The Journal of Spinal Cord Medicine

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/yscm20

Transcutaneous spinal cord stimulation effects on spasticity in patients with spinal cord injury: A systematic review

Anas R. Alashram, Elvira Padua, Manikandan Raju, Cristian Romagnoli & Giuseppe Annino

To cite this article: Anas R. Alashram, Elvira Padua, Manikandan Raju, Cristian Romagnoli & Giuseppe Annino (2021): Transcutaneous spinal cord stimulation effects on spasticity in patients with spinal cord injury: A systematic review, The Journal of Spinal Cord Medicine, DOI: 10.1080/10790268.2021.2000200

To link to this article: https://doi.org/10.1080/10790268.2021.2000200

Published online: 02 Dec 2021.

Submit your article to this journal

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=yscm20

Check for updates

Review

Transcutaneous spinal cord stimulation effects on spasticity in patients with spinal cord injury: A systematic review

Anas R. Alashram [1], Elvira Padua[2], Manikandan Raju[3], Cristian Romagnoli[4], Giuseppe Annino [5]

[1]Department of Physiotherapy, Isra University, Amman, Jordan, [2]Department of Human Sciences and Promotion of the Quality of Life, San Raffaele Roma Open University, Rome, Italy, [3]Clinical/Experimental Neuroscience and Psychology, Department of Neuroscience Umane, University of Sapienza, Rome, Italy, [4]PhD School in Science and Culture of Well-being and Lifestyle, Alma Mater University, Bologna, Italy, [5]Department of Medicine Systems, University of Rome "Tor Vergata", Rome, Italy

Context: Spasticity is one of the most prevalent impairments following spinal cord injury (SCI). It can lead to a decrease in the patient's functional level. Transcutaneous spinal cord stimulation (tSCS) has demonstrated motor function improvements following SCI. No systematic reviews were published examining the influences of tSCS on spasticity post-SCI.
Objectives: This review aimed to investigate the effects of tSCS on spasticity in patients with SCI.
Methods: PubMed, SCOPUS, PEDro, CINAHL, MEDLINE, REHABDATA, AMED, and Web of Science databases were searched until June 2021. The Physiotherapy Evidence Database (PEDro) scale was used to assess the methodological quality of the selected studies.
Results: Six studies met the inclusion criteria. Five studies were pilot studies, and one was a case series. The scores on the PEDro scale ranged from two to four, with a median score of four. The results showed heterogenous evidence for the effects of tSCS on spasticity reduction post-SCI.
Conclusions: TSCS appears safe and well-tolerated intervention in patients with SCI. The evidence for the effectiveness of tSCS on spasticity in chronic SCI patients is limited. Further randomized controlled studies are strongly needed to study the effects of tSCS on patients with SCI.

Keywords: Spinal cord stimulation, Spasticity, Spinal cord injuries, Rehabilitation, Therapy

Introduction

Spinal cord injury (SCI) is a leading cause of disability and morbidity worldwide.[1] Spasticity occurs in the upper motor neuron injury (above T12/L1).[2] Approximately 70% of patients with SCI exhibit spasticity.[3] Spasticity is characterized by increases in muscle tone, hyperreflexia, clonus sign, and muscle spasms, which can reduce a patient's functional level.[4–6]

Spasticity is caused by lesions of descending pathways.[7] It results from the loss of monoaminergic modulation of spinal interneurons and motoneurons. Also, it can result from plastic changes at the cellular level to compensate for the loss of these neuromodulators below the lesion level.[8,9] Consequences of spasticity are: Firstly, reduced depression of neurotransmitter release from Ia muscle spindle afferents upon their repeated activation.[10] Secondly, hyper-excitability of interneurons that mediate polysynaptic excitation [9]. Thirdly, a decrease in the inhibitory capacity of post-synaptic inhibitory circuits.[11] And fourthly, an increase in motoneuronal excitability.[12] Morphological changes in muscles and connective tissue secondary to spastic conditions may further accentuate resistance to passive stretch.[13]

Medications such as Botulinum toxin and Baclofen are commonly used for reducing spasticity post-SCI.[14,15] However, common adverse effects for these agents include muscle weakness, malaise, and pain at the injection site.[14,15] Despite their widespread use, there is inadequate evidence to guarantee

Corresponding to: Anas R. Alashram, Department of Physiotherapy, Isra University, Amman, Jordan. Email: anasalashram@gmail.com

© The Academy of Spinal Cord Injury Professionals, Inc. 2021
DOI 10.1080/10790268.2021.2000200

pharmacological agents for spasticity reduction.[16] In the last decade, many physical therapy modalities were prescribed for reducing spasticity and improving functional ability in patients with SCI and other neurological disorders.[17–22] However, they have disadvantages such as time-consuming and high cost.

Transcutaneous spinal cord stimulation (tSCS) reported unprecedented motor function improvements following severe SCI.[23] The computational modeling,[24] human physiological studies,[25–27] and microdialysis techniques in animal experiments suggest that spinal cord stimulation can recruit local inhibitory spinal circuits through stimulation of afferent fibers and promote the release of inhibitory neurotransmitters.[28,29] TSCS increases spinal reflex activity through evoked Hoffmann-like reflex (H-reflex) activity that may result from activation of proprioceptive afferents within the dorsal roots.[30–32] The non-invasive spinal stimulation may also evoke motor outcomes by facilitating spinal and residual supraspinal motor pathways.[31,32] To date, there are no systematic reviews published examining the impacts of tSCS on spasticity post-SCI. Therefore, this systematic review aimed to investigate the effects of tSCS on spasticity in patients with SCI.

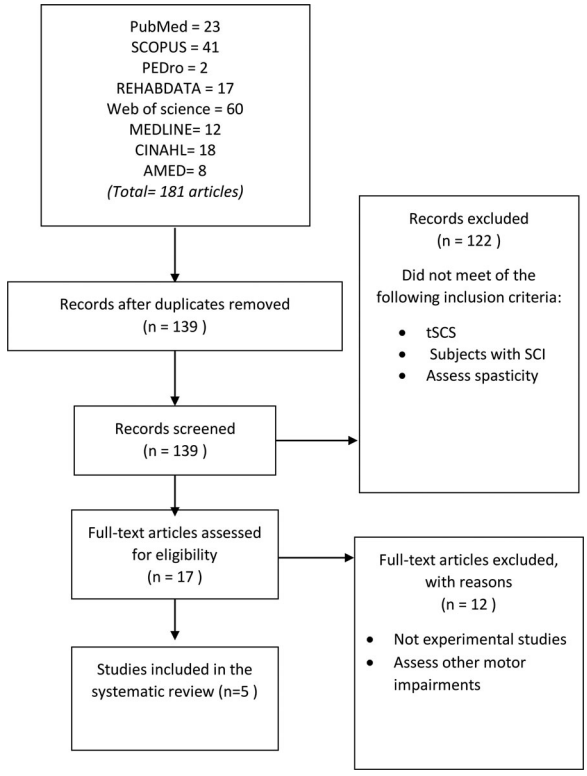

Figure 1 Summary of literature review process.

Methods

Search strategy

PubMed, SCOPUS, PEDro, CINAHL, MEDLINE, REHABDATA, AMED, and Web of Science databases were searched from inception to June 2021. The key search terms were: ("transcutaneous spinal cord stimulation" OR "tSCS" OR "spinal cord stimulation)" AND ("Spinal cord injuries [Mesh]" OR "SCI)" AND ("muscle spasticity [Mesh]" OR "muscle stiffness" OR "muscle hypertonia [Mesh]" OR "tone)" AND (Appendix A). Two authors independently identified the related studies according to the inclusion and exclusion criteria. The current study followed all guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) approach.[33] The process of study selection was presented in Figure 1.

Selection criteria

Patients, Intervention, Control, Outcomes, and Study design (PICOS) approach was followed.[34] Studies were included in the systematic review if they (a) P: assessed patients with SCI; I: tSCS; C: compared with active, passive, or no control groups; O: examined spasticity; and S: any study design published in English. Studies were excluded if they (a) assessed patients with other neurological (i.e. traumatic brain injury, multiple sclerosis) or musculoskeletal (i.e. fractures) disorders, (b) used animal models, and (c) combined tSCS with other stimulation forms (i.e. tDCS, rTMS). Two authors independently screened the included studies by reading titles and abstracts of the extracted research papers. If the abstracts were ambiguous and had no sufficient details, the authors would read the full text to make the final decision. Disagreements between the authors were resolved by discussion with the third author.

Data extraction

Upon selection process, the following data and descriptive information were extracted: (a) study design, (b) characteristics of the study, (c) parameters of tSCS and treatment protocols, (d) outcomes for pre and post-treatment in experimental and control groups, and (e) harm or adverse effects. The data were not pooled for meta-analysis because of the heterogeneity and the inability to contact the authors of the included studies.

Quality assessment

Two authors evaluated the methodological quality of the included studies using the Physiotherapy Evidence Database scale (PEDro). It provides a summary of the internal and external validity of the studies.[35] Four items of the PEDro scale have been validated, while the other points have face validity.[36] As well, acceptable

inter-rater reliability has been verified.[35,37] Table 1 displays the methodological quality scores for the included studies.

Results

Search strategy

An electronic search of PubMed (yielding 23 articles), SCOPUS (41), PEDro (2), REHABDATA (17), MEDLINE (12), CINAHL (18), AMED (8), and Web of Science (60) produced a total of 181 citations. After removing duplicates, 139 citations were reviewed. Of those, 122 publications were excluded because their abstracts showed that they did not match the inclusion criteria. After that, seventeen publications were subjected to more detailed analysis because the abstracts did not reveal the inclusion criteria. Subsequently, twelve articles were eliminated because they are not experimental studies and assessed other motor

Table 1 Study characteristics.

Study	Participants characteristics and study design	Protocol	Intervention	Adverse effects
Hofstoetter *et al.* 2014[38]	Study design: Case series Sample size: 3 Sex (M/F): 2/1 Age (Mean): 32.7 ASIA: D Neurological level: C5, T9 Time since injury (months): >12	Device: Schwamedico GmbH, Ehringshausen, Germany Size (cm^2): 25 Frequency (Hz): 50 Pulse width (ms): 2 biphasic rectangular pulses Duration (min): 30 Sessions (n): 1	Single session of tSCS Two interconnected stimulating skin electrodes were placed paraspinally at the T11/T12 vertebral levels, and two rectangular electrodes (8 × 13 cm) on the abdomen for the reference	No
Freyvert *et al.* 2018[39]	Study design: Pilot Sample size: 6 Sex (M/F): 4/2 Age (Mean): 19.1 ASIA: B Neurological level: C2-C6 Time since injury (months): >12	Device: NA Intensity (mA): 20–100 Frequency (Hz): 5–30 Duration: 60–120 Sessions (n): NS/6 weeks	tSCS + Drug (buspirone) + Grip strength exercises Cathode was placed over C5 and reference electrode was placed over the anterior superior iliac spine	No
Sayenko *et al.* 2018[40]	Study design: Pilot Sample size: 15 Sex (M/F): 12/3 Age (Mean): 31.2 ASIA: A,B,C Neurological level: C4-T2 Time since injury (months): >12	Device: A custom-built constant current stimulator Intensity (mA): 150 Current density (mA/cm^2): 15 Size (cm^2): 10 Pulse width (ms):1 monophasic pulses Frequency (Hz): 0.2–30 Duration (min): 120 Sessions (n): 12 3/wk for 4 wks	tSCS + Postural control exercises Cathode: between the spinous processes of the T11-T12 or L1-L2 vertebrae Anode: over the iliac crests	No
Hofstoetter *et al.* 2020[41]	Study design: Pilot Sample size: 12 Sex (M/F): 9/3 Age (Mean): 41.3 ASIA: A, C, D Neurological level: C4-T7 Time since injury (months): >12	Device: Schwamedico GmbH, Ehringshausen, Germany Pulse width (ms): 1 biphasic rectangular pulses Size (cm^2): 25 Frequency (Hz): 50 Duration: 30 Sessions (n): 1	Single session of tSCS Two interconnected stimulating skin electrodes were placed paraspinally at the T11/T12 vertebral levels, and two rectangular electrodes (8 × 13 cm) on the abdomen for the reference	No
Inanici *et al.* 2021[42]	Study design: Pilot Sample size: 6 Sex (M/F): 4/2 Age (Mean): 42 ASIA: C3-C5 Neurological level: B,C,D Time since injury (months): >12	Device: now ONWARD Medical BV, Eindhoven, Netherlands Intensity (mA): 0–120 Size (cm^2): 6 Frequency (Hz): 30 Duration (min): 120 Sessions (n): 8	tSCS + 24-session Upper extremity motor training Cathodes: were placed midline on the skin of the neck, one above and one below the injury level Anodes: were placed symmetrically over the anterior iliac crests of pelvis.	No

NS: Not Specified, M/F: Male/Female, tSCS: transcutaneous spinal cord stimulation.

impairments. A total of five studies were identified for the inclusion criteria in this systematic review. The process of article selection for systematic review was displayed in Figure 1.

Study characteristics

Participants

A total of forty-two patients were included in this analysis, 26.20% of whom were females. The mean age for all patients was 34.01 years old. In terms of the injury severity, two studies included patients with incomplete SCI with grade B[38] and grade D on the Americans Spinal Cord Injury Association (ASIA) scale,[39] and three studies included patients with mixed SCI (i.e. complete and incomplete) with various grades (i.e. A, B, C, D).[40–42] Concerning the injury level, the selected studies included SCI patients with an injury level (C3-T9).[38–42] All the selected studies included patients with chronic SCI (>12 months). The study characteristics were presented in Table 1.

Intervention

Five studies were met the inclusion criteria. Four studies were pilot studies [39–42], and one was a case series.[38] Two studies administrated a single session of tSCS on patients with SCI using (SchwamedicoGmbH, Ehringshausen, Germany) stimulator for 30 minutes.[38,41] Two interconnected stimulating skin electrodes were placed paraspinally at the T11/T12 vertebral levels and two rectangular electrodes (8 × 13 cm) on the abdomen for reference. Both studies used active electrode sizes of 25 cm^2, frequencies of 50 Hz, and 1–2 ms biphasic rectangular pulses.

In the study of Freyvert *et al*. (2018), the participants received combined tSCS, drug (buspirone), and grip strength exercises intervention for 60–120 minutes over six weeks, with no specific session number. The type of tSCS device was not reported in the study. The cathodes were placed over the C5 of a spine, while the anodes were placed over the anterior superior iliac spine as a reference. The intensity was set at 20–100 mA and frequency at 5–30 Hz.[39]

Moreover, the participants in the study by Sayenko *et al.* (2018) received tSCS plus postural control exercises intervention using a custom-built constant current stimulator for 30 minutes, three times per week, for four weeks. The cathodes were placed between the spinous processes of the T11-T12 or L1-L2 vertebrae, while the anodes were placed over the iliac crests as a reference. The size of the active electrodes that were used is 10 cm^2, the pulse width was 1 monophasic pulse, the current density was 15 mA/cm^2, the intensity was 150 mA, and the frequency was 0.2–30 Hz.[40]

Finally, in the study of Inanici *et al.* (2021), the participants received eight sessions of tSCS using (now ONWARD Medical BV, Eindhoven, Netherlands) device plus twenty-four sessions of upper extremity motor training. The session duration was 120 minutes each. The tSCS was administrated a single time per week over two months. The upper extremity motor training was applied three times weekly over two months. In the tSCS treatment session, the cathode electrodes were placed midline on the skin of the neck, one above and one below the injury level, while the anodes were placed symmetrically over the anterior iliac crests of the pelvis as a reference. The size of active electrodes was 6 cm^2, the intensity was set at 0–120 mA, and frequency at 30 Hz.[42]

Outcome measures

Except for the study of Hofstoetter *et al*. (2014),[38] the selected studies used the Modified Ashworth Scale (MAS) to assess spasticity in patients with SCI [39–42]. Hofstoetter *et al*. (2014) used the index of spasticity derived from the pendulum test[38] (Table 2).

Effects of tSCS on spasticity after SCI

In two studies, both quadriceps[38] and lower extremities muscle spasticity[41] were reduced after the tSCS intervention. Moreover, in the other two studies, the participants showed a reduction in the upper extremities' spasticity following combined tSCS interventions.[39,42] The spasticity reduction was maintained up to 10–15 days after the intervention.[42] Finally, in the study by Sayenko *et al*. (2018), the lower extremities muscle tone wan increased in severe paralyzed SCI patients after tSCS plus postural control exercises intervention.[40]

Adverse effects

The included studies did not show any adverse effects or harmful complications in patients with SCI after the tSCS interventions.[38–42]

Quality assessment

The score on the PEDro scale ranged from two to four, with a median of four. Overall, three studies met two criteria,[38,41,42] and two met four criteria[39,40] for low risk of bias. Table 3 displays the methodological quality scores for the included studies.

Discussion

To our knowledge, this is the first systematic review examining the impacts of tSCS on spasticity post-SCI. The main findings based on six studies showed

Table 2 Outcome measures.

Study	Outcome measure	Time of assessment	Intervention outcomes	Results
Hofstoetter *et al.* 2014[38]	Index of spasticity-pendulum test	At baseline and post intervention	Pre: 0.8 ± 0.4 Post: 0.9 ± 0.3	Spasticity of both quadriceps was reduced after tSCS
Freyvert *et al.* 2018[39]	MAS	At baseline and post intervention	Pre: 2 Post: 1+	Spasticity of both upper extremities was reduced after tSCS
Sayenko *et al.* 2018[40]	MAS	At baseline and post intervention	Pre: 0 Post: 1+	Lower extremities muscle tone increased in severe paralyzed patients
Hofstoetter *et al.* 2020[41]	*MAS	T0: baseline, T1: post intervention, and T2: 2 hours post intervention	T0: 31.75 (8.63–37.38) T1: 23.50 (14.63–32.25) T2: 24.75 (13.25–30.88)	Spasticity in lower extremities was reduced after tSCS
Inanici *et al.* 2021[42]	**MAS	At baseline, post intervention, and follow-up	3.5 ± 3.0	Reduction in upper extremity spasticity was progressive throughout stimulation sessions and maintained up to 10–15 days after stimulation treatment ended

MAS: Modified Ashworth Scale, tSCS: transcutaneous spinal cord stimulation.
*Median (interquartile range (IQR)).
**The average decrease in MAS score.

heterogenous evidence for the positive effects of tSCS on spasticity in patients with SCI. Similarly, Hofstoetter *et al.* (2021) demonstrated a significant reduction in spasticity in a patient with multiple sclerosis after receiving tSCS.[43] Megía García *et al.* (2020) showed improvements in motor functions, including voluntary movement, muscle strength, and function, in patients with chronic SCI after the tSCS intervention.[44]

Presynaptic inhibition from homonymous and heteronymous nerves is reduced after SCI,[45] thus the post-activation depression of repetitively activated Ia afferents.[9,10,46] Dysfunction in these presynaptic regulatory mechanisms after SCI results in an increased excitatory neurotransmitter release from Ia afferents. It contributes to the exaggerated stretch reflexes and hypertonia associated with spasticity.[9,14] The continuous generation of Ia activity in multiple roots by tSCS, especially in those containing afferents from flexor nerves, would increase the level of presynaptic inhibition distributed to Ia terminals connected with ipsilateral limb muscles.[26,47,48] Further, tSCS increases spinal reflex activity through evoked Hoffmann-like reflex activity resulting from activation of proprioceptive afferents.[30–32]

The MAS[49] and the pendulum tests were used in the selected studies to assess spasticity in patients with SCI. The pendulum test correlates with the MAS in patients with SCI.[50] These measures were complemented by the assessments of other presentations of spasticity, such as clonus and muscle spasms.[9] The latter being pathophysiologically distinct from exaggerated stretch reflexes.[9] Except for the study of Sayenko *et al.* (2018),[40] the selected studies showed positive effects of the tSCS intervention on spasticity in patients with chronic SCI.[38,39,41,42] The patients in the selected studies were chronic (>6 months) with various ASIA scale grades and injury levels. The session duration and frequency for the selected studies were 30–120 minutes per session, with sessions range 1–12 sessions. The treatment dosage, including the electrode site, intensity, frequency, pulse width, and electrode size was varied between the selected studies. It makes determining the population who most likely would benefit from the intervention, long-term effects, and the optimal treatment dosage is difficult.

The current review included four pilot studies and one case series with a methodological quality ranged from two to four, with a median of four. The methodological quality for the included studies was poor on the PEDro scale (range 2–4); hence, the clinical effects cannot be confirmed. Besides, the sample size for the selected studies was small (>20). As a small sample size, the calculation of the significant difference was difficult.[51] Thus, we cannot generalize and confirm the effects of the tSCS treatment in patients with SCI. Due to the insufficiency of randomized controlled trials, small sample sizes, poor methodological quality, and various tSCS treatment protocols used in the treatment of patients with SCI, it makes us unable to recognize the actual impacts of the tSCS treatment

Table 3 Methodological quality scores.

Study	Randome allocation	Concealed allocation	Groups similar at baseline	Participant blinding	Therapist blinding	Assessor blinding	<15% dropouts	Intention to treat analysis	Between-group differences reported	Point estimate and variability reported	Total (0–10)
Hofstoetter *et al.* 2014[38]							*	*			2
Freyvert *et al.* 2018[39]				*		*	*	*			4
Sayenko *et al.* 2018[40]				*		*	*	*			4
Hofstoetter *et al.* 2020[41]							*	*			2
Inanici *et al.* 2021[42]							*	*			2
Median = 4											

*Low risk of bias.

on spasticity in patients with SCI as it has a negative impact on patient's quality of life. Finally, as the studies included only chronic SCI, so we are unable to clarify the effects of tSCS on spasticity in those with acute and subacute SCI. Further high-quality studies with a large sample size and long-term follow-up are strongly warranted.

The present study has some limitations. First, the selected studies were published in English. Thus, studies published in alternate languages were not included in the analysis. Second, it included only pilot studies and case series due to the lack of randomized clinical trials on the present subject. Finally, the meta-analysis was not performed due to the heterogeneity between the included studies.

Conclusion

The tSCS intervention is safe and feasible in patients with SCI. The evidence for the effects of tSCS on spasticity in patients with SCI is limited. Further high-quality studies are strongly needed to study the impact of tSCS on patients with SCI.

Disclaimer statements

Funding The authors have no source of funding.

Acknowledgements None

Conflict of interest The authors have no potential conflicts of interest to disclose.

ORCID

Anas R. Alashram http://orcid.org/0000-0002-3066-3943

Giuseppe Annino http://orcid.org/0000-0001-8578-6046

References

1 Braddom R. Physical Medicine and Rehabilitation. 3rd ed. Philadelphia (PA): Saunders Elsevier; 2007.
2 Burchiel KJ, Hsu FP. Pain and spasticity after spinal cord injury: mechanisms and treatment. Spine (Phila Pa 1976) 2001;26(24 Suppl):S146–S160.
3 Rekand T, Hagen E, Grønning M. Spastisitet etter ryggmargsskade. Tidsskrift for Den norske legeforening 2012;132(8):970–3.
4 Sheean G. The pathophysiology of spasticity. Eur J Neurol 2002;9 (Suppl 1):3–9.
5 Rabchevsky AG, Kitzman PH. Latest approaches for the treatment of spasticity and autonomic dysreflexia in chronic spinal cord injury. Neurotherapeutics 2011;8(2):274–82.
6 Gorgey AS, Chiodo AE, Zemper ED, Hornyak JE, Rodriguez GM, Gater DR. Relationship of spasticity to soft tissue body composition and the metabolic profile in persons with chronic motor complete spinal cord injury. J Spinal Cord Med 2010;33 (1):6–15.
7 Trompetto C, Marinelli L, Mori L, Pelosin E, Currà A, Molfetta L, Abbruzzese G. Pathophysiology of spasticity: implications for neurorehabilitation. Biomed Res Int 2014; 2014:354906.
8 Jankowska E, Hammar I, Chojnicka B, Hedén CH. Effects of monoamines on interneurons in four spinal reflex pathways

from group I and/or group II muscle afferents. Eur J Neurosci 2000;12(2):701–14.
9 Nielsen J, Willerslev-Olsen M, Lorentzen J. Pathophysiology of spasticity. In: Pandyan A, Hermens H, Conway B, (eds.) Neurological Rehabilitation. Spasticity and Contractures in Clinical Practice and Research. Boca Raton: Imprint CRC Press; 2018. p. 25–57.
10 Grey MJ, Klinge K, Crone C, Lorentzen J, Biering-Sørensen F, Ravnborg M, Nielsen JB. Post-activation depression of soleus stretch reflexes In healthy and spastic humans. Exp Brain Res 2008;185(2):189–97.
11 Boulenguez P, Liabeuf S, Bos R, Bras H, Jean-Xavier C, Brocard C, *et al.* Down-regulation of the potassium-chloride cotransporter KCC2 contributes to spasticity after spinal cord injury. Nat Med 2010;16(3):302–7.
12 Murray KC, Stephens MJ, Ballou EW, Heckman CJ, Bennett DJ. Motoneuron excitability and muscle spasms are regulated by 5-HT_{2B} and 5-HT_{2C} receptor activity. J Neurophysiol 2011;105(2): 731–48.
13 Schubert M, Dietz V. Clinical management of spasticity and contractures in spinal cord injury. In: Pandyan A, Hermens H, Conway B, (eds.) Neurological Rehabilitation. Spasticity and Contractures in Clinical Practice and Research. Boca Raton: Imprint CRC Press; 2018. p. 135–73.
14 Elbasiouny SM, Moroz D, Bakr MM, Mushahwar VK. Management of spasticity after spinal cord injury: current techniques and future directions. Neurorehabil Neural Repair 2010; 24(1):23–33.
15 Kirshblum S. Treatment alternatives for spinal cord injury related spasticity. J Spinal Cord Med 1999;22(3):199–217.
16 Taricco M, Adone R, Pagliacci C, Telaro E. Pharmacological interventions for spasticity following spinal cord injury. Cochrane Database Syst Rev 2000;2:CD001131.
17 Alashram AR, Annino G, Mercuri NB. Rhythmic auditory stimulation in gait rehabilitation for traumatic brain and spinal cord injury. J Clin Neurosci 2019;69:287–8.
18 Alashram AR, Padua E, Annino G. Effects of whole-body vibration on motor impairments in patients with neurological disorders: a systematic review. Am J Phys Med Rehabil 2019;98(12): 1084–98.
19 Alashram AR, Annino G, Mercuri NB. Changes in spasticity following functional electrical stimulation cycling in patients with spinal cord injury: a systematic review [published online ahead of print, 2020 May 14]. J Spinal Cord Med 2020;14:1–14.
20 Annino G, Alashram AR, Alghwiri AA, Romagnoli C, Messina G, Tancredi V, *et al.* Effect of segmental muscle vibration on upper extremity functional ability poststroke: a randomized controlled trial. Medicine (Baltimore) 2019;98(7):e14444.
21 Alashram AR, Padua E, Romagnoli C, Annino G. Effectiveness of focal muscle vibration on hemiplegic upper extremity spasticity in individuals with stroke: A systematic review. NeuroRehabilitation 2019;45(4):471–81.
22 Alashram AR, Annino G, Al-qtaishat M, Padua E. Mental practice combined with physical practice to enhance upper extremity functional ability poststroke: a systematic review. Journal of Stroke Medicine 2020;3(2):51–61.
23 Gill ML, Grahn PJ, Calvert JS, Linde MB, Lavrov IA, Strommen JA, *et al.* Neuromodulation of lumbosacral spinal networks enables independent stepping after complete paraplegia [published correction appears in Nat Med. 2018 Oct 23]. Nat Med 2018;24(11):1677–82.
24 Moraud EM, Capogrosso M, Formento E, Wenger N, DiGiovanna J, Courtine G, Micera S. Mechanisms underlying the neuromodulation of spinal circuits for correcting gait and balance deficits after spinal cord injury. Neuron 2016;89(4): 814–28.
25 Pinter MM, Gerstenbrand F, Dimitrijevic MR. Epidural electrical stimulation of posterior structures of the human lumbosacral cord: 3. control Of spasticity. Spinal Cord 2000;38(9):524–31.
26 Hunter JP, Ashby P. Segmental effects of epidural spinal cord stimulation in humans. J Physiol 1994;474(3):407–19.
27 Hofstoetter US, Danner SM, Freundl B, Binder H, Mayr W, Rattay F, Minassian K. Periodic modulation of repetitively elicited monosynaptic reflexes of the human lumbosacral spinal cord. J Neurophysiol 2015;114(1):400–10.
28 Simpson RK Jr, Robertson CS, Goodman JC, Halter JA. Recovery of amino acid neurotransmitters from the spinal cord during posterior epidural stimulation: a preliminary study. J Am Paraplegia Soc 1991;14(1):3–8.
29 Simpson RK Jr, Robertson CS, Goodman JC. Segmental recovery of amino acid neurotransmitters during posterior epidural stimulation after spinal cord injury. J Am Paraplegia Soc 1993;16(1): 34–41.
30 Minassian K, Persy I, Rattay F, Dimitrijevic MR, Hofer C, Kern H. Posterior root-muscle reflexes elicited by transcutaneous stimulation of the human lumbosacral cord. Muscle Nerve 2007;35(3): 327–36.
31 Danner SM, Hofstoetter US, Ladenbauer J, Rattay F, Minassian K. Can the human lumbar posterior columns be stimulated by transcutaneous spinal cord stimulation? A modeling study. Artif Organs 2011;35(3):257–62.
32 Ladenbauer J, Minassian K, Hofstoetter US, Dimitrijevic MR, Rattay F. Stimulation of the human lumbar spinal cord with implanted and surface electrodes: a computer simulation study. IEEE Trans Neural Syst Rehabil Eng 2010;18(6):637–45.
33 Moher D, Liberati A, Tetzlaff J, Altman D. Reprint—preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Phys Ther 2009;89(9):873–80.
34 Liberati A. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009;151(4):65–94.
35 Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. Phys Ther 2003;83(8):713–21.
36 Moher D, Cook DJ, Jadad AR, P. Tugwell, M. Moher, A. Jones, B. Pham, T.P. Klassen Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses. Health Technol Assess 1999;3(12):1–98.
37 Foley NC, Bhogal SK, Teasell RW, Bureau Y, Speechley MR. Estimates of quality and reliability with the physiotherapy evidence-based database scale to assess the methodology of randomized controlled trials of pharmacological and nonpharmacological interventions. Phys Ther 2006;86(6):817–24.
38 Hofstoetter US, McKay WB, Tansey KE, Mayr W, Kern H, Minassian K. Modification of spasticity by transcutaneous spinal cord stimulation in individuals with incomplete spinal cord injury. J Spinal Cord Med 2014;37(2):202–11.
39 Freyvert Y, Yong NA, Morikawa E, Zdunowski S, Sarino ME, Gerasimenko Y, *et al.* Engaging cervical spinal circuitry with non-invasive spinal stimulation and buspirone to restore hand function in chronic motor complete patients. Sci Rep 2018;8(1): 15546. Published 2018 Oct 19.
40 Sayenko DG, Rath M, Ferguson AR, Burdick JW, Havton LA, Edgerton VR, Gerasimenko YP. Self-assisted standing enabled by non-invasive spinal stimulation after spinal cord injury. J Neurotrauma 2019;36(9):1435–50.
41 Hofstoetter US, Freundl B, Danner SM, Krenn MJ, Mayr W, Binder H, Minassian K. Transcutaneous spinal cord stimulation induces temporary attenuation of spasticity in individuals with spinal cord injury. J Neurotrauma 2020;37(3):481–93.
42 Inanici F, Brighton LN, Samejima S, Hofstetter CP, Moritz CT. Transcutaneous spinal cord stimulation restores hand and arm function after spinal cord injury [published online ahead of print, 2021 Jan 5]. IEEE Trans Neural Syst Rehabil Eng 2021; 29:310–319. doi:10.1109/TNSRE.2021.3049133.
43 Hofstoetter US, Freundl B, Lackner P, Binder H. Transcutaneous spinal cord stimulation enhances walking performance and reduces spasticity in individuals with multiple sclerosis. Brain Sci 2021;11(4):472.
44 Megía García A, Serrano-Muñoz D, Taylor J, Avendaño-Coy J, Gómez-Soriano J. Transcutaneous spinal cord stimulation and motor rehabilitation in spinal cord injury: a systematic review. Neurorehabil Neural Repair 2020;34(1):3–12.
45 Faist M, Mazevet D, Dietz V, Pierrot-Deseilligny E. A quantitative assessment of presynaptic inhibition of Ia afferents in spastics.

Differences in hemiplegics and paraplegics. Brain 1994;117(Pt 6): 1449–55.
46 Lev-Tov A, Pinco M. In vitro studies of prolonged synaptic depression in the neonatal rat spinal cord. J Physiol 1992;447: 149–69.
47 Pierrot-Deseilligny E, Burke D. The Circuitry of the Human Spinal Cord. Cambridge: Cambridge University Press; 2012.
48 Eccles JC, Schmidt RF, Willis WD. Presynaptic inhibition of the spinal monosynaptic reflex pathway. J Physiol 1962;161(2): 282–97.
49 Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther 1987;67(2): 206–7.
50 Katz RT, Rovai GP, Brait C, Rymer WZ. Objective quantification of spastic hypertonia: correlation with clinical findings. Arch Phys Med Rehabil 1992;73(4):339–47.
51 Portney L, Watkins M. Foundations of Clinical Research: Applications to Practice. 3rd ed Upper Saddle River: Prentice Hall; 2009.

Appendix A: Search strategy in MEDLINE

(1) Spinal cord injuries (MeSH).
(2) SCI
(3) 1 or 2
(4) transcutaneous spinal cord stimulation
(5) tSC
(6) 4 or 5
(7) Muscle spasticity (MeSH)
(8) Muscle stiffness
(9) Muscle hypertonia (MeSH)
(10) Tone
(11) 7 or 8 or 9
(12) 3 and 6 and 11