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Review

A Systematic Review of Experimental Strategies Aimed at Improving Motor Function after Acute and Chronic Spinal Cord Injury

Joyce Gomes-Osman,[1] Mar Cortes,[2] James Guest,[3] and Alvaro Pascual-Leone[1]

Abstract

While various approaches have been proposed in clinical trials aimed at improving motor function after spinal cord injury in humans, there is still limited information regarding the scope, methodological quality, and evidence associated with single-intervention and multi-intervention approaches. A systematic review performed using the PubMed search engine and the key words ''spinal cord injury motor recovery'' identified 1973 records, of which 39 were selected (18 from the search records and 21 from reference list inspection). Study phase (clinicaltrials.org criteria) and methodological quality (Cochrane criteria) were assessed. Studies included proposed a broad range of single-intervention (encompassing cell therapies, pharmacology, electrical stimulation, rehabilitation) (encompassing cell therapies, pharmacology, electrical stimulation, rehabilitation) and multi-intervention approaches (that combined more than one strategy). The highest evidence level was for Phase III studies supporting the role of multi-intervention approaches that contained a rehabilitation component. Quality appraisal revealed that the percentage of selected studies classified with high risk of bias by Cochrane criteria was as follows: random sequence generation = 64%; allocation concealment = 77%; blinding of participants and personnel = 69%; blinding of outcome assessment = 64%; attrition = 44%; selective reporting = 44%. The current literature contains a high proportion of studies with a limited ability to measure efficacy in a valid manner because of low methodological strength in all items of the Cochrane risk of bias assessment. Recommendations to decrease bias are discussed and include increased methodological rigor in the study design and recruitment of study participants, and the use of electrophysiological and imaging measures that can assess functional integrity of the spinal cord (and may be sufficiently sensitive to detect changes that occur in response to therapeutic interventions).

Key words: cell transplantation; electrophysiology; human studies; rehabilitation; spinal cord injury

Introduction

An estimated 30 persons sustain an injury to the spinal cord every day in the United States.[1] There are approximately 2 million persons living with the consequences of spinal cord injury (SCI) worldwide, a relatively low number thought to reflect the higher mortality associated with acute SCI in developing countries.[2] Injury to the spinal cord greatly disrupts information between the supraspinal centers and muscles, leading to varying degrees of paralysis that greatly impact one's functional ability and quality of life.

Despite the great advances in clinical management (including surgical decompression of the spinal cord, pharmacology, and rehabilitation) and investigational efforts, recovery of motor function is still considered limited. The International Standards for Neurological Classification System for Spinal Cord Injury (ISNCSCI) developed by the American Spinal Injury Association (ASIA)[3,4] is the most widely used system for the classification of residual neurologic function after SCI. According to the ISNCSCI, approximately 55% of cases are incomplete (i.e., presence of varying degrees of sensory or motor activity below the neurological level of injury), and in the remaining 45% of cases, there is no sensory and/or motor function in the S4-5 sacral segments (classified as motor-complete) as determined by the motor and sensory testing.

Traditionally in SCI research, potential therapeutic approaches targeting motor-incomplete lesions focus on harnessing the neural plasticity of the spared axonal fibers for the activation of muscles below the injury level. While neurological improvements do occur,

[1]Berenson-Allen Center for Noninvasive Brain Stimulation, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts.
[2]Non-Invasive Brain Stimulation and Human Motor Control Laboratory, Burke Medical Research Institute, Weill Cornell Medical College, White Plains, New York.
[3]Department of Neurological Surgery, The Miami Project to Cure Paralysis, Lois Pope LIFE Centre, Miller School of Medicine, Miami, Florida.

recovery of function is still variable and difficult to predict. The greatest challenge for the recovery of motor function, however, is axonal regeneration across the injury site and the formation of new functional synapses, the overarching goal of approaches targeting motor-complete SCI. While there is evidence of partial tissue sparing even after complete SCI,[5] the adult human injured spinal cord constitutes an inhospitable environment for regeneration because of many factors, including the limited axonal growth response that is because of the presence of many molecules in the myelin debris and glial scar tissue that cause growth cone collapse.[6]

In addition to the challenges imposed by the lesion itself, the success of potential therapeutic approaches has been linked to the adoption of better practices in scientific design, methodology of research studies, and the development of sensitive outcome measures of spinal cord integrity and residual connectivity.[2] These have to complement improved clinical assessments to better characterize the effects of the injury on the nervous system and changes that occur in response to therapeutic interventions.[2,7] In addition, the use of combinatorial approaches[8,9] may be more effective than single-intervention approaches by simultaneously targeting different injury mechanisms. There is recent promising evidence demonstrating recovery of stepping in rats with a transected spinal cord after a combinatorial approach incorporating locomotor training with electrical neuromodulation and a pharmacology agent.[10] There have not been many practical efforts in this direction in humans, however.

The aims of this review were to: (1) perform an appraisal of the methodology of studies targeted at improving motor function in persons with acute and chronic SCI; (2) identify the scope and evidence level associated with single-intervention (encompassing cell therapies, pharmacology, electrical stimulation, rehabilitation) and multi-intervention approaches (that combined more than one strategy) published in the literature to date; (3) identify the number of studies that incorporated an evaluation of spinal cord integrity and residual connectivity; (4) describe potential sources of bias in the selected studies; and (5) make recommendations for future clinical trials in SCI.

Methods

On October 1, 2014, a PubMed search using the following key words ''spinal cord injury motor recovery'' was performed to identify studies aimed at improving motor function after SCI. In addition, on January 1, 2015, a second search was performed using the following key words ''spinal cord injury motor recovery'' AND each of the following: ''cell therapies,'' ''electric stimulation,'' ''pharmacology,'' and ''rehabilitation.'' A filter was applied to limit the search to studies performed in humans. Studies were considered for eligibility if they were written in English and were published from 1990 until the search date (01/10/14). The remaining criteria for inclusion and exclusion can be seen on Table 1, and the protocol for the present review is publicly available.[11] Abstracts were screened for eligibility, and relevant studies were reviewed in full by two independent trained examiners (JGO and MC), and discrepancies were resolved in monthly meetings with a third author (APL). Reference lists of the included articles were screened to identify potential articles not captured by the initial search.

This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.[12] Data extraction of the included studies was performed in adherence to the population intervention comparison outcome framework,[12] wherein recommended study characteristics were collected (methods, interventions, participants, and outcomes) using the Revman 5 software (version 5.1, Cochrane Collaboration, Canada) and tables using Excel (Microsoft, Redmond, WA). A semi-quantitative analysis was performed by classifying studies

Table 1. Inclusion and Exclusion Criteria Used in the Present Study

	Inclusion criteria	*Exclusion criteria*
Population and condition	Adult human participants (19–70 years, sample size >5 participants) with a history of traumatic SCI: acute/subacute (defined as within min to 12 months post-injury) and/or chronic (after 12 months post-injury).	Studies exclusively in adolescents and children (age <19 years old); Case studies/case series (defined as having a sample size <5 participants); studies performed in animal models or experimental models of SCI; studies including individuals with nontraumatic SCI; studies with participants who have other neurologic, cognitive or orthopedic conditions associated with the SCI (metastatic cancer, etc).
Interventions	Cell therapies, pharmacology approaches, electrical stimulation/neuroelectric devices, rehabilitation or a combination of therapies including any of the above strategies.	Studies that: were not designed to assess the effects of an intervention (observational studies, studies carried out to assess an outcome measure); did not include a performance-based measure of motor function; assessed gangliosides and methylprednilosone, surgical decompression of the spinal cord, or were not available in full text.
Comparisons of interest	Intervention vs. active or inactive control; pre-intervention/post-intervention (for studies that did not include a control group).	None
Study design	Studies with an active control group (comparison group) were preferred, but studies with inactive controls (placebo or wait-list control), and safety/feasibility studies were also included.	Observational studies; studies carried out using retrospective analysis of clinical findings and studies with no original data (reviews)
Timing/setting	Longitudinal studies that occur in general and clinical settings.	None

SCI, spinal cord injury.

Table 2. Criteria Used to Classify Study Phase[a]

Study phase	*Description*
I	Study carried out to assess a new approach in a small sample for the first time to evaluate its safety, determine a safe dosage range, and identify side effects
II	Approach is given to a larger sample to see if it is effective, further evaluate safety, and determine optimal dose
III	Approach is to a large sample to confirm effectiveness, monitor side effects, make comparisons to commonly used treatments, and collect information that will allow the approach to be used safely
IV	Studies are done after the drug or treatment has been marketed to gather information on the drug's effect in various populations and any side effects associated with long-term use

[a]I, II, II, IV, from clinicaltrial.org.

according to the approach used (cell therapy, pharmacology, rehabilitation, electrical stimulation/neuroelectric device, combinatorial), stage of SCI (acute/subacute = study enrollment within minutes to 12 months post-injury; and chronic = study enrollment after 12 months post-injury) and the absence/presence of an assessment of spinal integrity/residual connectivity. Studies were classified according to the phase as per clinicaltrial.org criteria (Table 2).

Study quality appraisal and risk of bias assessment were performed as per the Cochrane Handbook for Systematic Reviews and Interventions.[13] A ''risk of bias'' table was constructed with all included studies, containing a description and judgment (low risk, high risk, or unclear risk) for the following potential sources of bias: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; (7) other sources of bias.

Results

The first and second searches yielded 1973 results (Fig. 1). On examination, 1931 citations that were not relevant to the topic, reviews or opinion articles were excluded. Upon further examination, 24 articles (18 that did not fulfill our inclusion criteria and 6 articles that were not classifiable) were excluded. Eighteen full-text articles met the inclusion criteria. Within the process of the review, 21 additional studies, which pertained to the topic but were not identified in the PubMed search, were included in the study, resulting in the inclusion of 39 full-text articles.

Quality assessment for all studies included can be seen in Figure 2a, and individualized scoring of each study for multiple sources of bias assessed is displayed in Figure 2b. Fourteen (36%) publications had low risk of bias, and the remaining 25 (64%) studies had high risk of bias for random sequence generation. Nine (23%) studies adopted and reported methods of allocation concealment, whereas 30 (77%) studies were at high risk of bias. Twelve (31%) studies adopted and reported blinding methods for the participants and personnel, whereas 27 (69%) studies were associated with high risk of bias. Fourteen (36%) studies adopted and reported methods for blinding of outcome assessment and thus were at low risk for bias from this source. The remaining 25 (64%) studies did not adopt or report methods for minimizing bias arising from outcome assessment.

Twenty-two (56%) studies reported and the remaining 17 (44%) studies did not report whether there was attrition in their samples. For selective reporting, 22 (56%) studies were classified as having low risk of bias, and the remaining 17 (44%) studies were classified as having high risk of bias. Seven (18%) studies were at high risk for other sources of bias, and the remaining 32 (82%) studies were classified as low risk for additional sources of bias.

Figure 3 displays the studies according to the time since injury (acute/subacute and chronic SCI) and study phase (I–IV). It can be seen that 37.5% of studies in the acute stage were Phase I, 18.8% were Phase II, and the remaining 43.8% were Phase III. In the chronic stage, 27.3% of studies were Phase I, 13.6% were Phase II, and 59.1% were Phase III studies. There were no Phase IV studies. Figure 4 displays the approaches used in each study stage, for both acute and chronic SCI.

Twelve studies[14–22] assessed spinal integrity using magnetic resonance imaging (MRI) (Tables 3 and 4). Five studies limited the inclusion criteria based on the MRI findings. Two studies proposed limits in the lesion size,[18,19] one study excluded participants depending on the presence of tethering in the spinal cord,[23] and two studies excluded persons who had complete transections.[15,24] Ten

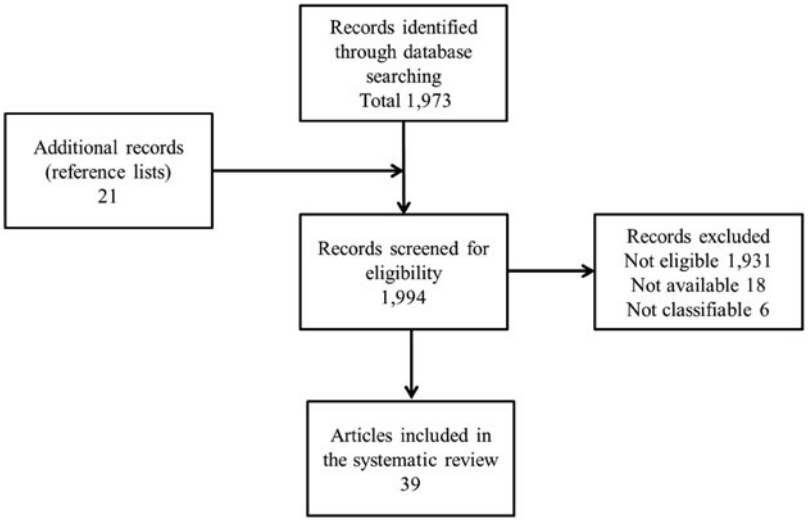

FIG. 1. Flow chart displaying the search strategy.

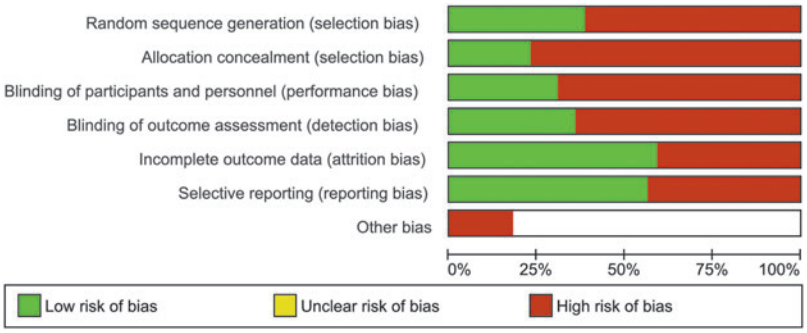

FIG. 2a. Risk of bias graph: review authors' judgments about each risk of bias item (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, other) presented as percentages across all included studies. Color image is available online at www.liebertpub.com/neu

studies assessed spinal cord residual connectivity using motor evoked potentials acquired with transcranial magnetic stimulation (TMS).[14,17,19,21,25–29]

Approaches used in acute/subacute SCI

Several approaches have been proposed in Phase I studies in acute SCI (Table 3, Fig. 4). Cethrin, a compound that decreases the activity in the rho pathway (involved in the growth cone collapse after central nervous system injury) was tested in one study.[30] Raffinee, a drug with free-radical scavenging properties has also been evaluated.[31] An electrical stimulation/neuroelectric device that consisted of an implanted oscillating electric field intended to guide neurite growth was also assessed in a study.[24] The remainder of Phase I studies have focused on cell therapies, resulting from reports of successful outcomes in experimental models of SCI. These included: cell transplantation of bone marrow derived mesenchymal stromal cells,[15] autologous activated Schwann cells,[16] and autologous activated macrophages.[17]

Grossman and associates[32] performed a Phase II study to assess the feasibility, safety, and preliminary efficacy of riluzole, a sodium-channel blocking medication shown to reduce excitotoxicity and improve outcomes of motor function in animal models of SCI (and with an established safety profile in humans). Twenty-four persons with SCI (ASIA Injury Impairment Scale [AIS] A–C, within 12 h post-injury) received 50 mg of riluzole (twice daily, for 14 days, enteric administration). Comparisons were made with a database control group, matched for sex, age, and neurological injury level. Persons who received riluzole made significantly greater improvements in AIS motor scores at a 6 months follow-up, when compared with the database control. Greatest improvements were made by those classified AIS B at study entry.[32]

Takahashi and colleagues[33] performed a Phase II study to assess the effects of granulocyte colony-stimulating factor (G-CSF), a compound shown to suppress neuronal apoptosis and expression of inflammatory cytokines. Sixteen participants injured less than 48 h before study enrollment received an intravenous dose of 10 μg/kg/day for 5 consecutive days and demonstrated significant improvements in the ASIA Impairment Scale (AIS) motor scores on the follow-up assessment performed 3 months later when compared with the pre-intervention assessment. No significant differences were found, however, when comparisons were made to a database control group.[33]

In a subsequent study in 37 participants with incomplete cervical SCI, Inada and coworkers[34] found that the same dose of G-CSF as used by Takahashi and colleagues[33] was associated with greater improvements in AIS motor scores than a control group at 1 year post-transplantation. Unfortunately, participants were allocated to the experimental group based on the institution they were treated at (in a nonrandomized manner), and it was not possible to assess whether clinical management differed between the sites.

Two studies have assessed the use of pharmacological agents. Casha and associates[35] performed a Phase III study with minocycline, following experimental evidence of decreased microglial activation and proliferation (and thus, reduced post-injury excitotoxicity after SCI). Fifty-two adults who had sustained an injury to the cervical or thoracic segments of the spinal cord within 12 h were included in the study and randomized to receive either minocycline (200 mg twice daily) or placebo. The investigators found no between-group differences in AIS scores, Functional Independence Measure (FIM) scores, and Spinal Cord Independence Measure (SCIM) between those treated with minocycline and placebo for up to 1 year post-intervention.[35]

Following evidence suggesting that dopamine can improve motor task acquisition, Maric and colleagues[36] performed a crossover study to compare the effects of L-dopa and placebo. Twelve participants received L-dopa (200 mg L-dopa, 5 days per week for 6 weeks) or placebo before physical therapy (45 min, twice daily for 6 weeks), and there were no differences between the outcomes between the two groups after 12 weeks (AIS scores, FIM, walking index for SCI [WISCI-II]).[36]

Kumru and coworkers[25] performed a Phase III study to assess the influence of noninvasive brain stimulation delivered in the form of high-frequency repetitive transcranial magnetic stimulation (rTMS), aimed at facilitating corticospinal excitability. Seventeen participants who had had a SCI between 3 and 12 months before study enrollment received rTMS or sham-rTMS (15 sessions, 5 days per week for 3 weeks) and engaged in a rehabilitation protocol for 5 h per day, 5 days per week for 5 weeks. There were no between-group differences, but pre-post changes reached significance for gait speed and lower extremity motor scores (LEMS) for the rTMS group.

Two Phase-III studies have proposed locomotor training in acute SCI. Alcobendas-Maestro and colleagues[37] compared the outcomes of 40 sessions of locomotor training delivered with a robotic orthosis (30 min per session) to overground walking training (1 h per session) in 75 participants with an SCI of less than 6 months. They found greater improvements in outcomes of walking function in the robotic orthosis group (FIM, WISCII, walking distance, and LEMS), but no between-group difference in walking speed was found.

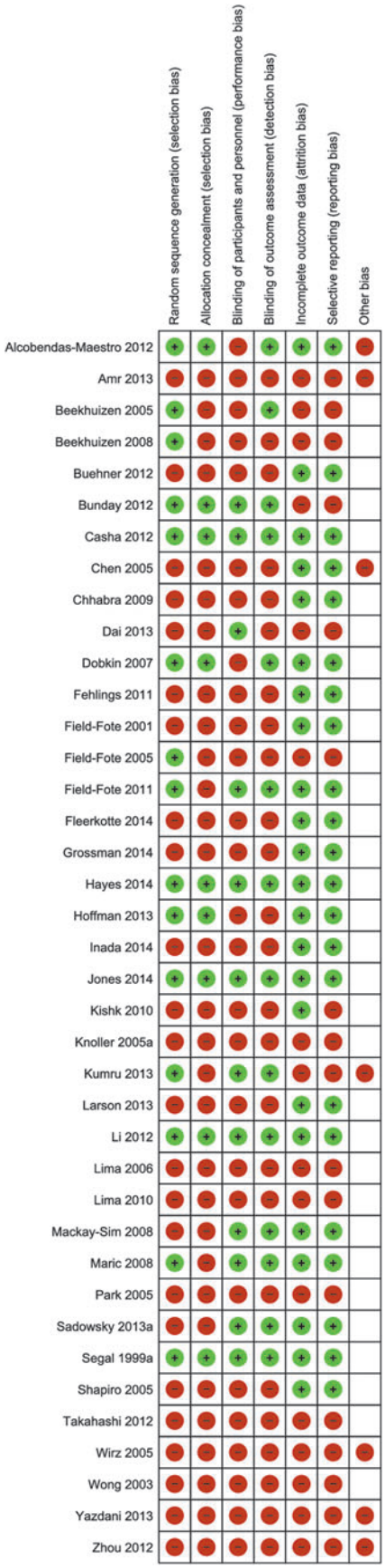

FIG. 2b. Risk of bias summary: review authors' judgments about each risk of bias item for each included study. Color image is available online at www.liebertpub.com/neu

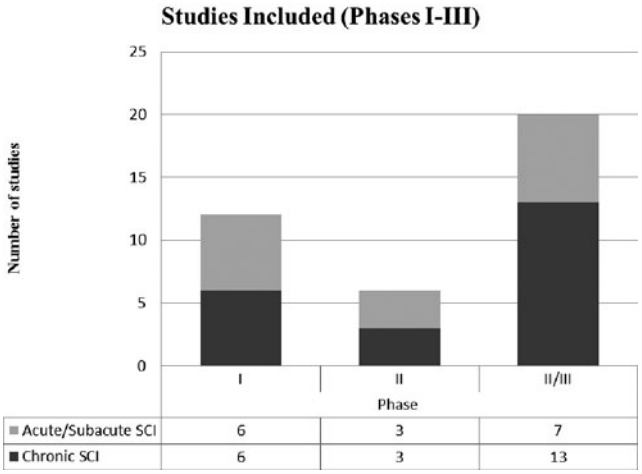

FIG. 3. Distribution of studies included in the review separated into acute/subacute spinal cord injury (SCI) (light grey) and chronic SCI (dark grey) and included in the review according to the study phase (I-III, see Methods).

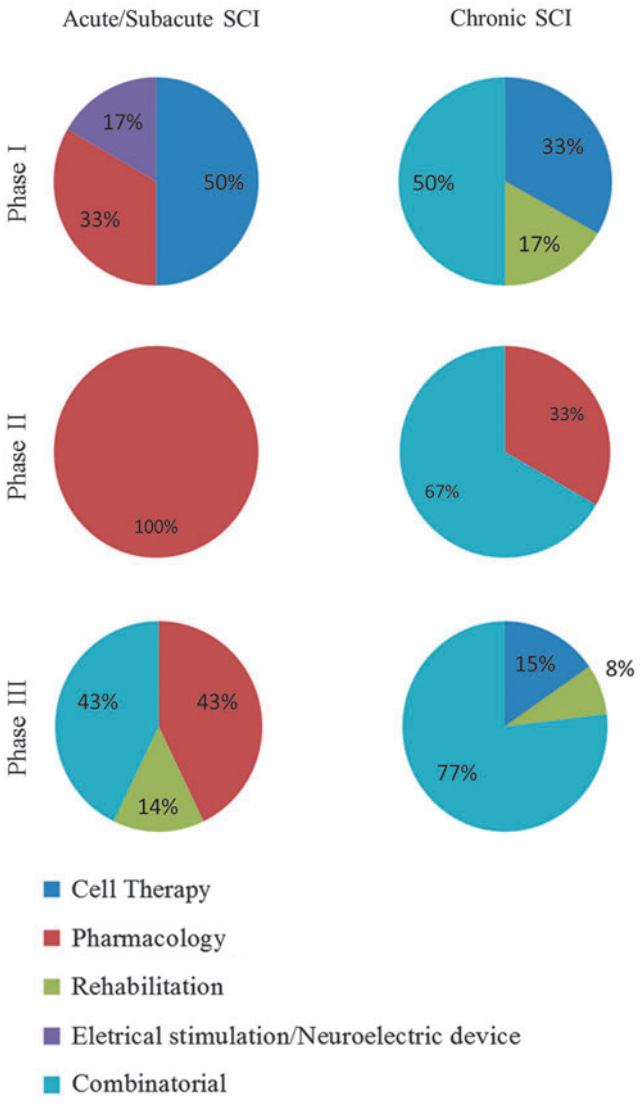

FIG. 4. Distribution of studies in acute/subacute and chronic spinal cord injury (SCI) groups divided per phase (see Methods) for all categories (cell therapy, pharmacology, rehabilitation, electrical stimulation/neuroelectric device, combinatorial). Color image is available online at www.liebertpub.com/neu

Table 3. Approaches Used in Acute/Subacute Spinal Cord Injury

Study	Study phase	Approach	Classification	Mechanism	Outcome measure/ effect (clinical neurological and/or motor performance)	Comparison/ control	Direction of results	Follow-up	CS integrity	CS connectivity
Fehlings et al, 2011	Phase I	Cethrin	Pharmacology	↓ excitoxicity	AIS scores	N/A	N/A	12 months	MRI	Absent
Chen et al, 2005	Phase I	Raffinee	Pharmacology	↓ excitoxicity	AIS scores	N/A	N/A	2–3 weeks	Absent	Absent
Shapiro et al, 2005	Phase I	Implanted oscillating electric field	Electrical stimulation/ neuroelectric device	Neural guidance	AIS scores	N/A	N/A	6 months, 12 months	MRI-excluded complete injuries	Absent
Park et al, 2005	Phase I	Bone-marrow derived mesenchymal stromal cells	Cell therapy	Neural regeneration	AIS scores	N/A	N/A	6–18 months	MRI-excluded complete injuries	Absent
Zhou et al, 2012	Phase I	Autologous activated Schwann cells	Cell therapy	Neural regeneration	AIS scores, FIM	N/A	N/A	15–18 weeks, 5–8 years	MRI	MEPs (post-test)
Knoller et al, 2005	Phase I	Autologous macrophages	Cell therapy	Neural regeneration	AIS scores	N/A	N/A	4–12 months	MRI	MEPs
Grossman et al, 2014	Phase II	Riluzole	Pharmacology	↓ excitoxicity	AIS motor scores,* SCIM	Database control	*= ↑ Riluzole	42 days, 3 months, 6 months*	Absent	Absent
Takahashi et al, 2012	Phase II	G-CSF	Pharmacology	↓ excitoxicity	AIS motor scores†	Database control	†= ↑ (G-CSF)	3 months	Absent	Absent
Casha et al, 2012	Phase III	Minocycline	Pharmacology	↓ excitoxicity	AIS scores, FIM, and SCIM	Placebo	No differences	3, 6, and 12 months	Absent	Absent
Inada et al, 2014	Phase II	G-CSF	Pharmacology	↓ excitoxicity	AIS motor scores*	Control (no intervention)	*= ↑ (G-CSF)	1 year	Absent	Absent
Kumru et al, 2013	Phase III	High-frequency rTMS	Combination of electrical stimulation/ neuroelectric device + rehabilitation	Plasticity	Gait speed† and LEMS (AIS)†	Sham-rTMS + rehabilitation	†= ↑ rTMS + rehabilitation	5 weeks	Absent	MEPs
Alcobendas-Maestro et al, 2012	Phase III	Locomotor training (overground vs. robotic orthosis)	Rehabilitation	Plasticity	FIM,† WISCI,† walking distance† and LEMS (AIS)†, walking speed	Overground locomotor training	†= ↑ robotic orthosis	8 weeks	Absent	Absent
Dobkin et al, 2007	Phase III	Locomotor training (overground vs. treadmill) + Physical therapy, nursing	Combination of rehabilitation+ nursing	Plasticity	Walking speed	Overground locomotor training	No differences	9 weeks	Absent	Absent
Wong et al, 2013	Phase III	Electrical and auricular acupuncture + rehabilitation	Combination of rehabilitation techniques	Unknown	AIS scores, Ffunctional Independence Measure†	Rehabilitation in isolation	†= ↑rehab + acupuncture	12 months	Absent	Absent
Li et al, 2012	Phase III	DHYZ	Pharmacology	Unknown	AIS scores*	Placebo	*= ↑ DHYZ group	12 weeks	Absent	Absent
Maric et al, 2009	Phase III	L-Dopa	Pharmacology	Plasticity	AIS scores, FIM, WISCI	Placebo	No differences	12 weeks	Absent	Absent

*Refers to between-group differences and †refers to pre-post differences.

Phase I studies do not include a control/comparison group and do not assess effectiveness (direction of results); therefore, these items have been noted as applicable (N/A).

AIS, American Spinal Cord Injury Impairment Scale; MRI, magnetic resonance imaging; MEP, motor evoked potentials; SCIM, Spinal Cord Independence Measure; G-CSF, granulocyte colony-stimulating factor; FIM, Functional Independence Measure; rTMS, repetitive transcranial magnetic stimulation; LEMS, lower extremity motor scores obtained from AIS assessment; WISCI, walking index for spinal cord injury; DHYZ, Di Huang Yin Zi, a traditional Chinese medicine.

Table 4. Approaches Used in Chronic Spinal Cord Injury

Study	*Study phase*	*Approach*	*Classification*	*Mechanism*	*Outcome measure (clinical Neurological nnd/or motor performance)*	*Comparison/ control*	*Direction of results*	*Follow-up*	*SC integrity*	*SC connectivity*
Lima et al, 2006	Phase I	Olfactory mucosal autografts	Cell therapy	Neural regeneration	AIS scores	N/A	N/A	6, 12, and 18 months	MRI	Absent
Chhabra et al, 2009	Phase I	Olfactory ensheathing cells	Cell therapy	Neural regeneration	AIS scores, WISCI, SCIM	N/A	N/A	6, 12 and 18 months	MRI (only included lesions 2–3 cm)	MEPs
Wirz et al, 2005	Phase I	Locomotor training (gait-driven orthosis)	Rehabilitation	Plasticity	LEMS, 6-min walk test, 10 meter walk, timed up and go, WISCI-II	N/A	N/A	Post-intervention (8 weeks)	Absent	Absent
Yazdani et al, 2013	Phase I	Bone-marrow mesenchymal stromal cells, Schwann cells and rehabilitation	Combination of cell therapy + rehabilitation	Neural regeneration+ plasticity	AIS scores	N/A	N/A	24 months	MRI-excluded stenosis and tethering of the spinal cord	Absent
Field-Fote et al, 2001	Phase I	Body-weight supported treadmill training + electrical stimulation	Combination of rehabilitation+ electrical stimulation/ neuroelectric device	Plasticity	2 min walk (speed), LEMS	N/A	N/A	Post-intervention (12 weeks)	Absent	Absent
Fleerkote et al, 2014	Phase I	Body-weight supported treadmill training (AAN-RO)	Combination of rehabilitation+ electrical stimulation/ neuroelectric device	Plasticity	10 meter walk† (distance), WISCI, TUG†, 6 min walk†, LEMS†	N/A	N/A	8 weeks	Absent	Absent
Segal et al, 1999	Phase II	4-amynopiridine (low, high dose)	Pharmacology	Plasticity	AIS motor scores†	Comparison (unblinded high dose)	†= groups collapsed	3 months	Absent	Absent
Buehner et al, 2012	Phase II	Manual facilitated body weight-supported step training on a treadmill + community reintegration	Combination of rehabilitation + other	Plasticity	LEMS,† UEMS,† 6-min walk (speed and distance),† and 10-meter walk (speed)†	N/A	†= pre-post difference	Mean of 60.3 ± 53.24 sessions (approximately 5 months)	Absent	Absent
Bunday et al, 2012	Phase II	Transcranial magnetic stimulation paired with electrical stimulation	Combination of electrical stimulation/ neuroelectric device	Plasticity	NHPT*	Comparison group	*= ↑ TMS + stim	post-test (single session)	Absent	MEPs

(*continued*)

TABLE 4. (CONTINUED)

Study	*Study phase*	*Approach*	*Classification*	*Mechanism*	*Outcome measure (clinical Neurological nnd/or motor performance)*	*Comparison/ control*	*Direction of results*	*Follow-up*	*SC integrity*	*SC connectivity*
Beekhuizen et al, 2005	Phase III	Upper extremity task-specific training and submotor threshold electrical stimulation (TST + stim vs. TST)	Combination of Electrical stimulation/ neuroelectric device + rehabilitation	Plasticity	JTT,* WMFT,* pinch strength*	Comparison group (TST)	Between-group difference = * ↑ TST+stim	3 weeks	Absent	MEPs
Beekhuizen et al, 2008	Phase III	Upper extremity task-specific training and submotor threshold electrical stimulation (TST+stim, TST, stim and wait-list control)	Combination of electrical stimulation/ neuroelectric device + rehabilitation	Plasticity	JTT,* WMFT,* pinch strength*	Control group (wait-list)	Between-group difference = * ↑ TST + stim	3 weeks	Absent	MEPs
Hoffman et al, 2010	Phase III	Upper extremity task-specific training (unimanual, bimanual) and electrical stimulation (submotor threshold and FES), and wait-list control	Combination of electrical stimulation/ neuroelectric device + rehabilitation	Plasticity	JTT,†	Rehabilitation in isolation	†=pre-post difference (groups collapsed)	3 weeks	Absent	MEPs
Sadowsky et al, 2013	Phase III	FES cycling	Combination of rehabilitation + electrical stimulation/ neuroelectric device	Plasticity	AIS scores†, AIS motor† scores, FIM†	Control (no intervention)	†=FES	Mean of 29.1 months	Absent	Absent
Field-Fote et al, 2005	Phase III	Body-weight supported treadmill training + electrical stimulation (TM, OG, TS, and LR)	Combination of rehabilitation + electrical stimulation/ neuroelectric device	Plasticity	6 min walk,† 2 min walk †	Comparison group	†=pre-post difference (groups collapsed)	12 weeks	Absent	Absent
Field-Fote et al, 2011	Phase III	Body-weight supported treadmill training + electrical stimulation (TM, OG, TS, and LR)	Combination of rehabilitation+ electrical stimulation/ neuroelectric device	Plasticity	10 meter walk (distance)*	Comparison group	Between-group difference = * ↑ OG	12 weeks	Absent	Absent

(*continued*)

Table 4. (Continued)

Study	Study phase	Approach	Classification	Mechanism	Outcome measure (clinical Neurological nnd/or motor performance)	Comparison/ control	Direction of results	Follow-up	SC integrity	SC connectivity
Jones et al, 2014	Phase III	ABT	Rehabilitation	Plasticity	AIS motor score, * LEMS, * 10 meter walk, * 6 min walk, * TUG, SCIM-III, SCI-FAI, * RNL index,	Wait-list control	*= ↑ ABT	24 weeks	Absent	Absent
Dai et al, 2013	Phase III	Mesenchymal stem cells (OS, CT, control)	Cell therapy	Neural regeneration	AIS scores†[1], MEPs, AIS motor scores†[2]	Control (no intervention)	†[1] = OS, CT †[2] = CT	6 months	MRI (guided injection site)	MEP
Mackay-Sim et al, 2008	Phase III	Olfactory ensheathing cell transplant	Cell therapy	Neural renegeration	AIS scores, FIM, IADL, COVS	Control group	No differences	3 years	MRI	MEPs
Lima et al, 2010	Phase III	Olfactory mucosal autografts + locomotor training	Combination of cell therapy + rehabilitation	Plasticity + neural regeneration	LEMS,† FIM† and WISCI†	Comparison group	†= pre-post difference (groups collapsed)	Mean of 27.7 months	MRI (only included lesions 3–4 cm)	Absent
Larson et al, 2013	Phase III	Locomotor training (olfactory mucosal transplant and control)	Combination of cell therapy + rehabilitation	Plasticity + neural regeneration	AIS scores†	Control group	†= pre-post difference (groups collapsed)	60 days	Absent	Absent
Kishk et al, 2010	Phase III	Bone-marrow + rehabilitation	Combination of cell therapy + rehabilitation	Plasticity + Neural regeneration	AIS scores	Control group	No differences	1 year	MRI	Absent
Hayes et al, 2014	Phase III	Daih + LT (Daih, Sham-Daih, Daih+LT, Sham-Daih+LT)	Combination of pharmacology + rehabilitation	Plasticity	10 meter walk (time) †, * 6 min walk†,†[1],†[2],*[1]	Sham-Daih, Sham-Daih+LT (crossover design)	†= Daih *= ↑ Daih †[1] = Sham-Daih †[2] = Daih + LT *[1] = ↑ Daih + LT	Day 1, Day 5, 1 week and 2 weeks	Absent	Absent

*Refers to between-group differences and †refers to pre-post differences.

SC, spinal cord; AIS, American Spinal Cord Injury Impairment Scale; MRI, magnetic resonance imaging; WISCI, walking index for spinal cord injury; SCIM, Spinal Cord Independence Measure; MEP, motor evoked potentials; LEMS, lower extremity motor scores obtained from AIS assessment; AAN-RO, assist-as-needed robotic orthosis; TUG, timed up and go; UEMS, upper extremity motor scores obtained from AIS assessment; TMS, transcranial magnetic stimulation; NHPT, nine-hole peg test; stim, electrical stimulation; TST, task-specific training; WMFT, wolf motor function test; FES, functional electrical stimulation; FIM, Functional Independence Measure; TM, treadmill training with manual assistance; OG, overground training; TS, treadmill training with electrical stimulation; LR, locomat robotic orthosis training; SCI-FAI, Spinal Cord Injury Functional Ambulation Index; RNL Index, Reintegration to Normal Living; ABT, activity-based therapy; OS, open surgery; CT, computed tomography-guided; IADL, Lawton's instrumental activities of daily living; COVS, clinical outcomes variable scale; daily acute intermittent hypoxia; LT, locomotor training.

Dobkin and associates[38] enrolled 145 participants with a SCI of at least 8 weeks in a study to compare the effects of a combined approach of locomotor training (either consisting of body weight supported treadmill training or conventional overground mobility training) and physical therapy, occupational therapy, and nursing care delivered in 45 1-h sessions. To minimize bias from differences in spontaneous recovery rates, the analysis was performed separately according to AIS classification at entry.[38] There was no between-group difference in walking speed, the primary outcome.[38]

Two Phase III studies assessed Chinese medicine approaches. Wong and coworkers[39] enrolled persons who were injured at approximately 2 months and compared the outcomes of a group whose members received standard rehabilitation program in isolation with a group whose members additionally received electroacupuncture targeting the Governic meridian. At the end of 1 year, the authors found significant pre-post changes in AIS scores in both groups, but only the acupuncture group exhibited significant pre-post changes in the FIM.[39]

Li and colleagues[40] performed a Phase III study to assess the influence of Di Huang Yin Zi (DHYZ), a pharmacological approach with unclear mechanisms, in 60 persons with acute SCI (approximately 4 weeks post-injury). Participants received either DHYZ or placebo (18 g, twice daily) for 12 weeks, and the authors reported greater increases in AIS motor scores in the DHYZ group when compared with placebo.

Approaches in chronic SCI

Table 4 lists all included studies in chronic SCI. There were a total of six Phase I studies. Lima and coworkers[18] proposed the transplantation of olfactory mucosal autografts into the chronically injured spinal cord. A second independent study proposed the use of olfactory ensheathing cells.[19] Yazdani and colleagues[23] proposed a combinatorial approach that consisted of cell transplantation of bone-marrow mesenchymal stromal cells and Schwann cells, combined with rehabilitation. The remaining Phase I chronic studies included a rehabilitation study that assessed automated locomotor training using a position-controlled gait-driven orthosis,[41] an impedance-controlled robotic orthosis,[42] and a study that assessed the effects of body weight supported treadmill training combined with electrical stimulation.[43]

Segal and associates[44] performed a Phase II study to assess the effects of 4-aminopyridine, a potassium-channel blocker that has been associated with improved axonal conduction, particularly in demyelinated nerve fibers. Participants (various AIS grades) were randomized to a 3-month regimen of 4-aminopyridine, either delivered in the form of a low dose (6 mg/day) or a high dose (30 mg/day). Comparisons were made with an unblinded group whose members received a high dose (30 mg/day). The authors reported significant pre-post increased AIS motor scores only when all groups were collapsed together.

One Phase II study has assessed the effect of locomotor training in 225 persons who had sustained a chronic incomplete SCI and also examined the effects of a combinatorial approach consisting of manual facilitated body weight supported step training on a treadmill and community reintegration.[45] The dose was variable, based on the participant's ambulatory capacity (five times/week for nonambulatory participants, four times/week for participants who needed pronounced assistance, and five times/week for ambulatory participants). After having completed a mean of 60.3 ± 53.24 sessions, the authors found significant pre-post improvements in the following outcome measures: LEMS, upper extremity motor scores (UEMS), 6-min walk (speed and distance), and 10-meter walk (speed). In addition, using pre-established functional walking stratifications,[46] 33% of nonambulatory participants became walkers, 47% of slow walkers improved to faster walkers, and overall AIS conversion rates from C to D was 28% (for AIS classification, see Table 1).[45]

Four studies assessed the effects of combinatorial approaches for upper extremity function improvement. One Phase II study assessed the effects of a single-session of transcranial magnetic stimulation paired with electrical stimulation on fine motor hand performance in 10 persons with chronic SCI and found significant improvements on the nine-hole peg test measured at 20 min and 30 min post-stimulation.[26] A Phase III study assessed the effects of task specific training (2 h/day, 5 days a week for 3 weeks) delivered in isolation or combined with electrical stimulation of the median nerve in 24 participants, and found greater improvements in hand motor performance in the combined approach.[27] In a latter study with the same sample size, the authors found that the combination of task-specific training and electrical stimulation was associated with significantly larger improvements in hand motor performance than either intervention used in isolation.[28]

The combination of task-specific training and electrical stimulation was further investigated by Hoffman and Field-Fote.[29] In this Phase III study, investigators compared the effects of functional electrical stimulation with submotor threshold electrical stimulation, each combined with either unimanual or bimanual task-specific training, using the same dose and sample size ($n = 24$) as in the previous studies.[29] While underpowered to detect changes between the approaches, the authors found that the unimanual group made greater changes in unimanual function, and the bimanual group made greater changes in bimanual function when compared with the control group, irrespective of stimulation type when compared with a wait-list control group.[29]

Sadowski and associates[47] assessed the effects of functional electrical stimulation during cycling in persons with chronic SCI ($n = 25$) and made comparisons with a control group ($n = 20$) of persons who were matched for age, sex, and duration, location, and severity of injury. The authors found that those who participated in an FES cycling protocol made significantly greater improvements in AIS total scores, motor scores, and FIM.[47]

Three Phase III studies proposed rehabilitation combinatorial strategies that included locomotor training. Field-Fote and colleagues[48] compared the effects of manually assisted treadmill training, treadmill training assisted with electrical stimulation, overground training assisted with electrical stimulation, and passive locomotor training using a robotic orthosis (all delivered for 1 h a day, 5 days a week for 12 weeks) in 27 persons. The authors found significant pre-post improvements in walking speed and distance (measured by the 2-min walk and 6-min walk) when all groups were collapsed.[48] In a follow-up study[49] of the same approaches with a larger sample size that was adequately powered to detect statistical differences between the interventions ($n = 75$), the authors found significant between-group differences for walking distance, with greatest effects observed with the overground training combined with electrical stimulation.

Jones and coworkers[50] conducted a study to assess the effects of activity-based therapy (ABT), which consists in an individualized rehabilitation program focused on muscle strengthening (including resistance and endurance) and locomotor training. Using a randomized delayed intervention design, 48 persons (AIS C and D) participated in ABT (up to three 3-h sessions/week over 24 weeks). The average documented treatment time was 89 ± 22.1 h.[50] At post-

test, there were significantly greater improvements in the ABT condition on AIS motor scores, LEMS, walking speed (10 meter walk) walking distance (6-min walk), and on the Spinal Cord Injury Functional Ambulation Index.[50]

Five studies assessed the effects of cell therapies, in isolation or combined with rehabilitation interventions, and found mixed results. Dai and associates[14] compared the delivery of mesenchymal stem cells using open surgery or delivered (dose: 4×10^7) using CT to an inactive control in 27 persons with chronic SCI with varying characteristics of injury severity. At a follow-up performed 6 months after, the authors reported significant pre-post improvements in AIS scores in the open surgery and CT-guided transplant group, and significant improvements in AIS motor scores only in the CT-guided transplant group.[14]

McKay-Sim and colleagues[21] assessed the effects of transplantation of culture-expanded autologous olfactory ensheathing cells (12–28 million) in 12 participants with thoracic complete injuries (6 persons received the transplants and 6 matched control patients with thoracic level injury 1–3 years before enrollment), and found no functional improvements in any of the outcome measures, which were assessed up to 3 years post-intervention. The authors attributed these results to the lack of a rehabilitation protocol.[21]

Lima and coworkers[20] assessed the influence of olfactory mucosal autografts and locomotor training in 20 participants with complete SCI. All participants engaged in rehabilitation (mean = 31.8 ± 6.8 h/week for 34.7 ± 30 weeks) before and after (32.7 ± 5.2 h/week for 92 ± 37.6 weeks) the olfactory mucosal autograft transplant. The authors found pre-post improvements in LEMS and walking function (FIM and WISCI). In addition, 15/20 participants (all whom had sustained motor-complete injuries) demonstrated electromyography activation below the level of injury, leading the authors to conclude that there was late neurological recovery.

Larson and associates[51] performed a Phase III study to compare outcomes of participation in an intense rehabilitation program between persons with and without a history of a previous olfactory mucosal autograft transplant. Using an open-label design, they recruited persons who had a previous olfactory mucosal cell transplant (privately performed), a matched control group (controlled for age, injury severity, sex, and AIS classification), and a second nonmatched control group. All 23 participants engaged in an intense exercise protocol for an average of 7.1 h/week for approximately 4.6 months (137.3 total hours).[51] With all groups collapsed, there were significant improvements in AIS scores at 60 days post-intervention, and no differences were found between those who received olfactory mucosal cell transplant and those who did not.[51] The authors concluded that the intense rehabilitation approach was likely a key factor responsible for the functional improvements.[51]

Kishk and coworkers[22] assessed the effects of transplantation of flask-adherent bone marrow stromal cells and rehabilitation in persons who had a SCI at least 6 months before study enrollment. Forty-four participants with variable injury levels and severity received mononuclear cells (dose: 5×10^6 to 10×10^6/kg, administered intrathecally every month for 6 months), and 20 participants who did not agree to study procedures comprised the control group. All persons who participated engaged in rehabilitation 2–3 times/week. The authors found that the intervention group made significantly greater gains in AIS scores, but the amount of improvement was correlated with having an incomplete injury. Because the groups were not balanced for injury severity, this finding was of limited clinical value.

One study assessed the combination of daily intermittent hypoxia (Daih) and rehabilitation on locomotor outcomes in SCI.[52] Using a double-blind, randomized crossover study, Daih (15–90 sec intervals, fraction of inspired oxygen = 0.9 for 5 days) or Daih-Sham were delivered in isolation or combined with subsequent walking training, in 19 persons with incomplete SCI.[52] The authors found that Daih increased walking speed (measured by the 6-min walk) 1 day and 2 weeks post-administration. Further, the combination of Daih and walking training was associated with greater improvements in walking endurance (measured by the 10-meter walk) than walking training alone and Daih alone at 5 days and 1 week post-administration.[52]

Discussion

A systematic assessment of the literature reveals that various strategies have been proposed to improve motor function after SCI (including cell therapy, pharmacology, rehabilitation, electrical stimulation/neuroelectric device (delivered individually, or in combinatorial approaches containing each of these strategies). The highest evidence level available (level III) supports combinatorial approaches that contained a rehabilitation component. Quality appraisal of the included literature highlights that there are still few well-designed studies producing high-level evidence that can appropriately answer questions regarding the effectiveness of many approaches proposed. Among the sources of bias encountered, the most concerning were: the inclusion of highly heterogeneous samples; the lack of randomization and concealed allocation procedures; the absence of blinding procedures; and the use of outcomes with limited sensitivity. In addition, only few studies included measures of integrity and residual connectivity of spinal pathways.

The finding that combinatorial approaches comprised 43% of Phase III studies in acute SCI and 77% of studies in chronic SCI is encouraging. Wenger and colleagues[10] demonstrated meaningful functional recovery of stepping in rats after a transection to the spinal cord after 4 weeks of body weight supported treadmill training delivered in combination with electrical neurostimulation and serotonin agonists administered systemically. Our study of the human literature supports this experimental evidence[10] by demonstrating that the strongest evidence for improved outcomes of motor function comes from trials that used combinatorial approaches containing a rehabilitation component.[25,27–29,38,39,48,49] Taken together, we believe that future clinical trials have greater potential for motor recovery if novel therapeutic strategies (such as neurostimulation and pharmacotherapy) are tested as adjuvant to rehabilitation.

The paucity of high-level evidence of studies from other modalities (including cell therapies, pharmacology, electrical stimulation/neuroelectric devices) should not be interpreted as a lack of effectiveness. Instead, this is partially an encouraging finding that reflects the high productivity in SCI research in the last 17 years, characterized by increases in the number of Phase I and Phase II studies suggesting promising novel treatment strategies. While the main objective of Phase I and II trials is the assessment of safety and feasibility of a given intervention, many methodological concerns with the early stage trials were identified, and future trials need to be more carefully designed to allow for inferences regarding preliminary efficacy that are useful in planning Phase III studies.

The inclusion of participants with broad age range and diverse clinical characteristics (time since injury, injury severity)

introduces insurmountable heterogeneity that is concerning when inferences regarding recovery are drawn based on group data. Spontaneous recovery rates have been shown to differ considerably based on the level and severity of the injury. There is evidence to support that as many as 10% of persons with complete (AIS A injuries) will convert to AIS C and D (incomplete injuries) within the first year in the absence of any therapeutic intervention.[2] For those initially classified as AIS B, 15–40% will convert to AIS C, and approximately 40% of the remaining will convert to AIS D.[2] Eighty percent of persons initially classified as AIS C will convert to AIS D within the first year.[2] In our opinion it is critical that future studies restrict the inclusion criteria to create homogeneous groups, especially in studies enrolling persons with acute and subacute injuries.[53] In studies with larger sample sizes, another option is to perform statistical analyses based on AIS level at entry.[38]

Further, nearly all studies used the ISNCSCI criteria as the primary outcome measure for neurologic recovery. While the AIS examination is the most widely used neurologic classification for SCI, it has a considerable degree of subjectivity and requires formal training for the investigators/clinical staff to achieve optimal rates in terms of intra-rater and test-retest reliability[54] (although rarely reported in the studies assessed). We found that 69% of the studies included did not adopt blinding of participants, and 64% of studies did not adopt blinding procedures for the investigators. This is an important concern, because when recovery occurs, we often do not know why it happens because of the lack of mechanistic discriminative power of our clinical assessments.

It is thus important to develop measures that allow change in particular pathways to be detected. Spinal cord integrity and residual connectivity was only assessed in a few studies (28% and 26%, respectively). Given its importance in motor function, the development of sensitive outcome measures of viability of corticospinal pathways is an important direction given the limited sensitivity of currently available outcome measures to quantify neurologic impairments and changes that may occur in response to novel therapies.

We believe that such neurophysiological and neuroimaging measures should be used to characterize spinal cord structure and physiology of the injury in future clinical trials. Potential approaches for assessing corticospinal conduction may involve the use of noninvasive or minimally invasive brain stimulation, electrophysiology, and imaging techniques.[7] For example, the quantification of motor evoked potentials elicited with TMS enables the assessment of functional integrity of the corticospinal tract, spinal nerve roots, and motor pathway's projections to the muscles.[55] Moreover, more advanced TMS protocols, particularly the triple-pulse protocol that combines central and peripheral stimuli, enable accurate quantification of the number of corticospinal fibers with preserved conduction across a putative spinal injury level.[56] Finally, such neurophysiologic studies can be combined with diffusor tension imaging and other advanced imaging methods[57] to provide anatomical characterization of the structural integrity of the corticospinal tract, including alterations in fractional anisotropy (that assesses the axonal count and myelin content), axial diffusivity, and radial diffusivity (that assesses the integrity of axons and myelin).[7]

Our search strategy captured only 18 or the 39 included articles. This can be explained by the difficulty in designing a search that identifies all of the different interventions of interest without requiring the need to review many thousands of abstracts. Although we used multiple queries and inspected reference lists, it is possible that the search strategy used herein may have been insufficient to detect all published studies for each approach (cell therapies, pharmacology, electrical stimulation, rehabilitation). Another limitation is that we did not include studies that assessed surgical decompression, which is a strategy with established efficacy.[58] In addition, the use of the Cochrane criteria of risk of bias may have resulted in a stringent evaluation of Phase I studies. While we acknowledge that the Cochrane criteria were primarily developed for application to randomized clinical trials, we thought it offered valuable insights.

Conclusions

Future research will benefit from addressing the methodological and conceptual concerns highlighted in the present study. The highest available evidence supports the use of combinatorial approaches containing rehabilitation techniques and, thus, novel therapeutic interventions should be tested in combinatorial approaches containing a well-defined rehabilitation component. Future research efforts that assess motor recovery should contain measures of viability of corticospinal fibers. We believe that this will lead to an improved understanding of the functional prognosis and the role of the corticospinal and other pathways critical for motor recovery after SCI, and their response to therapeutic interventions.

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Author Disclosure Statement

Dr. Pascual-Leone serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, Axilum Robotics, Magstim Inc., and Neosync and is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation with electroencephalography and magnetic resonance imaging. Dr. Guest serves on the scientific boards of Bioaxone and In Vivo Therapeutics. Mar Cortes' work is supported by grant NIH R21 HD069776. APL is supported in part by grants from the Sidney R. Baer Jr. Foundation, the National Institutes of Health (R01HD069776, R01NS073601, R21 MH099196, R21 NS082870, R21 NS085491, R21 HD07616), Harvard Catalyst|The Harvard Clinical and Translational Science Center (NCRR and the NCATS NIH, UL1 RR025758). For the remaining author, no competing financial interests exist.

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Address correspondence to:
Alvaro Pascual-Leone, MD, PhD
Berenson-Allen Center for Noninvasive Brain Stimulation
Department of Neurology
Beth Israel Deaconess Medical Center
330 Brookline Avenue
Boston, MA 02215

E-mail: apleone@bidmc.harvard.edu