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REVIEW ARTICLE (META-ANALYSIS)

Spinal Cord Stimulation Research in the Restoration of Motor, Sensory, and Autonomic Function for Individuals Living With Spinal Cord Injuries: A Scoping Review

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Abstract

Objective: To describe the status of spinal cord stimulation (SCS) research for the improvement of motor, sensory, and autonomic function for individuals living with a spinal cord injury (SCI).

Data Sources: This scoping review identified original research published before March 31, 2021, via literature searches using MEDLINE, Embase, PubMed, Science Direct, Cumulative Index to Nursing and Allied Health, Sport Discus, and Web of Science, as well as a targeted search for well-known principal investigators. Search terms included permutations of "spinal cord stimulation," "epidural spinal cord stimulation," "transcutaneous spinal cord stimulation," "magnetic spinal cord stimulation," and "neuromodulation."

Study Selection: Studies were included if they (1) were in English, (2) presented original research on humans living with a SCI, and (3) investigated at least 1 of the 3 forms of SCS.

Data Extraction: Extracted data included authors, publication year, participant characteristics, purpose, study design, stimulation (device, location, parameters), primary outcomes, and adverse events.

Data Synthesis: As a scoping review the extracted data were tabulated and presented descriptively. Themes and gaps in the literature were identified and reported. Of the 5754 articles screened, 103 articles were included (55 epidural, 36 transcutaneous, 12 magnetic). The primary research design was a case study or series with only a single randomized controlled trial. Motor recovery was the most common primary outcome for epidural and transcutaneous SCS studies, whereas bowel and bladder outcomes were most common for magnetic SCS studies. Seventy percent of the studies included 10 or fewer participants, and 18 articles documented at least 1 adverse event. Incomplete stimulation parameter descriptions were noted across many studies. No articles mentioned direct engagement of consumers or advocacy groups.

Conclusions: This review identified a need for more robust study designs, larger sample sizes, comparative studies, improved reporting of stimulation parameters, adverse event data, and alignment of outcomes with the priorities of the community with SCI.

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Modulation of neurologic tissues with the intent to modify a function has been a line of scientific inquiry for centuries.[1] Although many indications for neuromodulation with electrical stimulation have been explored, the treatment of chronic pain has been the primary driver. Epidural spinal cord stimulation (ESCS) is currently approved for the treatment of neuropathic pain for people living

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with spinal cord injury (SCI).[1] More recently, it was realized that the functions modulated by ESCS could be broadened to motor, sensory, and autonomic functions.

Although the exact mechanisms remain unknown, theories are based on preclinical work in animal models of SCI,[2-5] computational studies,[6-8] and electromyographic studies[9-11] in humans. Mediating the endogenous plasticity of the spinal cord circuitry has been the focus of past reviews.[1,12-14] Although a better understanding of underlying mechanisms will contribute to the field, evidence from clinical trials has shown the therapeutic potential of spinal cord stimulation (SCS) for SCI.

In 2011, ESCS rapidly advanced when it was documented that an individual with chronic SCI regained voluntary motor function,[15] followed by a flurry of supporting research documenting additional gains in function.[16-21] Stimulation of spinal cord pathways has expanded into less invasive modalities where the stimulation is applied over the surface of the skin either by transcutaneous spinal cord stimulation (TSCS) or magnetic SCS. While ESCS directly stimulates the spinal cord, modeling studies imply that a neuromodulatory mechanism of action for TSCS, magnetic SCS, and to a certain extent ESCS may be as a result of changes in the spinal circuits through the stimulation of afferent fibers in the posterior roots.[9] Although it may not be accurate to label TSCS and magnetic SCS as forms of SCS, the literature continues to refer to these modalities as SCS.[9] Recent studies are suggesting similar benefits to those seen with the application ESCS. TSCS combined with training has been shown to facilitate lower limb motor function [9,22-24] and improve voluntary control of hand function,[25] as well as spasticity[26-28] in participants with SCI. Magnetic SCS has also been applied to people with SCI, with improvements in spasticity[29] and respiratory muscle function,[30,31] although it focused primarily on bladder and bowel function.[32,33]

To effectively deliver SCS as a therapeutic option for those living with SCI, more research is needed to provide the level of evidence required to change practice. The need for a scoping review was identified owing to the rapid growth in this area and to support the translation process. Therefore, this scoping review was designed to describe the status of SCS research in the restoration and/or improvement of motor, sensory, and autonomic function for individuals living with SCI. The findings will enable researchers, clinicians, and the community with SCI to understand what has been done, who is doing this work, and the knowledge gaps that exist to inform future research priorities.

Methods

Search strategy

A scoping review protocol was developed using the scoping review methodological literature.[34-39] Given the rationale for this work and the definition of scoping studies, we did not assess the quality of the included studies.[40,41] A copy of the scoping review protocol is available from the corresponding author. The topic of SCS was divided into 3 parallel lines of exploration: ESCS, TSCS, and magnetic SCS. Although a few specific search terms varied between these 3 forms of SCS, the scoping review methodology was identical for each one. A research librarian was consulted to review the keywords used for the database searches (text box 1).

List of abbreviations:

AIS	**American Spinal Injury Association Impairment Scale**
ESCS	**epidural spinal cord stimulation**
SCI	**spinal cord injury**
SCS	**spinal cord stimulation**
TSCS	**transcutaneous spinal cord stimulation**

Inclusion and exclusion criteria

To be included in this scoping review, both the abstract and the article had to be available in English. Only original research articles published up to March 31, 2021, were included. Articles were required to address 1 of the 3 forms of SCS in human participants with SCI. All phases of the care continuum (ie, acute, rehabilitation, community) as well as acute and chronic SCI were included. Research designs that incorporated additional interventions such as pharmaceuticals, transcranial magnetic stimulation, or rehabilitative procedures were also included. No limitations were imposed on the types of outcomes addressed. Reviews, descriptions of protocols or proposed research, conference proceedings, abstracts, lectures, theses, editorials, and commentaries were excluded. These exclusions were applied because these formats did not contain an adequate amount of information for data extraction, were preliminary in nature, and/or were documented in multiple sources.

Search methodology

The following indexed databases were searched: MEDLINE, Embase, Cochrane Library Cochrane Systematic Reviews, PubMed, Science Direct, Cumulative Index to Nursing and Allied Health, Sport Discus, and Web of Science. The same search strategy was used for each of the databases using controlled and free-text (title and abstract) search terms while limiting to human and English studies. The database results were transferred to EndNote version X9.3.2[a] to remove duplicates and for further processing.

The 3 independent SCS searches were completed by the lead author, followed by a cursory vetting of the articles by title and abstract where only those that met the minimum criteria (ie, SCI, human, English, original research) were retained. Once the cursory screening was completed, 2 reviewers independently performed detailed inspection (evaluation of the abstract and/or full text) and placed the resultant articles into 1 of 3 bins; ESCS, TSCS, and magnetic SCS original. To be placed in 1 of the bins an article had to meet the inclusion/exclusion criteria and be judged relevant by both reviewers. If consensus could not be obtained, a third reviewer was consulted.

Data extraction and synthesis

Because of the large number of articles, data extraction was divided between 2 reviewers, with a random selection extracted by both reviewers for comparison and quality control. Data extraction fields included: authors, principal investigator or laboratory, funding sources, country of data collection, identification of consumer advocacy or commercial interest, study design, purpose/objective, methods, sample size, study participant characteristics (SCI type, lesion level, American Spinal Injury Association Impairment Scale [AIS] grades and acuity), stimulation anatomic location and parameters, specific outcomes, and reported adverse

reactions. Possible outcomes addressed by the studies were grouped in the following categories: consumer perspectives, risks and safety, motor recovery (sit to stand, standing, pregait activities), upper extremity function, sensory recovery, ambulation, autonomic effects (ie, sexual function, cardiovascular control, bowel and bladder function), patient-reported outcomes, spasticity, and pain. Categories for reported adverse reactions included infection, increased spasticity, increased paralysis, pain, fracture, intervention intolerance, lead migration, need for surgery, hardware failure, surgical revision of implant, and skin irritation or allergy. The extracted data were summarized in tabular and figurative formats for the 3 forms of SCS.

Results

Articles retrieved

The initial search of the 8 databases yielded 17,620 articles plus an additional 521 that were identified via an independent targeted search using the reference lists of several recent review articles[42-44] and via PubMed for well-known principal investigators and/or laboratories. After screening for duplicates, 5754 articles remained that were then vetted for human, SCI, SCS type, review articles, and full-text availability. The full texts of the remaining 437 articles were reviewed independently, leaving 103 articles (ESCS=55, TSCS=36, magnetic SCS=12) for data extraction (fig 1).[40,45-47] See supplemental appendix S1 for a listing of the articles (available online only at http://www.archives-pmr.org/).

Article characteristics

The earliest article for ESCS involving individuals with SCI was published in 1985.[48] On average there were 0-4 ESCS original research articles published per year through 2019; however, there were 7 in 2020 and 4 in the first months of 2021. For articles investigating TSCS, the earliest article was published in 2009,[49] and almost all were found between 2014-2021, with 11 published between 2018 and 2019 and 15 so far since 2020. The area of magnetic SCS was the least represented with only 12 articles and the

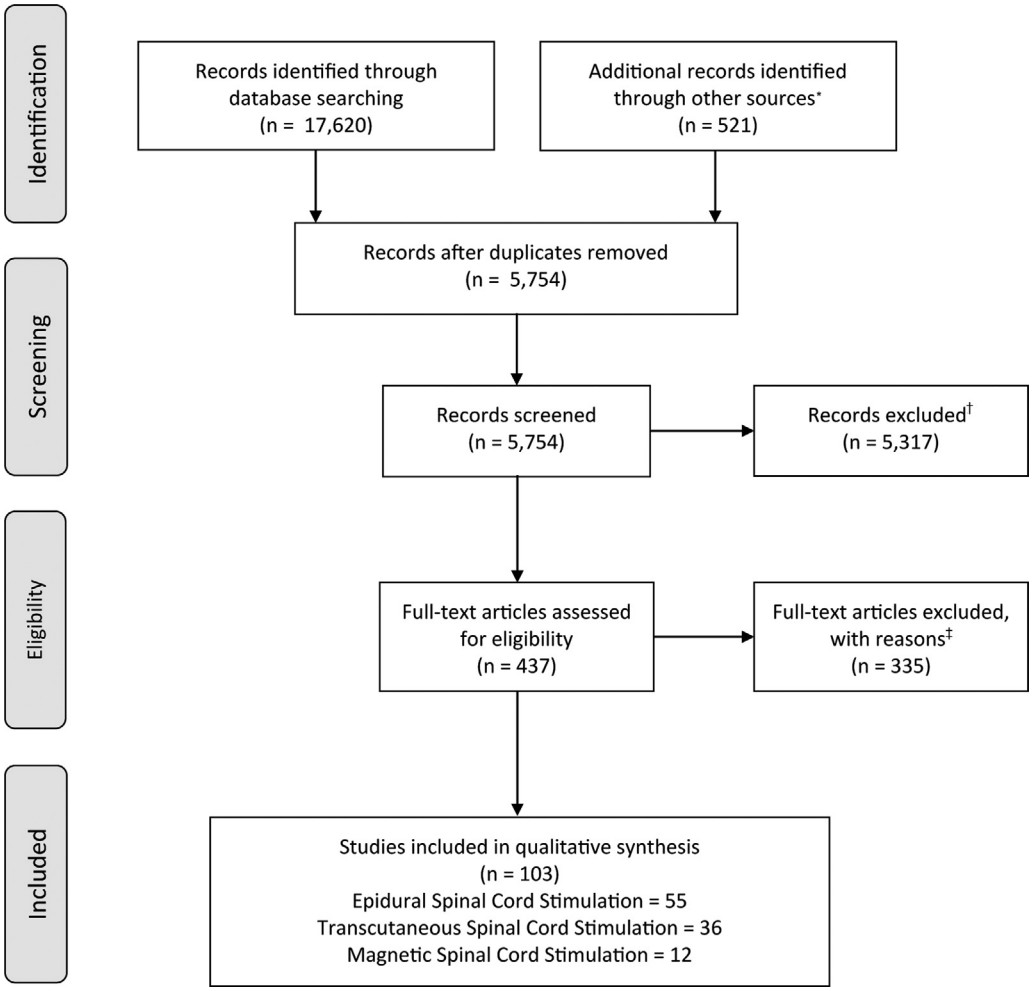

Fig 1 Flow diagram representing the article identification, review, and selection process. Figure adapted from Moher et al.[45] *Additional records identified through other sources: (1) independent targeted search via PubMed for well-known principal investigators and laboratories; (2) scan of review article reference lists.[40,46,47] †Records excluded non-English, nonhuman, poster or conference proceeding, review of literature or systematic reviews, no participants with SCI included, full-text not available. ‡Full-text articles excluded, with reasons, poster or conference proceeding, review of literature, or systematic reviews.

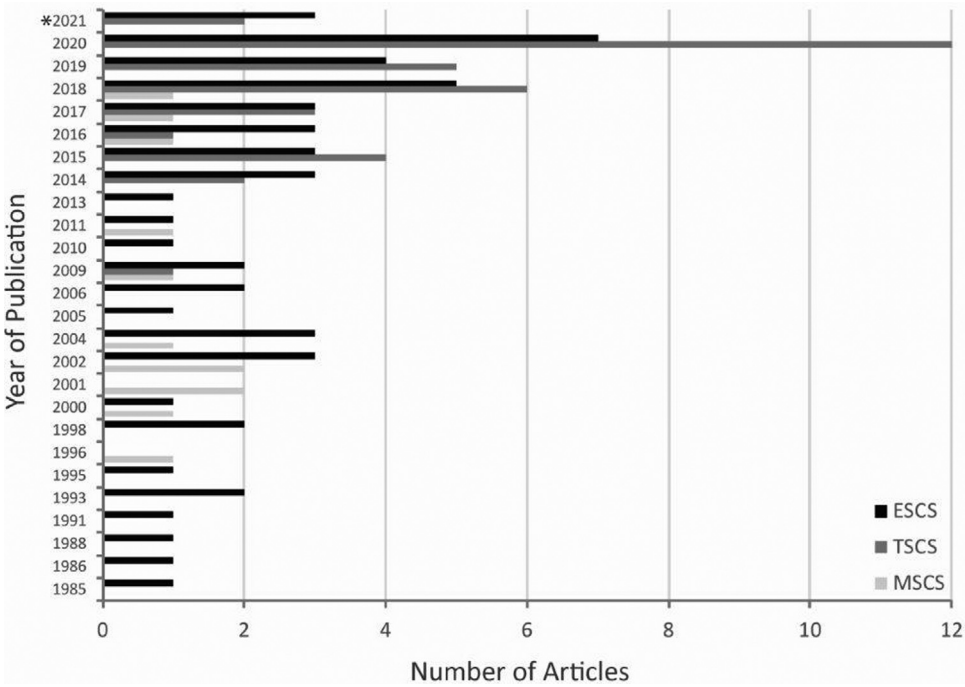

Fig 2 Publication trends for ESCS (n=55), TSCS (n=36), and MSCS (n=12) by year. *The year 2021 does not include the full year because of submission date; it includes articles published from January 1, 2021, to March 31, 2021. Abbreviation: MSCS, magnetic spinal cord stimulation.

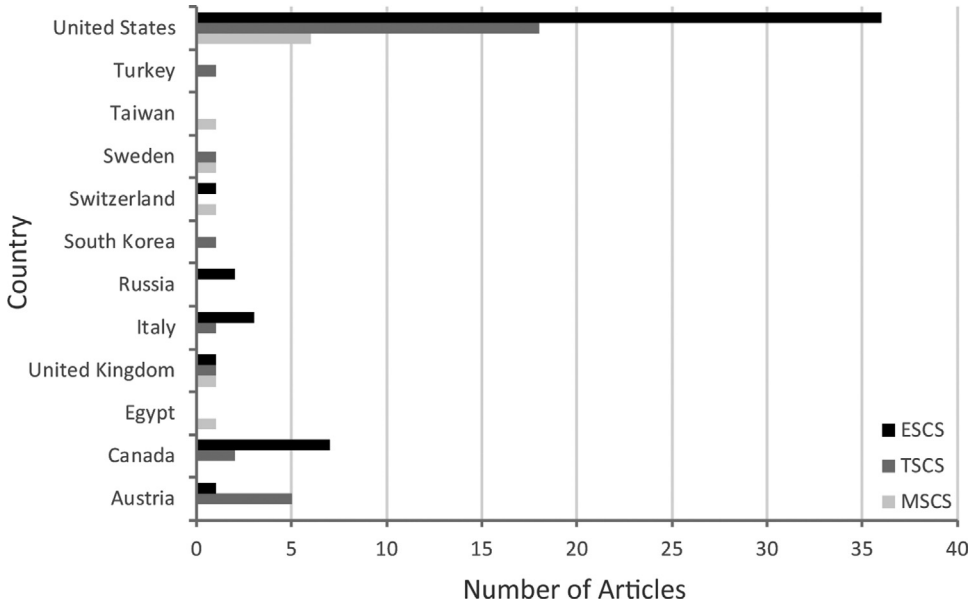

Fig 3 Country of experiment (if documented) for ESCS (n=51/55), TSCS (n=30/36), and MSCS (n=11/12). Abbreviation: MSCS, magnetic spinal cord stimulation.

earliest was from 1996,[50] with sporadic publication activity through 2018 and none identified since (fig 2). See supplemental appendix S1 for the final list of included articles (n=103) grouped by type of SCS and their objectives.

The country where the study took place was identified in 92 of the 103 articles extracted. Most publications (all: 66%, 60/91; ESCS: 71%, 36/51; TSCS: 62%, 18/29: magnetic SCS 55%, 6/11) originated from studies conducted in the United States. Articles originated from 6 different countries for ESCS, 7 for TSCS and 5 for magnetic SCS (fig 3).

Study design

Although it was sometimes difficult to determine the study design because of insufficient details reported, case studies or series were the most common form of study design accounting for 47% (48/103 of the articles reviewed). Case studies or series were slightly more common for ESCS articles (55%, 30/55) than for TSCS articles (42%, 15/36) (figs 4A and 4B). In contrast, 67% (8/12) of the studies examining magnetic SCS used a quasi-experimental design (see fig 4C). Study designs for TSCS

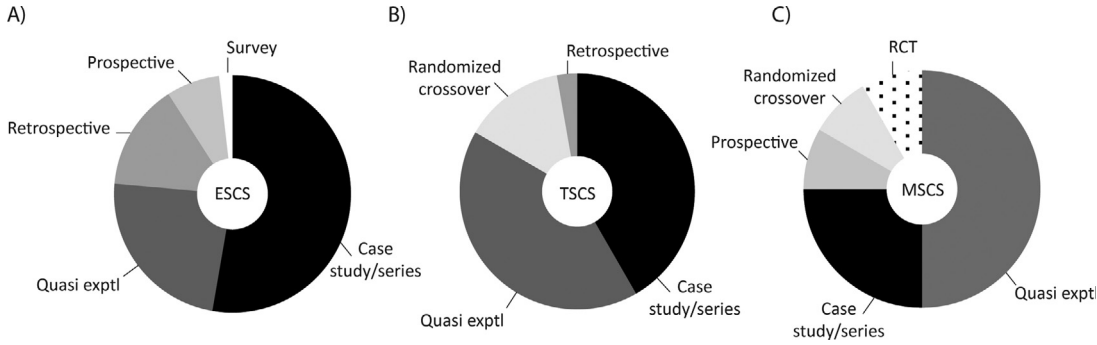

Fig 4 Reported study design for (A) ESCS, n=55; (B) TSCS (n=36); and (3) MSCS, n=12. Abbreviations: MSCS, magnetic spinal cord stimulation; Quasi exptl, quasi-experimental; RCT, randomized controlled trial.

included quasi-experimental and several crossover studies of which some used a degree of randomization. Two articles presented results from a multicenter trial, and both examined ESCS.[51,52] Of all the articles reviewed, there was a single randomized controlled trial that looked at the effectiveness of pulsed magnetic SCS and transcutaneous electrical nerve stimulation on neurogenic overactive bladder dysfunction.[31]

Stimulation devices, sites, and parameters varied widely among the studies, and a summary of this information is available in the supplemental appendix S2 in supplemental tables S1-3 (available online only at http://www.archives-pmr.org/). A major challenge in the reporting of the stimulation parameters is the inconsistencies of terminology. Although some articles failed to adequately articulate the specifics of the devices and stimulation parameters used, those that did so used a variety of terms. As an example, studies examining the effects of TSCS used active/reference/indifferent or anode/cathode in their description of the electrodes. Given that the authors are providing stimulation parameters, they should be using the terms anode/cathode, also including the differences in phases when the biphasic mode is used. However, it is beyond the scope of this review to interpret and/or translate the various terminologies that have been used, and therefore we have provided the stimulation parameters in detail as reported by the authors in supplemental appendix S2, tables S1-3.

Several studies using ESCS and TSCS incorporated concurrent therapy (eg, functional standing activities, gaiting, and functional upper extremity activities) as part of their intervention, the type of concurrent therapy is identified in supplemental appendix S2, tables S1-3. None of the articles mentioned the involvement of a consumer (an individual with lived experience) as a part of the research team or any consultation with those living with SCI as to their concerns and/or priorities.

The actual length of participant involvement (including follow-up assessments) for some articles was difficult to determine because of lack of detail (fig 5A). Of those that reported study durations, almost all ESCS studies (67%, 33/49) were at least 4 months in duration, with 43% (21/49) lasting 12 months or longer. Eleven of the ESCS studies (22%, 11/49) consisted of a single session. Conversely, the TSCS studies tended to be shorter in duration; 78% (28/36) were conducted for 2 months or less, with only 4 being 6 months or longer. Eight of the 12 studies exploring magnetic SCS were conducted in a single session. For many studies, a baseline period was allotted to optimize the stimulation parameters for each individual study participant. For complete study duration specifics, length of therapeutic intervention, and any longer-term follow-up please refer to supplemental appendix S2, tables S1-3.

Participants

Study sample sizes and participant characteristics for those living with SCI are presented in figs 5B, 5C, and 5D; details on those not living with a SCI and/or participants without SCI were also extracted. For sample size details of including participants other than those living with SCI, please see supplemental appendix S3, tables S1-3 (available online only at http://www.archives-pmr.org/). Most articles, 72% (74/103), presented results from studies conducted with the recruitment of 10 or fewer study participants (see fig 5B).

Of those studies that reported the sex of their study participants with SCI, approximately 888 were male and 321 were female participants living with SCI. Of these 1210 individuals, 480 men and 178 women participated in studies examining ESCS, TSCS recruited 267 men and 100 women, and the remaining 141 men and 44 women participated in magnetic SCS. Given the relative rarity of SCI and the small number of research laboratories investigating SCS, the number of 1210 may not represent unique individuals because it is possible that the same individual may have participated in more than 1 study. Twenty-eight of the 55 ESCS studies were conducted with men only, whereas 18 of the studies recruited both sexes, and a single study recruited only women. The majority (25/36) of the TSCS studies recruited both men and women. The magnetic SCS studies were evenly divided between men only and mixed (7 and 5, respectively).

Most studies had cohorts consisting of participants with either a cervical- or thoracic-level SCI, and in general, each study had variation between individuals in terms of the neurologic level of SCI (see fig 5C). Eighty-two of the 103 articles reviewed reported AIS grades. Of those that reported an AIS grade, there was no discernable pattern in the reported SCI severity within each of the studies (see fig 5D). For complete details regarding sample size and participants characteristics please refer to supplemental appendix 3, tables S1-3.

Primary outcomes

The word cloud presented in fig 6 illustrates that motor recovery and ambulation were the most frequently reported primary outcome for ESCS (26 of 55 articles), of which 1 was focused on the upper extremities, and TSCS (23 of 36 articles), of which 3 investigated improving upper extremity function. Other primary outcomes

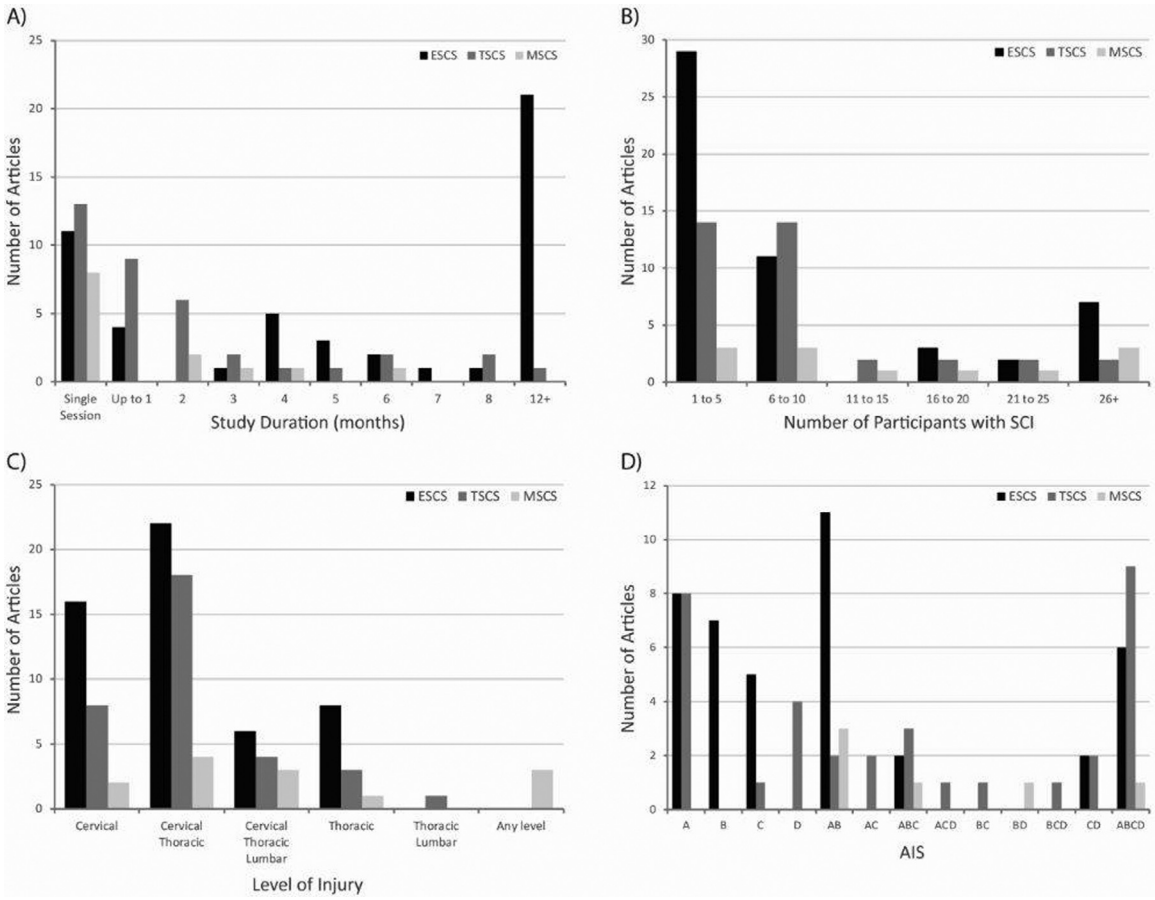

Fig 5 Comparing study and participant characteristics for the types of spinal cord stimulation by reported (A) study duration, (B) no. of participants, (c) participant level of injury, and (D) participant AIS scores. Study duration includes the intervention time and the follow-up period. Abbreviation: MSCS, magnetic spinal cord stimulation.

investigated using ESCS included ambulation specifically (5 of 55 articles), bladder and bowel function (9 of 55 articles), and risk/safety (4 of 55 articles). Neuropathic pain (3 of 36 articles), spasticity management (4 of 36 articles), and bladder and bowel function (2 of 36 articles) were identified as the primary outcome for those studies using TSCS. Ten of the 12 that examined the use of magnetic SCS focused on either bowel and/or bladder. See supplemental appendix S4, tables S1-3 (available online only at http://www.archives-pmr.org/) for a description of each article's extracted purpose/objective and supplemental appendix S2, tables S1-3 for a listing of each article's stated primary outcomes.

Adverse effects

Thirteen ESCS, 4 TSCS, and a single magnetic SCS article reported at least 1 adverse event incident during their study (table 1). The most common adverse event for ESCS was infection at the site of implant followed by pain, unusual sensations, and hardware failure. Reported adverse events for TSCS included unusual sensation at the electrode site, increased spasticity, and initial intolerance of the intervention. One participant experienced autonomic dysreflexia during the initial phases of 1 of the studies examining magnetic SCS. Tables S1-3 in supplemental appendix S5 provide a complete list of the adverse events and respective citations for the reporting articles (available online only at http://www.archives-pmr.org/).

Discussion

The primary focus of this review was to develop a broad understanding of the research that has been conducted in each of the 3 areas of SCS (ESCS, TSCS, magnetic SCS) to inform future research initiatives. This scoping review identified 103 original research articles investigating SCS in the population with SCI

Table 1 No. of articles reporting 1 or more adverse events

Reported Adverse Events	ESCS	TSCS	MSCS
Infection/skin breakdown	7	1	0
Unusual/unpleasant sensations	5	1	0
Hardware failure/lead migration	4	0	0
Pain	4	0	0
Surgical implant revision	5	0	0
Increased spasticity	2	1	0
Autonomic dysreflexia	1	0	1
Intervention intolerance	1	1	0
Skin irritation allergy	1	1	0
Altered bowel function	1	0	0
Boney fracture	1	0	0
Cerebral spinal fluid leak	1	0	0
Total no. of (unique) articles	13	4	1

Abbreviation: MSCS, magnetic spinal cord stimulation.

Fig 6 Reported primary outcomes for ESCS (black, n=55), TSCS (red, n=36), and MSCS (blue, n=12). Abbreviation: MSCS, magnetic spinal cord stimulation.

(ESCS=55; TSCS=36; magnetic SCS=12) (see fig 1). The extracted data were used to highlight what has been done, who is conducting the work, and any gaps that may exist to contribute recommendations for consideration in future research.

One such gap that will need to be addressed is that for studies identified as TSCS and magnetic SCS, where neuromodulation is likely a mechanism of the stimulation effect, the literature continues to persist with the nomenclature of SCS despite the stimulation being initiated outside of the spinal cord. Nonetheless this scoping review has included such studies. The term SCS is used throughout this article but with the recognition that this review includes studies both using direct SCS (ESCS) as well as those where the mechanism may be neuromodulation through stimulation of spinal cord posterior root afferents (TSCS and magnetic SCS).

With no limits applied to the publication year, the earliest article for SCS in the population with SCI was published in 1985 and involved ESCS.[48] In terms of volume and focus, investigations into ESCS (the more invasive form of SCS) clearly dominates in both total number and the annual publication output, with most years since 1985 having produced 1-3 contributions of original research per year and consistently 3-4 per year since 2014, with a sharp increase in 2020. While magnetic and transcutaneous stimulation are not new modalities, the investigation of magnetic SCS and TSCS are a more recent addition to the SCS literature, with the earliest publications in 1996 and 2009, respectively.[49,50] In contrast to the consistent average annual publication output of ESCS, 69% of the TSCS articles included in this review have been published in 2018 through 2021. This more recent burst of publication activity suggests an increasing interest in TSCS as a noninvasive form of SCS. TSCS, a form of SCS that is minimally invasive, less costly because of the absence of a surgical intervention and potentially the most consumer friendly of the current forms of SCS, is being investigated across a broad range of health priorities. We speculate that this surge in popularity of TSCS is not just that it is noninvasive but also because of factors such as lower costs for research and development, possible shorter pathways to commercialization, and ease of participant recruitment and consumer acceptance.

The majority of articles (66%) for all types of SCS were conducted in the United States (see fig 3). Case study or series was the most prevalent (46%) study design reported. Other common study designs included quasi-experimental, crossover with a sham, prospective/retrospective, or a variety of crossover and sham styles. Only a single study was identified as a true randomized controlled trial[31] (see figs 4A, 4B, and 4C), which is generally considered the criterion standard for measuring the effectiveness of a new treatment or intervention.[53] Given that SCS research in SCI is still in its infancy, it is not surprising nor is it a criticism that most of the studies are exploratory and pilot in nature. It is critical that as the field matures, efforts be made to use more robust study designs with sham conditions that can provide stronger evidence of an effect on the outcome of interest caused by the intervention being investigated.

Of the articles examined, most recruited small sample sizes, with 72% of articles reporting results from a cohort of <10 participants and almost half reporting on <5 (see fig 5B). The small sample sizes bring into question the robustness of the study findings. Given SCI is considered an orphan condition, multicenter trials are a powerful way to increase study participant numbers for relatively rarer health conditions such as SCI.[54,55] However, we noted that very few of the SCS studies have used this methodology. The sex distribution, severity, and neurologic level of the population with SCI represented by the articles reasonably represent the range and proportions of those in the community living with SCI, with the majority including male participants and incomplete injuries.[56] To deal with the heterogeneity of SCI, it is important for future studies to better differentiate and group study participants by their injury severity and neurologic level of injury (see figs 5C and 5D) to better inform treatment protocols. Furthermore, inclusion of SCI biomarkers (eg, imaging) and other clinical examinations may provide additional information to differentiate participants to better understand potential differences in response to SCS.

When looking at the primary outcomes of interest, the focus for ESCS has been overwhelmingly on motor recovery and ambulation (47%), with some attention to bladder function (15%). TSCS has also been vested some form of motor recovery (3 of 36 examined upper extremity function) and ambulation (66%) and to a lesser degree on bowel and bladder function, spasticity, and neuropathic pain (20%). In contrast, magnetic SCS has almost solely addressed bowel and bladder function (83%). While the focus initially of ESCS and TSCS was on lower extremity motor recovery and ambulation, which does not reflect the literature stressing the importance and prioritization of sexual, bladder, and bowel function for individuals living with paraplegia and arm and/or hand function in those living with tetraplegia,[57-59] this is currently not the case. Looking at the articles published from January 1, 2020, through March 31, 2021, we find 10 ESCS and 13 TSCS studies examining a diversity of primary outcomes that include bowel and bladder function, spasticity, autonomic dysreflexia, neuropathic pain, cough, cardiovascular function, upper extremity motor recovery, and other motor recovery (ambulation and trunk control).

Many of the articles reviewed did not clearly document the device used nor the stimulation parameters. In several cases, the methods section referred to a prior article that when examined may have also failed to report the device and/or stimulation parameters. While the devices varied, for the studies investigating ESCS, products manufactured by Medtronic Inc, US were the most common. Studies exploring magnetic SCS primarily used devices manufactured by 1 of 2 companies: Dantec Medical,

Denmark and Cadwell, United States/Europe. There was no trend in device use for the TSCS investigations. It has also been noted that even when reported, the variability in terminology makes it difficult to interpret the stimulation protocols of a given study, no less make comparisons across studies. One example of an effort for consistency is provided in the review by Merrill et al.[60] These authors suggest using terms such as working electrode to describe the electrode that is of interest, counter electrode to describe the electrode that completes the circuit, and the reference electrode as the one that is used as a reference to measure electrical potential. For the articles that documented the device and stimulation parameters used, please refer to supplemental appendix S2, tables S1-3.

Engagement of individuals with lived experience of SCI in the planning stages of research can help ensure SCS study outcomes align with the priorities of the SCI community[61]; however, none of the articles included in this scoping review mentioned engagement of consumers or advocacy groups to identify treatment and outcome priorities. A workshop in 2014 was held to develop a framework for clinical research in ESCS from the consumers perspective to better investigate the effects on bowel, bladder, and sexual functional improvement.[62] A 2012 systematic review by Simpson et al,[59] which explored the health and life priorities of those living with SCI, concurs with the aforementioned priorities but also highlighted restoration of motor function, in particular arm and hand function for those with tetraplegia.

A critical but poorly reported area of interest was risk and safety. A handful of studies specifically included the assessment of the risks and safety of ESCS[48,51,63-66] or the potential use of ESCS as a home therapy.[67] Unfortunately, not one study was designed and conducted to specifically examine risk and safety of TSCS or magnetic SCS for those with SCI, nor was an article found that addressed adverse events associated with research or the use of these devices in the community setting. In addition, a designated and independent data monitoring and/or safety committee should become the standard of practice; even though it is often required by the Ethics Committees only a few of the studies documented the presence of such procedures.

In general, if adverse events were reported, they were difficult to find within the article,[68] often buried[69] in the results or discussion, rarely provided in a table,[70] and not easily located using a heading[71] or given their own paragraph. Of the 18% of the articles where an adverse event could be identified, 13 of the 18 articles reporting adverse events were using ESCS and often were serious in nature, whereas the adverse events reported for TSCS tended to be more of an inconvenience (see table 1 and supplemental appendix S5, tables S1 and S2). There were very few examples where the authors clearly stated that no adverse events occurred, and the participants tolerated the intervention well[46]; we suggest that this be standard practice in the future.

As often mentioned in scoping reviews, one of the greatest challenges was the data extraction process because of inconsistencies in how data were presented as well as incomplete and/or missing data.[34,40,47,72] A significant challenge for both data extraction and reporting was the inconsistency and incomplete information on the devices and stimulation parameters used and the protocols in many of the studies. Details relating to timing of the stimulation, follow-up, rehabilitation activities, and even sample sizes were difficult to interpret from many of the articles' methods sections. Given that SCS is a relatively new area of research, it is expected that there will be inconsistency in the tools and protocols used; however, these details should be included to facilitate comparisons or study replication in the future. While not every study can be a randomized controlled trial, we suggest that at least the methodology and results of any clinical trial should follow a standardized checklist such as the one provided by the Consolidated Standards of Reporting Trials 2010.[73]

Lastly, there is a need for comparative studies of the 3 forms of SCS. These types of studies are required given that ESCS, TSCS, and magnetic SCS have been reported to produce similar outcomes. To date there have only been a few multimodal studies: 2 that investigated aspects of motor recovery using ESCS and TSCS[9,74] and 1 head-to-head magnetic SCS and TSCS randomized study looking at neurogenic bladder function.[31] The 2014 review of literature by Moreni-Duarte[42] is an example of an effort to compare different modes of SCS based on mode-specific original research, in this case ESCS vs TSCS. However, in the future multimodal studies should also examine the differing forms of TSCS including but not limited to direct current monophasic, alternating current biphasic, and stimulation parameters using high frequency carrier waves. Participant tolerance of these various forms of TSCS may differ. Furthermore, different stimulation waveforms may result in unique effects and/or prove optimal for a given outcome. A comprehensive comparison of stimulation parameters is beyond the scope of this review, and any attempt would be compromised by the variability in terminology and more so by the poor reporting. That said, of the 36 TSCS articles reviewed, 24 explicitly stated they used a continuous pulse mode vs the 10 where a train/burst mode was used. Using an alternating current or biphasic wave form was identified in 15 of the studies, 8 used a direct current or monophasic waveform, and 2 studies compared the efficacy of both. High-frequency carrier waves were used in 10 studies, 9 used 10 kHz, and 1 used 5 kHz. There was no consistency across studies in terms of which of these stimulation parameters were used for certain outcomes. Ultimately, TSCS is a promising and burgeoning field for those living with SCI. In due course and with continued research efforts, we expect specific waveforms and stimulation parameters will be identified to optimize the treatment of unique dysfunctions after SCI. For the TSCS stimulation parameters, please refer to the Stimulation Parameters column in supplemental appendix S2, table S2. A concerted effort is needed to determine if different types of SCS are comparable in improving functional outcomes or if specific types of SCS are more effective for certain injury profiles or indications. Given that the 3 SCS technologies vary greatly in the level of invasiveness, cost, ease of self-treatment, and level of risk, comparative data would help inform decision making and allow for personalized treatment.

SCS holds tremendous promise in the care and cure of SCI.[1,43,44] This scoping review summarized the state of SCS over the past 35 years. Although many reviews of SCS in SCI have been previously conducted, to our knowledge, this is the first scoping review that includes all modes of SCS and all types of functional recovery outcomes.[75-82] Furthermore, one of the aims of this scoping review was also to assess and provide a summary of study design features and methods that have been used.

There is clearly a need to engage individuals with lived experience in all phases of the research, using an integrated knowledge translation approach.[61] These consumers, those with lived experience as well as family or friends, caregivers, and community and/or advocacy organizations, must be meaningfully engaged and be heard from early and often, starting with the conceptualization of the study. Those affected by a decision have a right to be a part of the decision-making process. Using a community-based approach, Gainforth et al[61] documents a 4-step inclusive process of engaging

all vested parties to create a set of integrated knowledge translation guiding principles for conducting and disseminating SCI research. This article provides a roadmap to ensure that future research is both meaningful and relevant to all stakeholders.[61] For the researcher there is evidence that a concerted effort of consumer engagement pays dividends including increase study enrolment rate, improved success in securing extramural funding, as well as improved study designs, protocols, and the selection of relevant outcome measures.[83] These relevant outcome measures must also include patient-or participant-reported outcomes ranging in level from the individual to the community. In addition, more research is needed to optimize treatment protocols; consider dose response, risks, and safety; and compare of the effectiveness and efficacy of these forms of SCS. There is a growing body of evidence that suggests that after long-term ESCS[84] use and interventions with TSCS as brief as 8 weeks,[17,25,85] continued neuromodulation appears to persist even without the ESCS stimulator being active or continued sessions of TSCS. It remains to be seen whether this is also true for magnetic SCS. Even with these unanswered questions and the mechanistic understanding of SCS being in its infancy, electrical neuromodulation holds great promise in the care and cure of those living with SCI. It is both the quantity and quality of original research that will contribute to the necessary evidence and understanding. While beyond the intent of this scoping review, the efforts to understand and define the various mechanisms of action need to continue, which in turn will help improve the implementation of SCS.

Study limitations

This scoping review was limited to original human research that was published in English. To maximize the quality of data extracted we excluded reviews, descriptions of protocols or proposed research, conference proceedings, abstracts, lectures, theses, editorials, and commentaries from this scoping review. By doing so we limited sources with incomplete data and minimized the risk of the duplication of data. Because of the lack of complete documentation found in many of the articles selected for this scoping review, we were unable to discuss in detail specific areas of interest, such as whether the injuries were traumatic vs nontraumatic and the time since the injury occurred. Because of the piecemeal nature of some of the data reported, as well as inconsistencies of terminology used for the data extracted, in particular relating to stimulation parameters and the devices used, the data extracted are incomplete.

Conclusions

In summary, this scoping review has identified several areas that should be addressed to accurately assess the effectiveness and safety of these technologies for SCS to be a component of the standard of care. Recommendations include meaningful engagement of consumers, more robust study designs, larger sample sizes with appropriate representation, comparative SCS studies, improved reporting of the stimulation device and parameters, alignment of study outcomes with the priorities of the community with SCI, and comprehensive reporting of adverse events. These recommendations will help facilitate the translation of this critical research such that individuals living with SCI can benefit from these exciting innovations.

Supplier

a. EndNote version X9.3.2; Clarivate.

Keywords

Rehabilitation; Spinal cord injuries; Spinal cord stimulation

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