and F-wave parameters. *Electromyogr Clin Neurophysiol* 2001; 41: 23–28.

57. Hofstoetter US, Freundl B, Binder H, *et al.* Common neural structures activated by epidural and transcutaneous lumbar spinal cord stimulation: elicitation of posterior root-muscle reflexes. *PLoS ONE* 2018; 13: e0192013.

58. Stampas A, Korupolu R, Zhu L, *et al.* Safety, feasibility, and efficacy of transcutaneous tibial nerve stimulation in acute spinal cord injury neurogenic bladder: a randomized control pilot trial. *Neuromodulation* 2019; 22: 716–722.

59. Stampas A, Gustafson K, Korupolu R, *et al.* Bladder neuromodulation in acute spinal cord injury via transcutaneous tibial nerve stimulation: cystometrogram and autonomic nervous system evidence from a randomized control pilot trial. *Front Neurosci* 2019; 13: 119.

60. Israel H and Richter RR. A guide to understanding meta-analysis. *J Orthop Sports Phys Ther* 2011; 41: 496–504.