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ORIGINAL ARTICLE

Advances in Epidural Spinal Cord Stimulation to Restore Function after Spinal Cord Injury: History and Systematic Review

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Abstract

Epidural spinal cord stimulation (eSCS) has been recently recognized as a potential therapy for chronic spinal cord injury (SCI). eSCS has been shown to uncover residual pathways within the damaged spinal cord. The purpose of this review is to summarize the key findings to date regarding the use of eSCS in SCI. Searches were carried out using MEDLINE, EMBASE, and Web of Science database and reference lists of the included articles. A combination of medical subject heading terms and keywords was used to find studies investigating the use of eSCS in SCI patients to facilitate volitional movement and to restore autonomic function. The risk of bias was assessed using Risk Of Bias In Non-Randomized Studies of Interventions tool for nonrandomized studies. We were able to include 40 articles that met our eligibility criteria. The studies included a total of 184 patient experiences with incomplete or complete SCI. The majority of the studies used the Medtronic 16 paddle lead. Around half of the studies reported lead placement between T11-L1. We included studies that assessed motor ($n = 28$), autonomic ($n = 13$), and other outcomes ($n = 10$). The majority of the studies reported improvement in outcomes assessed. The wide range of included outcomes demonstrates the effectiveness of eSCS in treating a diverse SCI population. However, the current studies cannot definitively conclude which patients benefit the most from this intervention. Further study in this area is needed to allow improvement of the eSCS technology and allow it to be more widely available for chronic SCI patients.

Keywords: autonomic dysfunction; motor activity; spinal cord injuries; spinal cord stimulation

Introduction

Spinal cord injury (SCI) is a devastating complication of trauma and leaves little hope for recovery. Affecting approximately 1.5 million individuals, SCI is the second leading cause of paralysis in the United States.[1,2] While many groups have focused on therapies for subacute SCI, chronic SCI remains an unmet need, with an estimated 294,000 people (range of 250,000 to 368,000 individuals) currently living with chronic SCI in the U.S.[3] The surprising discovery that epidural spinal cord stimulation (eSCS) could have beneficial effects in patients with chronic neurological deficits was first reported in a

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case series in 1980 in patients with multiple sclerosis.[4] However, the significance of this finding was not recognized for many years afterwards.

The first report of recovery of volitional movement in a patient with complete motor loss was reported by Harkema and collealgues.[5] This led to increased interest in this area of investigation, and the number of papers published on the topic has gradually increased to 28 papers on restoration of volitional movement in 2021. The purpose of this review is to summarize the key findings to date regarding the use of eSCS in SCI and to allow this knowledge to guide our future studies. In addition, this review aims to characterize study participants across different institutions, evaluate their ability to volitionally move their lower extremities, assess the autonomic functional benefits, and to investigate the differences in devices and programming that are being used for eSCS.

A constellation of symptoms occurs following SCI, with the most obvious being motor deficits. In addition to direct morbidity and mortality, secondary complications from SCI are the result of a combination of immobility and morbid pressure ulcers, autonomic dysregulation, cognitive dysfunction, and complex pain syndromes, which consequently produces cardiovascular, respiratory, urinary, and gastrointestinal complications.[6] All of these complications have been targets of eSCS, either directly or indirectly. Other under-recognized complications include poor bone health and fragility, infertility, and depression,[6-8] which remain unexplored targets. These complications contribute to the high cost of this condition, which is estimated at $5.8 million over a lifespan.[2] It is not currently fully understood which of these disabilities can be addressed by eSCS and how best to optimize the eSCS systems for each indication. Further complicating the research results is the fact that the eSCS devices currently used were not designed for SCI, but rather for chronic pain syndromes and therefore are unlikely to be optimal for this use.

History of eSCS

In the late 1960s, Melzack and Wall introduced the ''gate control'' theory of pain and hypothesized that nonnoxious input could be used to suppress noxious input traveling in similar pathways.[9] Over the next several years, it was found that eSCS could generate regional anesthesia from nociceptive pain.[10-12] Since then, there have been numerous papers published on eSCS alleviating pain in humans, but relatively little on its effects for the treatment of either pain or volitional movement after SCI. Several groundbreaking studies demonstrated that spinally transected cats were able to generate movement with or without training.[13] This led to the conclusion that even after spinal cord transection, pathways controlling movement may still be active.[14] Therefore, it was hypothesized that eSCS could provide functional benefit by activating local spinal circuits in the lumbosacral spinal cord in decerebrate cats, and this was reported across multiple institutions.[15-17]

Animal models were then utilized to determine the efficacy and safety of eSCS to restore movement after SCI.[16] Spinally transected rats were implanted with an epidural stimulator at the T12-L6 levels and it was found that eSCS was able to generate some bilateral hindlimb locomotor activity. Movement was dependent on sensory feedback and was found to be most prominent when the L2 level was stimulated.[18] Other studies investigated the effects of eSCS in conjunction with pharmacologic agents and step training. These early rodent studies have provided evidence that the circuitry within the spinal cord remains intact even after complete transection of the spinal cord, suggesting that eSCS can be utilized in humans to activate these circuits and consequently generate movement even in the setting of a devastating injury.[19]

Human studies utilizing eSCS to treat SCI

In 2011, Harkema and colleagues theorized that after SCI, intact spinal circuitry may be functional with the addition of electrical input. Therefore, it was hypothesized that eSCS of the lumbosacral spinal cord coupled with physical training could facilitate standing and stepping in humans with motor complete SCI through the action of the central pattern generator (CPG).[5] The results from this study demonstrated that eSCS and intensive locomotor training enabled full weight-bearing standing in a 23-year-old male 3 years post-injury (injury level C7-T1 and American Spinal Injury Association [ASIA] Impairment Scale B). Surprisingly, this subject was able to generate movement volitionally rather than through the sole action of the CPG, thereby implicating supraspinal input. Since this initial report, similar results have been independently reported across three sites.[20-22]

While the mechanism has not been fully elucidated, there is now evidence that many clinically complete SCI patients have preserved viable tracts which are unable to overcome inherent spinal cord segmental excitation.[23] eSCS has been shown to uncover residual pathways within the damaged spinal cord by engaging the myelinated afferents in the posterior roots.[24,25] Researchers have further theorized that neuroplasticity after eSCS could result in an increase in axonal sprouting in the lumbosacral spinal cord, thereby allowing for enough excitation of the existing interneurons and motor neurons to result in movement.[5,26] More recent evidence has indicated that there is likely an element of neuroplasticity involved, as several patients have retained volitional movement even after the eSCS is turned off.[27,28] Other studies have utilized computer simulations and found that eSCS may increase the overall excitability of the spinal cord by recruiting proprioceptive afferent neurons, which in turn activate motor neurons.[29]

eSCS has also emerged as a novel and effective intervention for post-SCI autonomic dysfunction. It has been shown to enhance physiologic outcomes such as cardiovascular, bowel, bladder, and sexual function.[20,30] The effect of eSCS on autonomic function was first reported in 1991 by Katz and colleagues.[31] The mechanism of action likely differs from that of volitional movement, but is also not fully understood. eSCS can stimulate the autonomic and motor spinal circuits that affect bowel and bladder function.[31] Further, it has been reported in both animal[32] and human studies[33,34] that eSCS modulates cardiovascular parameters and subsequently can ameliorate cardiac dysfunction. It can also potentially activate neurocircuitry responsible for modulation of the skeletal muscle pump and increase venous return. During supine stimulation, increased blood pressure was attributed to increased strength of muscle contractions; activation of residual sympathetic fibers below the level of injury; and blood redistribution from the lower extremities.[35]

Current state of available eSCS

eSCS involves the implantation of one or more electrodes within the epidural space that are then connected to an implanted pulse generator (IPG), which delivers electrical current to the spinal cord. This device was initially tested in humans with placement of electrodes over the dorsal columns of the spinal cord, with the hypothesis that this would be the optimal location for the attenuation of pain signaling to the brain.[4,11] eSCS implantation surgery is a routine operation for many neurosurgeons and other pain management specialists, requiring no hospital admission. Complications, including hematoma, infection, migration of electrodes, hardware failure, SCI, and foreign body reactions, have been reported.

In a systematic review by Taccola and colleagues,[36] the authors reported that the complications are highly variable, with several large studies reporting overall complication rates of 20-75%. For example, lead migration complication rates were found to be between 13-22%, with cervical implant complication rates at the higher end of the spectrum. However, other studies reported low complication rates for lead migration, which occurred in only 1.4-2.1% of over 100 analyzed cases, infection (5%), paraplegia (2%) and pain (5-10%) resulting from the operation.[36] Despite these potential risks, in the experience of the authors complication rates were very low, rendering this intervention both safe and effective. Possible explanations for the lower complication rates could include increased attention to infection risk, including performing the procedure in an operating room rather than an ambulatory clinic setting. Another possibility is that procedures performed in clinical trials are generally performed by a select group of experienced surgeons, whereas in the community this might not be the case.[37,38]

Methods

Information sources and search strategy

The study was conduction according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline.[39] Electronic searches were carried out using MEDLINE, EMBASE, and Web of Science. The reference list of identified systematic reviews and review articles was hand-searched for other references. A combination of medical subject heading (MeSH) terms and keywords was searched: ''EES''; ''eSCS''; ''epidural stimulation''; ''epidural electrical stimulation''; ''epidural spinal cord stimulation''; ''spinal cord stimulation''; ''spinal cord injury''; ''SCI'' using the Boolean operator ''OR'' for each concept and ''AND'' to combine the different concepts. Search limit was applied to studies in English. Databases were searched from their inception to December 29, 2021.

Eligibility criteria

We systematically searched the databases for studies investigating the use of eSCS in SCI patients to facilitate volitional movement and to restore autonomic function. Since there are no alternative therapies for SCI, there are no comparators for this review. We excluded studies that used non-human subjects and subjects that were not implanted with eSCS. Functional outcomes unrelated to volitional movement or autonomic function, such as studies only focusing on pain or spasticity, were excluded. Further, we excluded publications that present secondary data, such as literature reviews. When several different studies used the same dataset at different time points, we utilized the study that displayed the most complete version of the dataset. We referred to each patient as a ''patient experience'' because we could not tell whether the same patient had been enrolled separately into different studies.

Study selection and data extraction

Studies were uploaded to DistillerSR Version 2.35 was utilized to conduct the review and remove duplicate studies. Three independent reviewers, D.F., I.P., and N.M., went through two tiers of screening: Abstract and Title and Full Text Review. Discrepancies were resolved through discussion and consensus between the reviewers. Reviewer extracted data included study characteristics (e.g. settings and countries); subject demographics (e.g., age and gender); time from injury; injury level; ASIA classification (and whether or not injury classification changed from the beginning of the study); postoperative time spent in the hospital; whether autonomic function was assessed (e.g., cardiovascular, neurogenic, bowel, and bladder, spasticity, and sexual function); outcome assessments that were utilized to quantify volitional movement and autonomic dysfunction; whether or not

quality of life was assessed; intervention characteristics including device specifications; programming and optimization of the stimulator settings; and the amount of time the stimulator was on; and if subjects underwent rehabilitation therapy and their effects.

Bias assessment

The risk of bias (Supplementary Section S1) was assessed by two independent reviewers, N.M. and I.P., using the Risk Of Bias In Non-Randomized Studies of Interventions (ROBINS-I) tool for nonrandomized studies of the effects of interventions (NRSIs).[40] It was conducted on DistillerSR software. A detailed description of the bias assessment process can be found in the Supplementary Section S1.

Results

Study selection

The PRISMA flow diagram (Fig. 1) presents the results of the literature search and selection process of eligible studies. The initial search led to the identification of 1344 articles. After the removal of duplicates, 840 studies were reviewed for abstract and title and a further 734 studies were excluded. Each of the remaining 106 articles were submitted for full-text screening. Finally, 40 articles were deemed eligible and were included in the review. We could not identify any published randomized controlled trials on this subject.

Study and participant characteristics

Characteristics of the analyzed studies and included participants are reported in Table 1. All included studies are from the U.S. except for seven; one is from Russia; four are from Canada and the other two are from Switzerland. Of the 40 studies, 15 were conducted at Louisville, KY. The majority of the studies were case studies or case series. Katz and colleagues had the largest sample size in their study ($n=33$).[41]

The studies included a total of 184 patient experiences. These patient experiences included 157 males; 25 females, and two unspecified. Their age ranged from 18 years to 66 years. The shortest time from injury was 7.0 months and the longest was 31.5 years. In terms of injury levels and severity, the majority of patients had injury levels in the cervical ($n=29$ studies) and thoracic ($n=25$ studies), with 16 studies reporting both regions. The highest reported level was C2 included in two studies.[37,38] The most studied ASIA scores were ASIA A and B, ($n=26$ and 22, respectively), followed by ASIA C ($n=11$) and ASIA D ($n=3$).

Stimulator placement and optimization

Most studies used a Medtronic stimulator (32 of 40) with 16 paddle leads. The highest level of lead placement was C5 reported by two studies Lu and colleagues[42] and Moshonkina and colleagues.[43] The lowest was at S2.[24,42,43] Half of the studies reported lead placement between T11 and L1 (28 of 40). Duration of ''stimulation on'' was reported in six studies: two times for 30 min 43; 2 h/training session and 1 h/day[44]; 1 h/session[45]; 5 to 21 h/day, with a mean of 13.7 ± 5.8 h/day[28]; average 52 ± 13 h/session[5]; and 24 h/day.[46] Only Darrow and colleagues[20] reported ambulatory surgery regarding the time spent in the hospital after stimulator implantation, with the remainder not reporting time in hospital. Moreover, parameter details of optimization including frequency, amplitude, pulse width, and placement of electrodes varied greatly between studies as shown in Table 2.

Outcomes assessment

We included studies that assessed motor ($n=28$); autonomic ($n=13$); and other outcomes ($n=10$) including metabolic activity; sympathetic nerve activity, a sense of effort; and proprioception. Quality of life was assessed by three studies.[5,20,47]

The most assessed autonomic outcomes were bladder and cardiovascular function. Both were reported in seven and six studies, respectively, while bowel function was assessed by only three studies.[20,31] The majority of the studies assessing autonomic function used plethysmography ($n=6$) for the cardiovascular system and urodynamic investigations for bladder function ($n=5$). A full list of outcome assessment methods is documented in Table 3.

The volitional and autonomic outcomes measured by the included studies varied greatly as shown in Tables 4 and 5. All of the studies reported improvement of outcomes assessed with eSCS except Katz and colleagues[41] indicated an insignificant change for urodynamic investigations and Formento and colleagues[29] reported reduced proprioception and a narrow range of locomotor facilitation that required training. All studies evaluated movement in the lower limbs except for Lu and colleagues[45] who studied hand function. Electromyogram (EMG) and gait analysis were the most employed methods for volitional outcome assessment. For evidence of motor recovery, four studies reassessed the ASIA score post intervention.[21,22,24,48] However, only two patients showed improvement in the score. Angeli and colleagues[44] reported a change in ASIA score from B to C and Wagner and colleagues[22] reported a change from C to D.[22,44]

Rehabilitation therapy

Rehabilitation therapy was described pre-implantation in 19 of 40 studies and post-implantation in 21 of them. The number and duration of sessions varied considerably as shown in Table 6. Of the 25 publications that

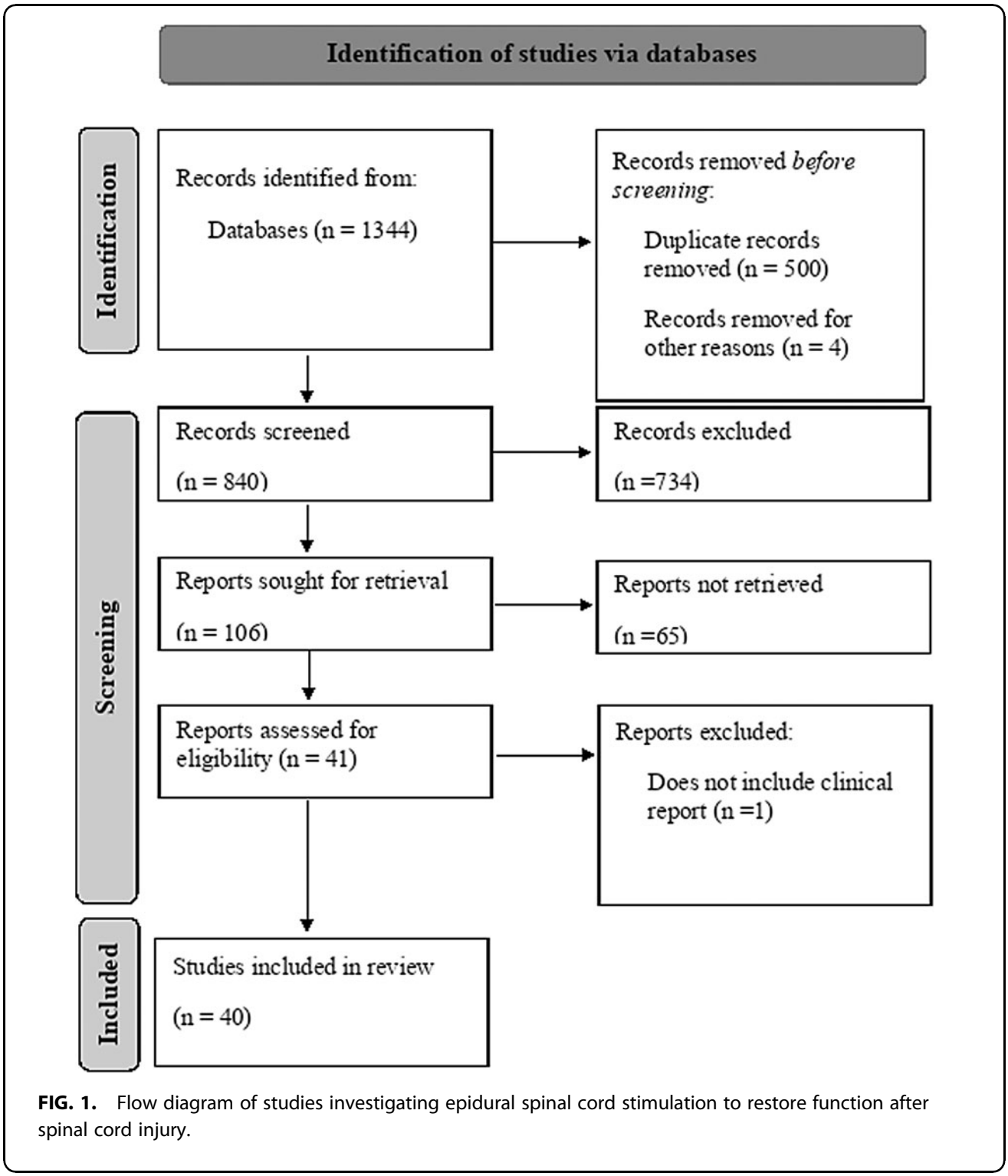

FIG. 1. Flow diagram of studies investigating epidural spinal cord stimulation to restore function after spinal cord injury.

reported specific rehabilitation training, only eight studies reported improvement of the measured outcomes without stimulation. However, they all indicated that increased improvement was observed with eSCS. For example, three studies reported improvement in volitional movement with training but it was insufficient to restore over ground walking.[49-51]

ROBINS-I risk of bias assessment

A detailed list of risk of bias assessments using ROBINS-I is provided in Supplementary Section S1. The risk of bias within each study was judged overall as serious for all publications. The measurement of outcomes was the primary source because blinding of the assessor was not reported by any of the studies. Further, while patients

Table 1. Study and Participant Characteristics

Author (Year)	Site	Males:females	Age range (years)	Time since injury (range, years)	Lowest injury site (range)	ASIA score
Angeli et al. (2014)	Louisville, KY / Los Angeles, CA, USA	4:0	23-32	2.2-4.2	C7-T5	A and B
Angeli et al. (2018)	Louisville, KY, USA	3:1	22-32	2.2-3.3	C5-T4	A and B
Calvert et al. (2021)[63]	Los Angeles and Rochester, MN, USA	8:1	22-36	2-13	C5-T6	A, B, and C
Cheng et al. (2019)[64]	Pasadena, CA / Louisville, KY, USA	2 (Not specified)	Not specified	Not specified	Not specified	A
Gill et al. (2021)[65]	Rochester, MN, USA	2:0	26-37	3-6	T3-T6	A
Gorgey et al. (2020)	Richmond, VA, USA	1:0	26	2	C7	C
Grahn et al. (2017)	Rochester, MN, USA	1:0	26	3	T6	A
Herman et al. (2002)	Phoenix, AZ, USA	1:0	43	3.5	C6	C
Huang et al. (2006)[66]	Tempe/Phoenix, AZ, USA	2:0	43-48	3.5-8	C6- T8	C
Ibanez et al. (2021)[67]	Louisville, Kentucky, USA	5:0	24-52	2.2-16.6	C4- T4	A and B
Mesbah et al. (2021)[68]	Louisville, KY, USA	15:5	19.9-60.6	2.4-16.6	C3-T4	A and B
Linde et al. (2021)[69]	Rochester, MN, USA	2:0	26-37	3-6	T3-T6	A
Moshonkina et al. (2012)	St.-Petersburg, Russia	1:3	22-58	Not specified	C5-L1	A, B, and C
Peña Pino et al. (2020)	Minneapolis, MN, USA	4:3	42 ± 11.4	3 -17	T4-T8	A and B
Rejc et al. (2015)[70]	Louisville, KY / Los Angeles, CA, USA	4:0	24-33	2.2-4.2	C7-T4	A and B
Rejc et al. (2017a)[71]	Louisville, KY/ Los Angeles, CA, USA	1:0	32	4.2	C7	B
Rejc et al. (2017b)[72]	Louisville, KY / Los Angeles, CA, USA	4:0	24-33	2.2-4.2	C7-T4	A and B
Smith et al. (2022)	Louisville, KY, USA	8:3	21-45	2.4-8.6	C2- T1	A and B
Darrow et al. (2019)	Minneapolis, MN, USA	0:2	48-52	5-10	T4-T8	A
Harkema et al. (2011)	Louisville, KY/ Los Angeles, CA, USA	1:0	23	3.4	T1	B
Barolat et al. (1986)	Philadelphia, PA, USA	1:0	22	0.75	C5	C
Gill et al. (2018)	Rochester, MN, USA	1:0	26	3	T6	A
Calvert et al. (2018)[73]	Rochester, MN, USA	2:0	26-37	3-6	T3-T6	A
Carhart et al. (2004)	Phoenix, AZ, USA	1:0	43	3.5	C6	C
Ganley et al. (2005)	Tempe, AZ, USA	2:0	43-48	3.5-8.0	C6-T8	C
Lu et al. (2016)	Los Angeles, CA, USA	2:0	18-20	2-2.5	C5-C6	B
Sayenko et al. (2014)[74]	Louisville, KY / Los Angeles, CA, USA	3:0	23-32	2.2-4.2	C7-T4	A and B
Wagner et al. (2018)	Lausanne, Switzerland	3:0	28-47	4-6	C4-C8	C and D
Aslan et al. (2018)[75]	Louisville, KY, USA	7:0	26.7 +- 4.1	2.0 - 3.5	C5-T4	A and B
Harkema et al. (2018a)	Louisville, KY, USA	4:0	Not specified	Not specified	Not specified	A and B
Harkema et al. (2018b)	Louisville, KY, USA	3:1	24-35	3.8-8	C4	A and B
West et al. (2018)	Vancouver, BC, Canada	1:0	Early 30's	Not specified	C5	B
Squair et al. (2021)	Calgary, Alberta, Canada	1:0	38	1	C5	A
Beck et al. (2021)[76]	Rochester, MN, USA	2:0	26-37	3-6	T3-T6	A
Herrity et al. (2018)	Louisville, KY, USA	1:0	31	3.3	C5	B
Herrity et al. (2021)	Louisville, KY, USA	16:4	20-51	1-15	C2-T4	A and B
Katz et al. (1991)	Richmond, VA, USA	31:2	24-66	0.58-31.5	C4-T10	A, B, C, and D
Walter et al. (2018)	Vancouver, BC, Canada	1:0	32	4	C5	B
DiMarco et al. (2021)[77]	Cleveland, OH, USA	5:0	30-50	2-4	C3-T1	A
Formento et al. (2018)	Laussane, Switzerland	3:0	28-47	4-6	C4-C7	C and D

ASIA, American Spinal Injury Association.

acted as their own controls with ''stimulator on'' and ''stimulator off,'' patients themselves report being able to discern whether or not the stimulator is on or off, and therefore cannot be reliably blinded.

The judgment for risk of pre-intervention domains: Confounding, selection, and classification biases ranged from moderate to serious, where moderate was the lowest possible risk of bias for intervention studies. Regarding confounding factors, 17 out of 40 studies confirmed the electrode array span position on appropriate vertebral levels as a potential confounder using intraoperative fluoroscopy. Therefore, they were considered as moderately biased. Many publications were considered low risk for deviations from intended interventions ($n = 26$). The majority of the studies did not report any missing data ($n = 36$). Thus, they were classified as low risk, but that could also be considered ''no information.'' The risk of bias for selective reporting ranged from low to moderate.

Discussion

Chronic SCI is a significant public health issue with no treatments readily available. eSCS has been available for many decades for the treatment of pain; however, it has only recently been recognized as a potential therapy

Table 2. Outcome and Assessment Methods

Author (Year)	Outcomes assessed	EMG	Gait analysis	Plethy	EKG	Urody	Other assessment methods
Angeli et al. (2014)	Volitional	X	X				BMC, joint angles, tensile force data, modulation of volitional leg flexion force in response to three auditory signals Transcranial Magnetic Stimulation
Angeli et al. (2018)	Volitional	X	X				Kinematics, body weight support harness, treadmill distance travelled
Calvert et al. (2021)	Volitional	X					
Cheng et al. (2019)	Volitional (synergy)	X					Clinician-assigned standing score
Gill et al. (2021)	Volitional	X					Vertical ground reaction forces (vGRF)
Gorgey et al. (2020)	Volitional	X					Modified Borg scale
Grahn et al. (2017)	Volitional	X					Electrophysiological assessment
Herman et al. (2002)	Volitional		X				Whole–body metabolic rate and fuel oxidation Time for 15 m walk
Huang et al. (2006)	Volitional (neuromodulation)	X	X				Borg scale sense of effort
Ibanez et al. (2021)	Volitional	X					
Mesbah et al. (2021)	Volitional	X					Neurophysiological spatiotemporal mappings
Linde et al. (2021)	Volitional						Force sensitive resistors (FSRs)
Moshonkina et al. (2012)	Volitional	X					Diagnostic Spinal Cord Electrical Stimulation (ESSC)
Peña Pino et al. (2020)	Volitional	X					BMCA, Modified Ashworth Scale (MAS), and Muvi 300 cycle
Rejc et al. (2015)	Volitional	X					Ground reaction forces
Rejc et al. (2017a)	Volitional	X	X				High speed optical motion capture system, high resolution pressure sensing mat, and two force platforms
Rejc et al. (2017b)	Volitional	X	X				Body weight support
Smith et al. (2022)	Volitional	X					Standing time
Darrow et al. (2019)	Volitional and autonomic (cardiovascular, bowel, bladder, and sexual function)	X		X	X		BMCA, neurogenic bowel and bladder symptom scores
Harkema et al. (2011)	Volitional and autonomic (bladder and sexual function)	X	X				Joint angles, foot switch, ground reaction forces, body weight support
Barolat et al. (1986)	Volitional and other (spasticity)	X					Subjective description
Gill et al. (2018)	Volitional and other (spasticity)	X	X				Goniometers, video recordings, ground reaction force during stepping
Calvert et al. (2018)	Volitional and other (intraoperative mapping for lead placement)	X					Subjective description and goniometers
Carhart et al. (2004)	Volitional and other (sense of effort)	X	X				Gait analysis with kinematics (motion capture systems), Borg scale for sense of effort
Ganley et al. (2005)	Volitional and other (metabolic activity)	X	X				Kinematics, muscle force, metabolic activity
Lu et al. (2016)	Volitional (hand strength) and other (pain)	X					Handgrip force, clinical scores (ARAT, SCIM, UEMS)
Sayenko et al. (2014)	Volitional and other (neuromodulation, epidural evoked potentials)	X					Body weight support
Wagner et al. (2018)	Volitional and other (spatiotemporal stimulation vs. continuous stimulation, closed loop stimulation technology, system that supports activities of daily living [walking and cycling])	X	X				Motion capture system, video, EEG
Aslan et al. (2018)	Autonomic (cardiovascular)	X		X	X		
Harkema et al. (2018a)	Autonomic (cardiovascular)			X			
Harkema et al. (2018b)	Autonomic (cardiovascular)	X		X			Oscillometric
West et al. (2018)	Autonomic (cardiovascular)	X		X			Transthoracic echocardiography, and transcranial doppler
Squair et al. (2021)	Autonomic (cardiovascular) and sympathetic nerve activity			X			Microneurography
Beck et al. (2021)	Autonomic (bladder)	X				X	Neurogenic bladder symptom score (NBSS)
Herrity et al. (2018)	Autonomic (bladder)	X				X	Cystometry

(*continued*)

Table 2. (Continued)

Author (Year)	Outcomes assessed	EMG	Gait analysis	Plethy	EKG	Urody	Other assessment methods
Herrity et al. (2021)	Autonomic (bladder)					X	Cystometry
Katz et al. (1991)	Autonomic (bladder)					X	Filling cystometry pressure flow study with simultaneous electromyography
Walter et al. (2018)	Autonomic (bladder and bowel)	X			X	X	Neurogenic Bowel Dysfunction (NBD) Score
DiMarco et al. (2021)	Autonomic (bowel and cough)						Bowel management questionnaire; BIOPAC Data Acquisition and Analysis System with AcquKnowledge software, MP100 system with TSD 160 pressure transducer.
Formento et al. (2018)	Other (proprioception)	X	X				Volitional motor task (auditory cues)

EMG, electromyography; Plethy, plethysmography; Urody, urodynamic; EKG, electrocardiography; ESSC, electrical stimulation of the spinal cord; BMCA, Brain Motor Control Assessment; ARAT, Action Research Arm Test; SCIM, Spinal Cord Independence Measure; UEMS, upper extremity motor score; EEG, electroencephalography; TSD, transonic small disturbance.

for chronic SCI. Recent studies have focused on improving volitional movement and autonomic dysfunction including cardiovascular, bowel, and bladder, although outcomes have also included spasticity, pain, and quality of life. In this review, we focused on studies that utilized outcomes for which these devices are not approved such as volitional movement and autonomic dysfunction with the goal of bringing attention to the potential benefits of off-label use of eSCS in chronic SCI.

This systematic review includes a comprehensive list of publications reporting the impact of eSCS on motor and autonomic function in incomplete and complete SCI. We identified 40 articles that studied a total of 184 patient experiences. We refer to total number of ''patient experiences'' rather than ''patients'' because we could not determine whether some patients were included in more than one study with different outcome measures. Patients were mostly males ($n = 157$), indicating a gender bias. Although males are more commonly injured than females (approximately 4:1), these results suggest that more females should be included in this research in order to identify gender differences. Ages ranged from 18 to 66 years. It has been suggested that the age recommended for implantation may differ depending on the indication for spinal cord stimulation.[52,53] Twenty-two years is the youngest age approved by the U.S. Food and Drug Administration for eSCS implantation. None of the studies reported the race or ethnicity of the participants, which should also be a consideration in future studies. The time range from injury to enrollment was between 7.0 months and 31.5 years indicating that late implantation is not a contraindication.

The ASIA impairment scale is the most utilized system for measuring and classifying SCI.[54] The majority of participants were ASIA A or B. Only two patients out of nine in two separate studies[22,44] demonstrated a change in grade post intervention. This may suggest that ASIA grading may be too crude of a measure to utilize in this context. The majority of the studies included patients with injury levels in the cervical ($n = 29$) followed by thoracic ($n = 25$) regions, indicating that both of these injury types may be considered for implantation. The inclusion of diverse injuries and outcomes may demonstrate the effectiveness of eSCS in treating a diverse patient population. However, it also makes it difficult to draw conclusions regarding which patients could benefit the most from this intervention.

More than half of the publications studied volitional movement. However, autonomic dysfunction including cardiovascular, bowel, bladder, and sexual function remain key concerns of chronic SCI patients, as they significantly impact quality of life.[55,56] Only three studies assessed the quality of life of SCI participants. All studies reported some improvement in outcomes in some or all included participants with eSCS except two studies, with one reporting an insignificant change for urodynamic investigations and the other reporting reduced proprioception and a narrow range of locomotor facilitation that required training.

The most commonly used stimulators were the Medtronic 16 paddle lead placed between T11 and L1. Lu and colleagues[45] reported a higher stimulator placement between C5-T1 in an effort to target hand function. Moshonkina and colleagues[43] included placement at different levels (C5, T5, L2-L5, and S2). Since eSCS has been designed for use in the treatment of chronic pain, currently available devices are neither the ideal design nor are they optimal for the programming required to generate volitional movement, to restore autonomic function, or to help with other physiologic disruptions arising from SCI. Investigating the parameter space to optimize the clinical delivery of stimulation has indicated that there are regions of optimal pulse width, frequency and amplitude. This has provided evidence for the importance of mapping the functional neuroanatomy of the spinal cord in order to correlate specific stimulation parameters with volitional movement and autonomic function.

Table 3. Device and Parameter Optimization

Author (Year)	*eSCS Used*	*Leads placement*	*Number of electrodes per lead*	*Brief description of stimulator settings (optimization)*
Angeli et al. (2014)	Medtronic	Paddle	16	Cathodes and anodes for leg movement, frequencies 25 or 30 Hz.
Angeli et al. (2018)	Not specified	Paddle	16	Stimulation (2 Hz) to identify settings for standing and stepping movements. EMG used to decide on final settings. During training, settings modified every 2-4 weeks.
Calvert et al. (2021)	Medtronic	Paddle	16	Stimuli were delivered as biphasic charge balanced rectangular pulses with a 0.21 msec pulse width frequency 0.2-2.0 Hz
Cheng et al. (2019)	Medtronic	Paddle	16	Frequency (20 Hz) and pulse width (210 μs) were constant between trials. For limited trials, four different configurations were interleaved at 10 Hz
Gill et al. (2021)	Medtronic	Paddle	16	Refinement across training sessions voltage amplitude (2.0-4.1 V), pulse frequency (20-30 Hz), and pulse width (200-450 μs) applied continuously.
Gorgey et al. (2020)	Medtronic	Paddle	16	EMG (baseline) 100% EAW–no eSCS and (post-intervention) 100% EAW–no eSCS, EAW–with eSCS, 35% EAW–no eSCS, and 35% EAW–with eSCS, 40 Hz, 420 sec, 6-7 V
Grahn et al. (2017)	Medtronic	Paddle	16	Used algorithm to test wide field vs. local field electrode configurations. Tested parameters: 15-40 Hz, 0.21 msec, 0-6V.
Herman et al. (2002)	Medtronic	Percutaneous	4	Electrical parameters tested for efficacy in promoting gait
Huang et al. (2006)	Medtronic	Percutaneous	4	Tested different parameters for gait improvement. Narrowed down to 20-40 Hz, 800 μs, caudal cathodes, and stimulation intensity above sensory threshold but below motor threshold.
Ibanez et al. (2021)	Medtronic	Paddle	16	Multiple stimulation programs were delivered in an interleaved fashion, or with independent frequencies
Mesbah et al. (2021)	Medtronic	Paddle	16	Bipolar electrode with single adjacent anode and cathode and wide field configurations pulse width 450 or 1000 msec. Intensity at low frequency (2 Hz) or high frequency (30 Hz)
Linde et al. (2021)	Medtronic	Paddle	16	Participants determined stimulation parameters, BWS, and treadmill speed
Moshonkina et al. (2012)	Cooner Wire Co.	Unspecified	2-4	Therapeutic mono/bipolar ESSC (stimulation frequency of 1-12 Hz) 2 times for 30 min and routine pharmacotherapy
Peña Pino et al. (2020)	Abbott	Paddle	16	eSCS program selected based on participants' preferences. EMG at 600 Hz.
Rejc et al. (2015)	Medtronic	Paddle	16	Standing optimization: sub-motor threshold, frequency of 25 Hz. Parameters were then optimized; ii. Stimulation frequency of 25 Hz, iii. Wide-field electrode configuration with cathodes positioned caudally
Rejc et al. (2017a)	Medtronic	Paddle	16	Not specified
Rejc et al. (2017b)	Medtronic	Paddle	16	Initial wide field caudal-cathode configuration at 25 Hz and amplitude at near-motor threshold. Parameters then optimized for standing. Frequency was modified for more tonic activation.
Smith et al. (2022)	Medtronic	Paddle	16	Not described
Darrow et al. (2019)	Abbott	Paddle	16	Initial broad stimulation followed by adjustments based on an adaptive Bayesian approach with inputs such as patient surveys and a home accelerometer task
Harkema et al. (2011)	Medtronic	Paddle	16	Optimal parameters for standing and stepping assessed in ranges: 0.5-10 mV, 5-40 Hz, 210 or 450 μs
Barolat et al. (1986)	Clinical Technology Corporation	Percutaneous	1	Optimized for paresthesia, tested frequencies of 30-100 Hz, pulse width of 200 μs. Final frequency chosen was 75 Hz.
Gill et al. (2018)	Meditronic	Paddle	16	Electrode configuration from intraoperative EMG motor evoked responses. Initial frequency based on prior literature. Subsequently, parameters and configurations were modified.
Calvert et al. (2018)	Medtronic	Paddle	16	EMG recorded motor-evoked responses (0.5-1 Hz). Electrode configurations from previous literature used to assess volitional activity
Carhart et al. (2004)	Medtronic	Percutaneous	4	Parameters tested: 0.1-7 V, 240-900 μs, 10-100 Hz. Stimulation was titrated above sensory threshold but below motor threshold.
Ganley et al. (2005)	Not specified	Percutaneous	4	Stimulation adjusted at individual level, long pulse widths (800 μs), frequencies 20-60 Hz, amplitudes between motor and sensory threshold
Lu et al. (2016)	Boston Scientific	Paddle	16	Bipolar electrode configurations optimized for greatest hand motor responses

(*continued*)

Table 3. (Continued)

Author (Year)	eSCS Used	Leads placement	Number of electrodes per lead	Brief description of stimulator settings (optimization)
Sayenko et al. (2014)	Medtronic	Paddle	16	Epidural evoked potentials at 2 Hz, 210 μs stimulation, intensity ranging from 0.5-10 V
Wagner et al. (2018)	Medtronic	Paddle	16	Motor pool atlas and eSCS guided spatial configurations tested as monopolar pulses in EMG. Selected configurations were tested for joint torque production. Simulations performed using computational models of eSCS and personalized using MRI scans
Aslan et al. (2018)	Medtronic	Paddle	16	EMG and cardiovascular response were assessed to rostral and caudal electrode configurations, frequency was constant at 2 Hz and amplitude increased until maximum tolerance
Harkema et al. (2018a)	Medtronic	Paddle	16	Tested stimulation parameters that increased systolic blood pressure within 105 to 120 mmHg
Harkema et al. (2018b)	Medtronic	Paddle	16	In seated position, stimulation was optimized to maintain a target SBP of 110-120 mmHg without reaching motor threshold. This took 7-8 2-h sessions for each subject.
West et al. (2018)	Medtronic	Paddle	16	In seated position, blood pressure 2 weeks optimization final settings, 35Hz, 300 μs, 3.5V
Squair et al. (2021)	Medtronic	Paddle	16	The stimulation was increased by 0.5 V every 30-60 sec, 0 to 7.5 mV; 120 Hz; 450 μs pulse width
Beck et al. (2021)	Medtronic	Paddle	16	Optimization period of 3 weeks and adjusted over 12 months
Herrity et al. (2018)	Medtronic	Paddle	16	Optimized during 16 urodynamic sessions. Initial electrode configuration reduced in distance if necessary. Tested frequencies: 5-60 Hz for effects on voiding. Determined amplitude near-motor threshold at fixed frequency and pulse width (5 Hz, 450 μs)
Herrity et al. (2021)	(5-6-5 Specify, Medtronic, Minneapolis, MN	Paddle	16	
Katz et al. (1991)	Medtronic	Paddle	4	Optimal settings for spasticity used to assess bladder function
Walter et al. (2018)	Medtronic	Paddle	16	Variety of pre-set stimulation programs used designed to activate specific groups of skeletal muscles. Participant utilized the stimulator as needed by turning it on and selecting a program. In contrast to frequency and pulse width, were pre-set
DiMarco et al. (2021)	Not specified	Percutaneous	2	Subjects self-selected the number of stimulations and voltages. Typically, 2-3 applications of SCS (20-30V, 50 Hz, 0.2 pulse width) were applied every 2-7 min and repeated several times.
Formento et al. (2018)	Medtronic	Paddle	16	EMG used to find electrode configurations for left and right L1-2 and L4-L5 motor pools with simultaneous set of four configurations. Frequencies at 5-60 Hz and optimal levels were selected by visual inspection of EMG and kinematics. Amplitudes were similarly tested.

EMG, electromyography; EAW, exoskeletal-assistted walking; eSCS, epidural spinal cord stimulation; BWS, body weight support; ESSC, electrical stimulation of the spinal cord; MRI, magnetic resonance imaging.

eSCS in SCI patients can vary greatly between individuals for the same activity and previous studies have shown that the optimal settings for volitional movement are distinct from those required for autonomic function.[20] In our experience, optimizing spinal cord stimulation using preference modeling, we found general convergence in the frequency domain for maximizing motor function with statistically significant variation in pulse width.[57] In addition, we found significant variation across multiple domains of preference across motor and autonomic function, suggesting that optimization strategies may need to account for domain trade-offs and synergies in addition to personalization.

Only six studies reported the duration of ''stimulator on''; thus, it is difficult to make recommendations regarding optimal stimulator usage from these reports. Stimulator settings and optimization methods also varied significantly between publications. Moreover, the diversity of targeted outcomes and included participants make it challenging to determine the optimal parameters and are likely specific for each patient for both their injury and their goals of treatment. It remains important for patients to have the choice of different stimulator settings, as patients may have different preferences. Devices were not designed with the needed flexibility in programming stimulation parameters. Further, for safety reasons, company restrictions of certain stimulation parameters and the number of different programs available for patients are some of the limitations of these devices. Ideally, in the future companies will work with physicians and patients to design new devices that will both allow this flexibility while still maintaining safety parameters and improve patient experience.

Not only are the settings and location of the stimulator variables that require optimization, but also higher

Table 4. Volitional Outcomes

Author (Year)	GMA	I. sit	BWS	A/I Stand	STS	TSW	A/I step	OGW	Gait	HCA	IWS	Cycling	SOE	Prop	Spasticity	ASIA
Angeli et al. (2014)	X		X			X										B to C
Angeli et al. (2018)	X	X	X	X		X		X	X		X			spared		
Calvert (2021)	X															
Cheng et al. (2019)	X															
Gill et al. (2021)	X		X			X	X		X					X		
Gorgey et al. (2020)	X			X			X	X			X					
Grahn et al. (2017)	X			X												
Herman et al. (2002)	X		X			X		X	X	X	X		X		X	
Huang et al. (2006)	X		X			X		X	X		X		X			
Ibanez et al. (2021)	X			X	X											
Mesbah et al. (2021)	X															
Linde et al. (2021)	X					X			X							
Moshonkina et al. (2012)	X		X								X					
Peña Pino et al. (2020)	X											X				
Rejc et al. (2015)	X		X	X												
Rejc et al. (2017a)	X		X	X	X											
Rejc et al. (2017b)	X		X	X	X											
Smith et al. (2022)	X			X	X											
Darrow et al. (2019)	X															
Harkema et al. (2011)	X		X	X			X							X		
Barolat et al. (1986)	X														X	
Gill et al. (2018)	X		X	X		X	X	X	X		X				Non-sig	
Calvert et al. (2018)	X															
Carhart et al. (2004)	X		X			X		X	X		X		X			
Ganley et al. (2005)	X		X			X		X	X	X	X		X			
Lu et al. (2016)	X															
Sayenko et al. (2014)	X															
Wagner et al. (2018)	X		X		X	X	X	X	X	X	X	X		Loss		C to D
Formento et al. (2018)	Limited													Reduce/ abolish		

GMA, general muscle activity; I.sit, independent sitting; BWS, body weight support; A/ I Stand, assisted /independent standing; STS, sit to stand transition; TSW, treadmill step/ walk; A/I step, assisted/independent stepping; OGW, overground walking; HCA, home/community ambulation; IWS, increase walking speed; SOE, sense of effort; Prop, proprioception; ASIA, American Spinal Injury Association pre–post intervention ; Non-sig, non-significant.

Table 5. Autonomic Outcomes

	Hemodynamic					Bladder				Bowel	Sexual	
Author (Year)	BP	Orthostatic	Heart rate	Cardiac function[1]	Middle cerebral artery	Storage and voiding	Incontinence	Synergy	Urodynamic parameters[2,3,5,4]	Synergy	Orgasm	Response
Darrow et al. (2019)	X	X	X	X	X	X	X	X		X	X	
Harkema et al. (2011)						X						X
Aslan et al. (2018)	X	X	X									
Harkema et al. (2018a)		X	X									
Harkema et al. (2018b)	X		X									
West et al. (2018)	X	X		X	X							
Squair et al. (2021)	X	X	X									
Beck et al. (2021)							X		X			
Herrity et al. (2018)						X			X			
Herrity et al. (2021)						X			X			
Katz et al. (1991)									Non-sig			
Walter et al. (2018)									X		X	
DiMarco et al. (2021)											X	

[1]Contractility, stroke volume, and cardiac output.
[2]Beck (2021). Filling phase and a voiding phase cystometrogram.
[3]Katz et al. (1991). Bladder volume, max detrusor contraction, external sphincter dyssynergia, voided volume, and peak urinary flow.
[4]Herrity (2018; 2021). Standard urodynamic evaluations with recommendations from the International Continence Society.
[5]Walter et al. (2018). External anal sphincter/pelvic floor muscle tone and detrusor pressure.

Table 6. Rehabilitative Therapy

Author (Year)	Outcomes assessed	Rehabilitation effect		Rehabilitative therapy pre- Implantation	Rehabilitative therapy post-implantation
		With eSCS	Without eSCS		
Angeli et al. (2014)	Volitional	X		80 locomotor sessions ranging from 19-37 weeks	~2 h per session, 36-83 weeks of sessions
Angeli et al. (2018)	Volitional	X		2 h, 5 days a week, for 8-9 weeks	1 h sessions, 1-2 sessions/day, daily sessions, for 24-85 weeks >100 h
Calvert et al. (2021)	Volitional	X		Six months of task-specific training,	performed 12 months of multi-modal rehabilitation which paired task specific rehabilitation with ESS
Cheng et al. (2019)	Volitional	X		1 h sessions, 5 times/week, total of 80 sessions	No
Gill et al. (2021)	Volitional	X		Six months of locomotor training	Multi-modal rehabilitation during the initial 12 months focused on standing and stepping utilizing a BWST system, along with a computer-controlled motorized treadmill.
Gorgey et al. (2020)	Volitional	X	X	No	24 sessions over 12 weeks (up to 75 mins per session) of Exoskeleton assisted walking
Grahn et al. (2017)	Volitional	X		1 h 30 min per session, 3 sessions per week for 22 weeks (61 sessions)	5-7 h per session, 8 sessions in 2 weeks
Herman et al. (2002)	Volitional	X	X	No	4 months of continual training
Huang et al. (2006)	Volitional			Not described	Not described
Ibanez et al. (2021)	Volitional			Not described	Not described
Mesbah et al. (2021)	Volitional			Not described	Not described
Linde et al. (2021)	Volitional	X		6 months of locomotor training	Following each month of body weight supported treadmill training
Moshonkina et al. (2012)	Volitional	X		Patient TA trained in a verticalizer, which maintained vertical posture with foot support. The training sessions were carried out daily for 30-60 min for 35 days	Patient TP was trained in a treadmill with a body-supporting facility (a driven-gait orthosis) for 30 days two times daily prior to ESSC session
Peña Pino et al. (2020)	Volitional			No	No
Rejc et al. (2015)	Volitional	X		80 sessions	Stand training: 1 h/session, 5 sessions/week, 80 sessions
Rejc et al. (2017a)	Volitional	X	X	1 h/session, 80 sessions in 5 months	Stage 1 and 2: 1 h/day, 160 sessions in 9.5 months. Stage 3: 1 h/day home training for 12 months. Stage 4: 2 h/day, 60 sessions in 3 months. Stage 5: 1 h/day at home for 14 months. Stage 6: 1 h/day, 100 sessions in 5.5 months
Rejc et al. (2017b)	Volitional	X		80 sessions	1 h/session, 5 sessions/week, 81 ± 1 sessions (stand), 81 ± 2 sessions (step), total 55 weeks 80 h
Smith et al. (2022)	Volitional			Not described	Not described
Darrow et al. (2019)	Volitional and autonomic			No	No
Harkema et al. (2011)	Volitional and autonomic	X		170 sessions over 26 months (total of 162 h)	80 sessions
Barolat et al. (1986)	Volitional and other			No	No
Gill et al. (2018)	Volitional and other	X		1 h 15 min each session, 61 sessions in 22 weeks	113 rehab sessions +72 sessions of 3-h home based exercises over 43 weeks
Calvert et al. (2018)	Volitional and other	X		1 h 30 min, 3 times a week for 22 weeks (approx. 60 sessions) 6 months	No
Carhart et al. (2004)	Volitional and other	X	X	2h/day, 5 days/week, around 45 sessions	4 months, around 105 sessions
Ganley et al. (2005)	Volitional and other	X	X	3.5 months	No
Lu et al. (2016)	Volitional and other	X		No	180 min testing session, 7-8 sessions, 1–8 weeks
Sayenko et al. (2014)	Volitional and other			Not described	Not described

(*continued*)

Table 6. (Continued)

Author (Year)	Outcomes assessed	Rehabilitation effect		Rehabilitative therapy pre- Implantation	Rehabilitative therapy post-implantation
		With eSCS	Without eSCS		
Wagner et al. (2018)	Volitional and other	X	X	No	1–2.5 h, 4–5 times a week for 5 months
Aslan et al. (2018)	Autonomic			Not described	Not described
Harkema et al. (2018a)	Autonomic	X		No	89 ± 13 2 h sessions of CV-eSCS training
Harkema et al. (2018b)	Autonomic			Not described	Not described
West et al. (2018)	Autonomic			No	No
Squair et al. (2021)	Autonomic			No	No
Beck et al. (2021)	Autonomic	X		six months of locomotor training (LT) via a bodyweight support treadmill and overground activities three times per week	2 months multi-modal rehabilitation three sessions a week
Herrity et al. (2018)	Autonomic	X	X	80 sessions	3 h per session, 160 sessions
Herrity et al. (2021)	Autonomic	X		No	160 sessions of activity-based recovery training. Stand training over-ground lasted 1 h per session (five sessions per week). Step training (1 h, five sessions per week) 160 sessions of cardiovascular training 80 sessions of voluntary training. (1 h per session, five sessions per week.
Katz et al. (1991)	Autonomic			No	No
Walter et al. (2018)	Autonomic			No	No
DiMarco et al. (2021)	Autonomic	X		No	No
Formento et al. (2018)	Other	X	X	Not described	Not described

eSCS, epidural spinal cord stimulation; ESS, epidural electrical stimulation; BWST, body-weight support training; ESSC, electrical stimulation of the spinal cord.

stimulation settings and increased usage depletes the battery life at a faster rate. Thus, multiple surgeries throughout an individual's lifetime may be required to replace the IPG, which could lead to more postoperative complications.[58-60] While the majority of SCS device companies have rechargeable IPGs available, this is a more expensive option and often is not covered by insurance.[61] In order to improve the functional outcomes for the SCI patient population, research efforts should focus on improving the design and functionality of the epidural stimulator and IPG. Individualizing this therapy for SCI patients is crucial, as each patient may have different goals based on the functional benefit that is most important to them.

The current published studies had several limitations. All the included publications were case reports and case series; thus, each study had only a small sample size. As mentioned, we could not identify whether some patients were enrolled in more than one trial after completing their initial one, making total patient numbers difficult to assess. Therefore, the number of patient experiences represents those enrolled in each individual study. In addition, the heterogeneity of the reported outcomes and the absence of randomized controlled trials hindered the performance of a meta-analysis.

Moreover, none of the studies had a true control group; reported performance of randomization; blinding to participants; investigators; or assessors. Control groups have been limited to patients with stimulator on versus stimulator off. While this has certain advantages such as the elimination of inherent differences between patients when utilizing a different patient as a control, without randomization, bias in patient selection may be a confounding factor. Further, participant blinding may not be possible as most patients report the ability to sense when the stimulator is on. It has been suggested that settings that have not been shown to be useful in a particular patient could be utilized as controls; however, this presents the problem of how to determine these ''nonfunctional'' settings. Despite these difficulties, in future studies assessors should be blinded to the treatment to allow for unbiased assessment. Finally, a limitation to this study is that the search method was limited to MEDLINE, EMBASE, and Web of Science, and did not include other trial registries.

Nonetheless, we anticipate that other groups will be interested in this novel treatment modality for chronic SCI, including SCI patients; physicians; and the scientific community. In this vein, Boakye and colleagues have published a guide for initiating clinical trials in this area.[62] They indicated that trials are conducted in uncontrolled mono-centers and include small sample sizes. Thus, in order to move to the second stage of the clinical trial phase studies should adopt robust research designs, include control groups; begin randomization before implantation to limit selection bias, and at a minimum the

data assessor should be blinded to minimize bias. They propose rigorous safety examinations to allow the inclusion of a larger number of patients. They also propose that organizations should collaborate in collecting and analyzing existing data on the topic to create a comprehensive database. Moreover, they suggest adopting a multicenter approach in conducting future trials to improve the quality of eSCS research. Further randomization after implantation may also be considered in a cross-over design with stimulator on and off to further control for possible implantation related effects, and to provide information about timing of intervention.

We support these recommendations and also add that future studies should include patient-specific variables such as diverse SCI populations reflecting the SCI patient population. These variables should include gender, race and ethnicity, injury level and severity as examples. Stimulator-specific variables could also include stimulator type, location, duration of stimulation, and methods of optimization. Studies should also adopt longer follow-up periods to further investigate long-term effects. Further study in this area is badly needed to allow eSCS technology to move forward and be more widely available for chronic SCI patients.

Authors' Contributions

AP conceived and designed the study. NM, IP, and DF carried out the bibliography search and acquisition of data. KC and SV prepared the first draft of the manuscript; AP and NM contributed to the design, interpretation, and preparation of the manuscript. AP, US, and DD provided expertise in epidural stimulation and critically reviewed the final manuscript.

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Supplementary Material

Supplementary Section S1

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