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Review

The Efficacy of Spinal Cord Stimulators in the Reduction of Multiple Sclerosis Spasticity: A Narrative Systematic Review

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HIGHLIGHTS

- Spinal cord stimulation (SCS) has potential for reduction of multiple sclerosis (MS)-induced spasticity.
- SCS for MS literature is highly variable regarding outcomes.
- SCS may provide some relief for refractory spasticity induced by MS.

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The Efficacy of Spinal Cord Stimulators in the Reduction of Multiple Sclerosis Spasticity: A Narrative Systematic Review

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

ABSTRACT

A systematic review was employed utilizing Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, to analyze all primary clinical data on the efficacy of spinal cord stimulation (SCS) in the treatment of multiple sclerosis (MS) induced spasticity. Databases include: Embase, PubMed, Scopus, Cochrane, and Web of Science. The review included case series, case studies, and clinical trials. Outcomes of interest were spasticity reduction. Grading of Recommendations Assessment, Development and Evaluation criteria was utilized to grade the certainty of evidence. Five hundred thirty-two articles were retrieved following database systematic review. One hundred eighty-eight articles were removed as duplicates utilizing the "Detect Duplicates" function on Rayyan.ai. A further 344 articles were excluded following abstract and title appraisal. As a result, 16 articles were subjected to full text appraisal. The dates of publication ranged from 1973 to 2019. Although a unique modality, there is not enough evidence to support the employment of SCS over current medical standard of care. Further high-quality randomized control trials are required to elucidate SCS's role in MS induced spasticity algorithm.

Keywords: Spinal Cord Stimulation; Multiple Sclerosis; Muscle Spasticity

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disorder with demyelination of the central nervous system (CNS) and its structures [1]. Symptoms of MS can present with widespread, unpredictable, and highly variable clinical manifestations [2]. The most recent studies on prevalence estimate more than 2.3 million people worldwide live with MS. The United States alone has nearly 1 million people over the age of 18 who live with MS [3]. Living with MS is burdensome to patients and their families due to the physical, cognitive, and emotional consequences. Patients can experience deficits in learning, memory, information processing, executive function, language, and social cognition. These cognitive impairments experienced by MS patients can lead to unemployment for many of them, decreasing their quality of life and autonomy [4]. Additionally, the disability associated with MS affects one's ability

to partake in deep social interactions [5]. A cross-sectional study by Kobelt et al. [6] found that the ability to work in this patient population decreased from 82% to 8% as the disease progressed, adding to the financial burden that is already exacerbated by the high cost of medications and a necessity for caretakers.

Additionally, patients experience a wide range of motor deficits, such as gait and balance difficulties due to progressive motor impairments associated with demyelination of the corticospinal tract [7]. Injury to the corticospinal tract produces weakness and spasticity, and with motor neuron involvement, can lead to muscle atrophy [7]. These symptoms arise due to the widespread neuronal degeneration within the CNS, spinal cord tracts, and peripheral nerves. Spasticity is defined as an involuntary shortening and contracture of a muscle secondary to upper motor neuron damage [8,9]. In MS, spasticity is believed to be due to demyelination of the inhibitory descending CNS motor tracts [8]. Spasticity is also said to be a velocity dependent increase in muscle tone with exaggeration of tendon jerks [8]. Due to the nature of the uncontrollable muscle hypertonicity, many individuals often have significant impairment in their activities of daily living [9]. The 90% of patients suffering from MS have experienced spasticity [10,11].

Currently, MS targeted pharmacological treatments are grouped into 3 categories based on the intended effects of acute relapse management, disease-modifying treatments, and symptomatic treatments [5]. Pharmacological treatments frequently include medications such as baclofen, diazepam, dantrolene and tizanidine but have limited effectiveness and are associated with various systemic side effects such as muscle weakness and cognitive impairment [8,12]. In the last 2 decades, immunomodulatory therapies using interferons have helped to reduce the frequency of MS relapses and T2 lesions. There are currently 6 self-injectable, 3 infusion based, and 3 oral medications. However, out of the 12 available options, 9 medications have significant side effects that can affect a patient's quality of life [13]. While immunomodulatory therapies have shown promise with relapsing-remitting MS, the medication has shown mixed results in patients with progressive disease [13].

Another pharmacological option is anti-CD20 B-cells depleting drugs, which is a form of disease-modifying therapy. Ocrelizumab and ofatumumab fall into this category of medications, and show similar levels of efficacy in treating relapse remitting MS. However, the annual cost for ocrelizumab and ofatumumab is $65,000 and $83,000 respectively. The out-of-pocket cost for Medicare patients can range from $0 to $13,000; the price can vary significantly for patients who are insured through work or for those that purchase privately, making the medication financially burdensome [14]. This highlights the need for treatment options that are more effective and less financially taxing on patients.

Spinal cord stimulation (SCS) has been studied as a non-pharmacological alternative for patients suffering from symptoms of spasticity. Stimulation is provided either through percutaneous electrodes into the posterior epidural space or through surgical paddle lead placement that is delivered via a laminotomy [15]. Historically, SCS was conducted through stimulating the dorsal column [16]. Dorsal column stimulation was initially employed as a means of pain management, but some began to notice it harbored potential benefit for spasticity [17]. In modern medicine, spinal stimulation has become a standard practice for types of neuropathic pain, however its employment as a treatment for spasticity from either MS, spinal cord injury, or stroke remains ill-defined [18].

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Spinal cord stimulators have also been shown to improve spasticity and help patients regain function in hereditary disorders as well. A recent case study by Tufo et al. [19], a patient with hereditary spastic paraplegia was treated with spinal cord stimulator to the cervical region. Three months after treatment, the patient showed improvement in motor symptoms such as gait and spasticity, as well as dysarthria, urinary symptoms, and cognitive function [19].

Given how effective spinal cord stimulators have been in treating spasticity in both traumatic and hereditary musculoskeletal disease, one can suppose that patients with MS may also benefit from the use of this treatment modality. This systematic review investigates the potential benefit of SCS on MS induced spasticity, ranging from historical therapeutics to modern modalities.

METHODS

This systematic review was conducted utilizing the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines (**Fig. 1**) [20]. Due to the heterogenicity in study designs of included articles design, no meta-analysis was conducted. For instance, there were 0 randomized controlled double-arm studies, 10 single-arm studies, and 2 case reports/series. Due to this paucity, no meta-analysis was conducted. This manuscript is not registered on Prospero.

Inclusion criteria

All studies containing primary clinical data on the employment of SCS for the treatment of MS induced spasticity were included. Case studies, case series, double-arm and single arm clinical trials were included. Outcomes of interest included decreased disability scores, decreased muscle tonicity/spasticity scores, and improved motor function.

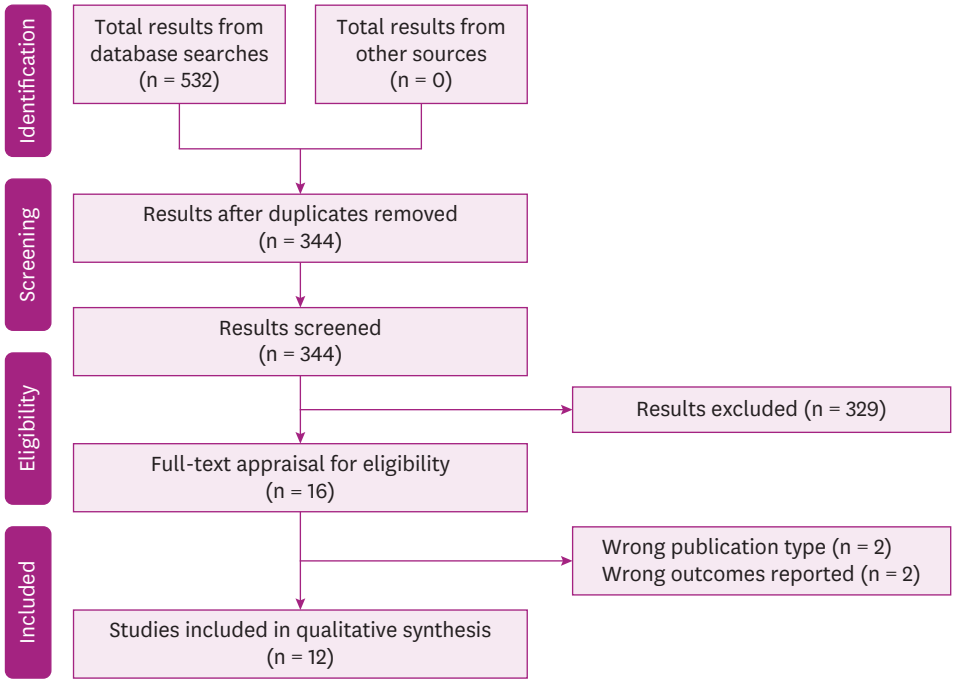

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for article selection.

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Exclusion criteria

Articles excluded from analysis included: posters, abstracts, articles lacking full text, studies still in progress, and articles which did not include SCS treatment in their study design/case reporting. Basic science and animal study articles were also excluded. Due to the historical perspective of this review, articles were not excluded due to date.

Information sources and search strategy

A systematic review through 4 medical databases was conducted to look for articles on the efficacy of SCS for MS spasticity reduction. These databases include: Embase, PubMed, Cochrane Library, and Web of Science. Search terms utilized were: ("Spasticity" OR "spastic") AND ("MS" OR "multiple sclerosis" OR "sclerosis") AND ("spinal cord stimulator" OR "spinal cord stimulation" OR "spinal cord stim" OR "spinal stim" OR "SCS" OR "dorsal column stimulation" OR "dorsal column stimulator" OR "dorsal column electrical stimulation" OR "dorsal column electrical stimulator" OR "epidural stimulation" OR "epidural stimulator" OR "epidural electrical stimulation" OR "epidural electrical stimulator" OR "electrostimulation" OR "electrical stimulation"). The initial article search was conducted by Goodwin BJ and Murray WV on 09/14/2022.

Duplicate studies were identified using a function on Rayyan.ai where the retrieved studies were stored. Following the automated detection of duplicates, 2 reviewers (Goodwin BJ and Murray WV) sorted through the remaining articles to ensure there were no further duplicates.

Study selection

Following the removal of duplicates, there was an abstract and title review to parse down the results based on relevance. After title and abstract appraisal, full-text appraisal was then conducted by 2 reviewers (Goodwin BJ and Murray WV). In the event of contention, a third reviewer (Mahmud R) acted to break ties. The remaining studies then continued on to the data extraction phase.

Data collection

Following eligibility screening, a study was then subjected to data collection. Full-text appraisal was performed by 2 reviewers and collected on a data sheet. Extracted data was examined for relevance and proper reporting of data. Due to the historical nature of some of the publications, leniency towards reporting was provided due to varying historical reporting standards. The primary measured outcome extracted was reduction in muscle spasticity following implantation and trial with SCS at 3 months or study completion. Spasticity measures varied from electromyography (EMG) to modified Ashworth scale. Historical studies that did not include an objective measure were included, however were graded with a lower strength of evidence. As a second measure, functional improvement was collected for study. Research quality and data reliability and generalizability was then determined by 2 reviewers.

Article grading

Articles were scored under the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria for certainty of evidence by 2 trained reviewers (Mahmud R and Goodwin BJ) [21]. A third reviewer was brought in to break ties and resolve conflict in grading. Articles also underwent bias assessment. The Newcastle-Ottawa Scale was employed for case studies and series, while single-arm studies were subjected to evaluation by the Risk of Bias In Non-randomized Studies – of Interventions criteria [22,23]. Like GRADE, 2 reviewers (Mahmud R and Goodwin BJ) reviewed the articles with a third reviewer in the event of ties.

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RESULTS

The initial database search found 532 articles, of which 188 were duplicate articles. From those articles, 66 were excluded following title and abstract screening. Full-text appraisal was then conducted, on 16 articles, with 4 being excluded. Two of the articles did not contain the outcome of interest, and the other 2 were the wrong type of publication. The remaining 12 articles were then stratified based on date and type, and then subjected to GRADE criteria for certainty of evidence (**Table 1**) [21]. Following GRADE, studies were assessed for bias (**Table 2**). Seven of the included studies were clinical trials, while the remaining 2 were case studies. These studies ranged from 1973 to 2019 and were from multiple nations and languages.

Historical studies

In 1973, Cook and Weinstein [24] describe some of the first cases of SCS employment benefitting spasticity in individuals with MS. The researchers placed 4 electrodes into the subarachnoid space of the upper thoracic spine, with a pulse width of 200 ms, voltage ranging from 0.4–4.0 V, and frequency ranging from 150–200 Hz. In their case report on 3 females and 2 males (n = 5), Cook and Weinstein [24] depict that with a they had noticed improvement of spasticity in flexion of lower extremities, and extension of upper extremity. The dorsal column stimulation occurred between 1.5–21 months. Due to the reporting of the time, statistical analysis and reporting in this study is heavily lacking, leading to a weakening of the overall strength of the publication's results. Conversely, this seminal paper allowed for further studies to investigate the usage of SCS for MS spasticity.

Five years later, in 1977, Dooley and Sharkey [25] report a retrospective case report of 42 patients with MS' experience with prolonged dorsal column stimulation. The authors report that only 4 out of the 42 participants with MS had improvement in their spasticity (9.5%) [25]. The authors fail to report what levels of SCS, pulse width, voltage, and frequency was employed. Additionally, the authors fail to display adequate statistical analysis of their improvement, leading to the question of accuracy and efficacy of reporting.

Three years later in 1980, Siegfried [26] published on MS spasticity, however this time it was a case series including 19 patients. The patients went on to describe improvements in hypertonicity following stimulation. The researcher reports that when applying dorsal column stimulation to the cervical or upper thoracic levels, 7 patients would go on to implantation. Out of the 7 patients, all saw some improvement in spasticity, with 6 reporting moderate improvement and 1 reporting slight improvement. Muscle spasticity was tested by EMG. Like many papers of the time, adequate statistical reporting is absent by today's standards. Additionally, the researcher does not report the settings used for stimulation.

In 1980, Dimitrijevic et al. [27] reported employment of SCS in the reduction of spasticity in 11 patients over 18 months. Of the 11 patients included, 6 of the patients suffered from spasticity secondary to MS. In this study, all participants were provided implanted epidural spinal cord stimulators at T1 and T2 levels, and then followed up with EMG and polyelectromyographic recordings. The degree of all patients' spasticity was recorded before and after T1–2 epidural SCS implantation. Dimitrijevic et al. [27] reported reduced lower extremity spasticity in all subjects, however failed to report to what degree. Additionally, there was a claim that SCS's role in reducing spasticity was likely due to the connection between the brain and the segmental reflexes. Due to the different reporting standards of the time, no p values or statistical significance was reported, and whatever graphics provided

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Table 1. Modified Grading of Recommendations Assessment, Development and Evaluation criteria for included articles

Authors	Year	Title	Limitations	Inconsistency	Imprecision	Indirectness	Publication bias	No. of patients (treatment group)	Initial grade	Final grade	Importance	Conclusion
Cook and Weinstein [24]	1973	Chronic dorsal column stimulation in multiple sclerosis	Serious due to small sample size and being a case report.	No serious inconsistency.	No serious imprecision.	No serious indirectness.	Not industry funded.	5	Very weak	Very weak	Very low	Transient improvement in fatigue, endurance, strength, and energy.
Dooley and Sharkey [25]	1977	Electrostimulation of the nervous system for patients with demyelinating and degenerative diseases of the nervous system and vascular diseases of the extremities	Serious due to small sample size and being a retrospective case review.	Severe due to potential variations in unreported lead placement, duration, and frequency.	No serious imprecision.	No serious indirectness.	Not industry funded.	42	Very weak	Very weak	Very low	The 50% of patients with multiple sclerosis, primary lateral sclerosis, and hereditary spinocerebellar disorders improved over 15–27 months; those least disabled or with vasospastic disorders saw the most benefit.
Siegfried [26]	1980	Treatment of spasticity by dorsal cord stimulation	Serious due to small sample size and being a case series.	Severe due to variations in lead placement, duration, and frequency.	No serious imprecision.	No serious indirectness.	Not industry funded.	7	Very weak	Very weak	Very low	Moderate improvement in medullary spasticity most noticeable in patients without complete section.
Dimitrijevic et al. [27]	1980	Neurophysiological evaluation of chronic spinal cord stimulation in patients with upper motor neuron disorders	Serious due to small sample size and mixed comorbidities.	Severe due to variations in lead placement, duration, and frequency.	No serious imprecision.	No serious indirectness.	Not industry funded.	6	Very weak	Very weak	Very low	Improvement in voluntary motor control and reduced spasticity.
Read et al. [28]	1980	The effect of spinal cord stimulation on function in patients with multiple sclerosis	Serious due to small sample size and mixed comorbidities.	Moderate due to variations in lead placement.	No serious imprecision.	No serious indirectness.	Not industry funded.	11	Weak	Very weak	Low	Improved bladder function and reduced lower limb spasticity.
Hawkes et al. [29]	1980	Stimulation of dorsal column in multiple sclerosis	Moderate due to low sample size.	No serious inconsistency.	No serious imprecision.	No serious indirectness.	Not industry funded.	19	Moderate	Weak	Low	Improvement was primarily seen in walking and bladder function, but improvements in sphincter control and speech were unclear.
Illis et al. [30]	1980	Spinal cord stimulation in multiple sclerosis: clinical results	Moderate due to low sample size.	No serious inconsistency.	No serious imprecision.	No serious indirectness.	Not industry funded.	19	Weak	Very weak	Low	The 5/18 patients had temporary improvement in sensation and mobility, but only 1/13 with severe limb ataxia improved. 12/16 with bladder symptoms, 7/11 severe bladder disturbance improved; heterogeneity of intervention limits generalizability.
Siegfried et al. [31]	1981	Electrical spinal cord stimulation for spastic movement disorders	Serious due to small sample size and mixed comorbidities.	Moderate due to variations in lead placement.	No serious imprecision.	No serious indirectness.	Not industry funded.	6	Weak	Very weak	Very low	Improvement in movement, tonicity, and stretch.

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Table 1. (Continued) Modified Grading of Recommendations Assessment, Development and Evaluation criteria for included articles

Authors	Year	Title	Limitations	Inconsistency	Imprecision	Indirectness	Publication bias	No. of patients (treatment group)	Initial grade	Final grade	Importance	Conclusion
Klinger et al. [32]	1981	Epidural spinal electrostimulation (ESES) in patients with chronic pain and central motor disturbances	Moderate due to low sample size.	No serious inconsistency.	No serious imprecision.	No serious indirectness.	Not industry funded.	12	Moderate	Weak	Low	Spinal spasticity and range of motion improved by 20%–30%, cramps and pain markedly improved.
Scerrati et al. [33]	1982	Effects of spinal cord stimulation on spasticity: H-reflex study	Serious due to small sample size and being a case report.	Moderate due to variations in lead placement.	No serious imprecision.	No serious indirectness.	Not industry funded.	4	Very weak	Very weak	Very low	Three patients reported subjective improvement in spasticity but no objective changes in the exam were observed.
Provenzano et al. [34]	2016	Treatment of neuropathic pain and functional limitations associated with multiple sclerosis using an MRI-compatible spinal cord stimulator: a case report with two year follow-up and literature review	Serious due to small sample size and being a case report.	No serious inconsistency.	No serious imprecision.	No serious indirectness.	Not industry funded.	1	Very weak	Very weak	Very low	Two years after placement, the patient reported 77% reduction in pain and 99% reduction in opiate use, with improved sensation, spasticity, and ambulation.
Lam and Monroe [35]	2019	Successful treatment of central pain and spasticity in patient with multiple sclerosis with dorsal column, paresthesia-free spinal cord stimulator: a case report	Serious due to small sample size and being a case report.	No serious inconsistency.	No serious imprecision.	No serious indirectness.	Not industry funded.	1	Very weak	Very weak	Very low	Reduced pain and spasm, improved strength and mobility, improved sensation.

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Table 2. Bias grading for included articles

Authors	Title	Year	Selection				Comparability	Exposure			Risk assessment							
			1) Is the case definition adequate?	2) Representativeness of the cases	3) Selection of controls	4) Definition of controls	1) Comparability of cases and controls on the basis of the design or analysis	1) Ascertainment of exposure	2) Same method of ascertainment for cases and controls	3) Non-response rate	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Newcastle-Ottawa	(Case series/Studies)																	
Read et al. [28]	The effect of spinal cord stimulation on function in patients with multiple sclerosis	1980	*	0	*	0	0	*	*	*								
Hawkes et al. [29]	Stimulation of dorsal column in multiple sclerosis	1980	*	0	*	0	*	*	*	*								
ROBIN-I	(Single-arm studies)																	
Cook and Weinstein [24]	Chronic dorsal column stimulation in multiple sclerosis: preliminary report	1973									Moderate	Moderate	Low	Low	Low	Low	Moderate	Low
Dooley and Sharkey [25]	Electrostimulation of the nervous system for patients with demyelinating and degenerative diseases of the nervous system and vascular diseases of the extremities	1977									Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Dimitrijevic et al. [27]	Neurophysiological evaluation of chronic spinal cord stimulation in patients with upper motor neuron disorders	1980									Moderate	Moderate	Moderate	Low	Low	Low	Serious	Moderate
Illis et al. [30]	Spinal cord stimulation in multiple sclerosis: clinical results	1980									Moderate	Low	Low	Low	Low	Low	Low	Low
Klingler et al. [32]	Epidural spinal electrostimulation (ESES) in patients with chronic pain and central motor disturbances (author's transl)	1981									Moderate	Moderate	Low	Moderate	Low	Moderate	Moderate	Moderate
Scerrati et al. [33]	Effects of spinal cord stimulation on spasticity: H-reflex study	1982									Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate
Provenzano et al. [34]	Treatment of neuropathic pain and functional limitations associated with multiple sclerosis using an MRI-compatible spinal cord stimulator: a case report with two year follow-up and literature review	2016									Moderate	Low	Low	Low	Moderate	Moderate	Low	Moderate
Lam and Monroe [35]	Successful treatment of central pain and spasticity in patient with multiple sclerosis with dorsal column, paresthesia-free spinal cord stimulator: a case report	2019									Moderate	Serious	Moderate	Moderate	Moderate	Serious	Serious	Serious

were insignificant evidence to support the published claim. Additionally, the study did not report what levels of the spinal cord were stimulated, for how long, and at what frequency. As such, the power of this study is weak by modern standards.

Furthermore in 1980, Read et al. [28] investigated 16 patients with neurologic spastic pathology, 11 of which were afflicted with MS. The researchers provided stimulation for 2 weeks in which pulse width was 200 μs and frequency was 33 Hz. Read et al. [28] compared physiotherapy test batteries before SCS, at 1 week, and 2 weeks post SCS. For continuity of treatment, the same observer conducted the physical tests at each time increment. At 2 weeks, the researchers reported 2 patients with no effect from SCS, 6 patients with reduced muscle hypertonicity, and retained lower extremity muscle strength, 1 patient with normal muscle spasticity before SCS, and 2 patients with worsened muscle hypertonicity. In regard to level of lead placement, the researchers report that they employed 6 SCS electrodes at the upper thoracic, and 10 others at the mid-to-lower thoracic vertebral levels but did not distinguish which levels saw the improvement in spasticity reduction. It is important to note that the researchers reported no correlation between resistance and voltage to overall benefit, however they suspected most improvement came from the lower end of the range employed.

Contrary to current findings in 1980, Hawkes et al. [29] reported contradictory results. The researchers implanted 2 electrodes between T1–T9 exactly 2 cm apart in 19 patients. The pulse width was 200 μs and frequency was 33 Hz, copying that of Read et al. [28] The stimulators were activated continuously for 2 weeks, with no physiotherapy allowed concurrently. Neurological examinations were conducted before implantation, at day 5, after the 2-week trial period. Hawkes et al. [29] reported that there were no changes to spasticity in any of the patients during this time. Conversely, the researchers reported improvement in neuromuscular activation as seen in improved walking speed, grip strength, and hip flexor strength in 8, 2, and 7 patients respectively.

In 1980, Illis et al. [30] reported limited success with SCS in improvement of spasticity. Utilizing the standard pulse width of 200 μs and frequency of 33 Hz of the time, the researchers recorded Kurtzke disability index and neurophysiological performance after 10 days of sustained sufficient stimulation. It is important to note that in some instances, it took 2–3 weeks of stimulation for individuals to reach sufficient stimulation with the epidural electrodes. Following the experimental duration, Illis et al. [30] reported an overall improvement in mobility and micturition of most patients. However, the researchers only noted that 2 patients had improvement in chronic muscle spasm.

In 1981, Siegfried et al. [31] reported the utilization of implanted SCS for the reduction of spasticity in 10 patients from various nervous etiologies. In their 2-center single-arm study, 6 of the 10 patients suffered from spasticity secondary to MS. The researchers discerned that after a few minutes of percutaneous cervical or thoracic stimulation to the dorsal cord, the most significant reduction in spasticity was seen in the patients with MS. To measure change in muscle tone and spasticity, the researchers employed an average threshold of H reflex and tonic muscle stretch. The researchers then rechecked the reflex after soft, medium, and strong stimulations. Siegfried et al. [31] noted an 84% decrease in H reflex threshold amplitude following soft stimulation. However, it is important to note that due to the different reporting standards of the time, p values were not included in the report, and the data of all patients was lumped together, not allowing for adequate analysis of solely the MS patients. Additionally, the adequate delineation of volts, amps, and duration of stimulation

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was not properly reported per each of their stimulation conditions (i.e., soft, medium, strong), detracting from the power of the reported study.

In 1981, Klingler et al. [32] investigated the potential benefit of implanted spinal cord stimulators for MS through the lens of chronic pain and spasticity. After 20 trials of SCS, 12 of the patients elected to proceed with implantation. Interestingly, the researchers were one of the earliest trials reporting an electrostimulator trial prior to implantation. Additionally, Klingler et al. [32] planted their electrodes epidurally. Following 4 weeks of implantation, neuromuscular measurements were reassessed. As such, Klingler et al. [32] reported that of the 12 patients, the 8 with MS saw a 20%–30% improvement in range of motion and muscle spasticity. Additionally, the researchers reported complete remission of pain secondary to spastic cramps in all cases. Again, the historic constraints limited the reporting power of the study.

In 1982, Scerrati et al. [33] conducted a small single-armed trial on 5 patients with spasticity—4 of which having MS. The researchers investigated the benefit of SCS to the T1 or T9–10 levels on H reflex. Of the 3 participants with MS induced spasticity that remained after a year, all reported improvement in spasticity symptoms. However, the paper does not detail or statistically delineate the improvement in spasticity. Furthermore, the paper is significantly underpowered to be considered a clinical trial.

Modern studies

There is a noted paucity in the literature from 1981 until 2016, when Provenzano et al. [34] reported the case of a 68-year-old male who saw improvement in symptoms following SCS. The patient was stated to have a 29-year history of MS, with noted demyelinated lesions at the level of T8–T9. Provenzano et al. [34] conducted a SCS trial and then implanted the percutaneous leads at T9, following up with their patient at 24 months. The researchers reported that following 24 months of implantation, the patient's pain decreased 77% on numerical rating scale (from 9/10 to 2/10) and decreased consumption of opioids, from 105 mg morphine per day to 5 mg morphine per month. In regard to spasticity, the patient had some improvement, decreasing from a 1+ to 0 on the modified Ashworth scale. Further detracting from the low power of case report, Provenzano et al. [34] did not report any statistical analysis for significance. As such, the generalizability of their data is severely limited.

In 2019, a second case report was published, this time from Lam and Monroe [35]. The researchers reported the treatment of a woman with a 13-year history of MS whose symptoms were refractory to Teriflunomide, nonsteroidal anti-inflammatory drugs, muscle relaxers, and gabapentin. The patient initially reported discomfort as a 6/10 on the visual analog scale (VAS). The patient was trialed with a percutaneous single lead at T8, and subsequently implanted with paddle lead placement over T9. The patient saw significant improvement in pain at 2-month follow up with VAS, decreased to a 2/10, and complete resolution of pain and spasticity after 4-months. The patient continued to have relief of pain and spasticity for up to 10 months following implantation.

Articles excluded during full-text appraisal

Four articles were excluded following full text appraisal. One article was a narrative review of methodology and process [36]. The second article was a prospective methodology report for another study included in this systematic review [37]. Two more articles were excluded due to not reporting on improvement in spasticity [38,39].

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Critical assessment of study design and methodology

Included articles range from case reports to clinical trials. It is important to note that there is an ethical dilemma in conducting a double-blinded randomized controlled trial in these populations, and as a result, few if any 2-armed studies exist. Furthermore, there is a lack of standardization in regard to how spasticity is reported. In the historical studies, they often include pooled data and populations with a multitude of etiologies and treatments. Modern studies shy away from this old schema, however, and some still lack proper statistical reporting. As such, the smaller nature of these studies and the inability to easily parse out reported data for a specific group weakens the overall strength of the evidence.

DISCUSSION

We report the most up to date systematic review on the efficacy of SCS on MS induced spasticity. As of October 2022, there is still limited consensus as to the benefit of SCS in MS spasticity.

The evidence provided in the analyzed studies shows conflicting results. Most studies showed improvement in spasticity, albeit to a variable degree. For instance, Provenzano et al. [34] noted an improvement in spasticity from a 1+ to a 0 on Ashworth scale, while Siegfried et al. [31] noted improvement in all 6 of their patients through H reflex and tonic stretch. One study showed no improvement in spasticity in its respondents. Hawkes et al. [29] saw no improvement in spasticity following implantation of 2 electrodes between T1–T9 with a pulse width of 200 μs and frequency 33 Hz. Curiously, none of the studies compared SCS to the current standard of care which includes baclofen or other anti-spasticity medications. As a result, there is no definitive evidence to claim that SCS is superior to modern standards of care, as this modality is often employed when others have failed.

In this study, we conducted a systematic review of the existing literature into the utilization of SCS in treating MS induced spasticity. Our systematic review found 177 articles and examined 9 articles, the largest systematic review on this topic to date. Additionally, our study included historical employment of this modality, comparing outcomes to that of modern studies. Although the types of studies varied heavily, as did their standards and reporting of data, some conclusions can be drawn. SCS is potentially a therapeutic modality for spasticity refractory to other therapeutics, although potentially inferior to modern standard of care.

Currently, the literature on employment of SCS in MS induced spasticity is heavily mixed. As a result, further larger studies are needed to elucidate the role neuromodulation plays in spasticity management. Due to the potential concern of ethics in conducting a double-blinded, 2 arm study, larger sample sizes can be used in a single-arm treatment study. Additionally, while there are various modalities to perform neuromodulation, elucidation of the most beneficial spinal levels of SCS implantation, and degree of stimulation should be further explored. While there are various modalities of measuring and assessing spasticity, reporting effect size would allow for ease of comparison and meta-analysis of data, allowing for easier generalizability.

Although further research has been conducted to investigate the efficacy of SCS in the treatment of MS induced spasticity, there is still no clear consensus as to where the modality fits in current treatment paradigms. Historic and modern literature are both highly variable in terms of outcomes, quality, and generalizability. SCS has been shown to decrease spasticity in

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most studies, although in varying degrees. As such, further larger single-arm studies should be conducted to discern the degree of improvement in spasticity, optimal spinal cord levels, and degree of neuromodulation for SCS utilization. At present, standard of care has not been shown to be inferior to employment SCS in MS induced spasticity.

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