

The Effectiveness and Safety of Exoskeletons as Assistive and Rehabilitation Devices in the Treatment of Neurologic Gait Disorders in Patients with Spinal Cord Injury: A Systematic Review

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Abstract

Study Design Systematic review.

Clinical Questions (1) When used as an assistive device, do wearable exoskeletons improve lower extremity function or gait compared with knee-ankle-foot orthoses (KAFOs) in patients with complete or incomplete spinal cord injury? (2) When used as a rehabilitation device, do wearable exoskeletons improve lower extremity function or gait compared with other rehabilitation strategies in patients with complete or incomplete spinal cord injury? (3) When used as an assistive or rehabilitation device, are wearable exoskeletons safe compared with KAFO for assistance or other rehabilitation strategies for rehabilitation in patients with complete or incomplete spinal cord injury?

Methods PubMed, Cochrane, and Embase databases and reference lists of key articles were searched from database inception to May 2, 2016, to identify studies evaluating the effectiveness of wearable exoskeletons used as assistive or rehabilitative devices in patients with incomplete or complete spinal cord injury.

Results No comparison studies were found evaluating exoskeletons as an assistive device. Nine comparison studies (11 publications) evaluated the use of exoskeletons as a rehabilitative device. The 10-meter walk test velocity and Spinal Cord Independence Measure scores showed no difference in change from baseline among patients undergoing exoskeleton training compared with various comparator therapies. The remaining primary outcome measures of 6-minute walk test distance and Walking Index for Spinal Cord Injury I and II and Functional Independence Measure–Locomotor scores showed mixed results, with some studies indicating no difference in change from

Keywords

- ▶ exoskeleton
- ▶ robotics
- ▶ rehabilitation
- ▶ spinal cord injury

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baseline between exoskeleton training and comparator therapies, some indicating benefit of exoskeleton over comparator therapies, and some indicating benefit of comparator therapies over exoskeleton.

Conclusion There is no data to compare locomotion assistance with exoskeleton versus conventional KAFOs. There is no consistent benefit from rehabilitation using an exoskeleton versus a variety of conventional methods in patients with chronic spinal cord injury. Trials comparing later-generation exoskeletons are needed.

Introduction

According to the National Spinal Cord Injury Statistical Center, ~282,000 persons live with spinal cord injury (SCI) in the United States, and ~17,000 new SCI cases occur each year.¹ SCIs have intense consequences, such as the loss of motor or sensory functions in the lower or upper limbs, depending on the level of injury. Therefore, the rehabilitation of locomotion has always been the key priority for patients suffering from SCIs.²

The greatest functional and neurologic recovery is to be expected during the first year after initial SCI; even with continuous and extensive rehabilitation, further improvements are usually not seen.³

Devices have been developed to assist patients suffering from SCI with mobility and to facilitate locomotion rehabilitation.⁴ One such device is a powered exoskeleton. Powered exoskeletons are motorized orthoses placed over a person's limb with joint parts corresponding to those of the human body. Their purpose is to facilitate standing and walking, as well as assist in rehabilitation.⁵

The first powered exoskeleton—the Lokomat (Hocoma, Switzerland)—was a residential (fixed) exoskeleton, also known as a driven gait orthosis.⁶ However, in recent years, innovative mobility devices have been developed, such as powered lower limb exoskeletons, that help individuals with low-level SCI walk as naturally as possible. Despite the similar frame structure, assistive and rehabilitative exoskeletons differ in their application and clinical objective. Assistive exoskeletons (e.g., Rex-Bionics [Auckland, New Zealand], Wearable Power-Assist Locomotor exoskeleton [WPAL; Fujita Health University, Japan], Re-Walk [Argo Medical Technologies Ltd, Yokneam Ilit, Israel]) allow patients to walk, and rehabilitative exoskeletons (e.g., Lokomat [Hocoma, Switzerland], Hybrid Assistive Limb [HAL; Cyberdyne, Inc., Tsukuba, Japan], Kinesis [Technaid, Madrid, Spain], and to some extent, Ekso-Bionics [Eksobionics Ltd, Richmond, California, USA]) focus on long-term gait improvement. Another difference is the control mechanism of the exoskeletons, such as joystick control (Rex-Bionics, Lokomat, WPAL, Kinesis), posture control (Re-Walk, Ekso-Bionics, Indego [Parker Hannifin Corp., Macedonia, Ohio, USA]), and electromyographic (EMG) control (HAL).

The aim of this systematic review is to determine if powered exoskeletons are effective as assistive and rehabilitation devices in improving locomotion in patients with SCI. We sought to answer the following clinical questions:

1. When used as an assistive device, do wearable exoskeletons improve lower extremity function or gait compared with knee-ankle-foot orthoses (KAFOs) in patients with complete or incomplete SCI?
2. When used as a rehabilitation device, do wearable exoskeletons improve lower extremity function or gait compared with other rehabilitation strategies in patients with complete or incomplete SCI?
3. When used as an assistive or rehabilitation device, are wearable exoskeletons safe compared with KAFOs for assistance or other rehabilitation strategies for rehabilitation in patients with complete or incomplete SCI?

Materials and Methods

Reporting of the methods and results follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for reporting systematic reviews.

Study design: Systematic review.

Information sources and search: PubMed, Cochrane, and Embase were searched for publications from database inception to May 2, 2016; bibliographies of included articles were also searched. The search strategy can be found in the online supplementary material.

Eligibility criteria: The inclusion criteria were as follows: (1) SCI resulting in a gait disorder; (2) age ≥ 18 and < 75 years; and (3) randomized controlled trials. The exclusion criteria were as follows: (1) neurologic conditions other than SCI; (2) no neurologic gait disorder; (3) studies where the intervention is a robotic end-effector device (e.g., Gait Trainer GT1 [Reha-Stim Medtec GmbH & Co. KG, Berlin, Germany]); (4) studies measuring only upper extremity outcomes; and (5) studies measuring only physiologic or metabolic outcomes. A more detailed patient, intervention, comparator, and outcome table can be viewed in the online supplementary material.

Outcomes: Primary outcomes include gait outcomes (e.g., walking speed, 6-minute walk test [6MWT], 10-meter walking test [10MWT]), functional improvement (e.g., Functional Independence Measure [FIM], Spinal Cord Independence Measure [SCIM]), and safety (e.g., fracture, pain, cardiopulmonary episodes); secondary outcomes include neurologic improvement, motor strength, bladder and bowel function, spasticity, and requirement of walking aid. A summary table

of the primary outcome measures can be found in the online supplementary material.

Data collection process and items: Data was extracted by a single individual and verified independently by a second using a pre-established data abstraction form. We attempted to contact authors of publications in cases where data needed confirmation or clarification. The following data items were sought: study design, time from SCI, injury level, study purpose, and rehabilitation treatment details.

Risk of bias evaluation: Randomized controlled trials were evaluated for risk of bias using criteria to judge articles on therapy. Crossover studies were evaluated for risk of bias using criteria outlined by Ding et al.⁷ These ratings are described in the online supplementary material.

Analysis and synthesis of results: When possible, the differences between groups' mean change in scores from baseline to follow-up were reported or calculated for continuous outcomes; otherwise, the mean or median differences between groups' scores at last follow-up were calculated.

Overall strength of evidence: We used the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) System to evaluate the quality of the evidence base for each key question. Details about this system can be found in the online supplementary material.

Results

Study Selection and Characteristics

From among 175 citations identified from our search, we excluded 155 after two individuals reviewed the titles and abstracts. We reviewed the full text of 20 articles and identi-

fied 9 randomized trials in 11 publications meeting the inclusion criteria (►Fig. 1). Nine studies were excluded. A list of excluded articles and reason for exclusion can be found in the online supplementary material. A majority of the patients in the included studies were male with subacute or chronic incomplete SCI of cervical or thoracic etiology. Among the 11 studies identified, 10 utilized the robotic exoskeleton Lokomat,⁸⁻¹⁷ and the remaining study utilized the robotic exoskeleton MBZ-CPM1 (ManBuZhe [Tianjin] Rehabilitation Equipment Co. Ltd., PR China).¹⁸ Nine of the included randomized trials were of parallel design, and two were of crossover design. Most studies were of moderately high risk of bias (►Table 1).

Efficacy of Wearable Exoskeletons as an Assistive Device

No studies were identified comparing the efficacy of wearable exoskeletons as an assistive device to standard KAFOs in patients with complete or incomplete SCI.

Efficacy of Wearable Exoskeletons as a Rehabilitation Device

Ten-Meter Walk Test

Six randomized controlled trials in eight publications evaluated walking velocity using the 10MWT comparing exoskeleton training to a control group with follow-up ranging from 4 to 12 weeks (►Table 2); two measured fast walking velocity,^{10,12} one self-selected walking velocity,⁹ one measured both fast and self-selected walking,¹⁵ and two did not report the velocity pace for the test.^{8,14}

In general, patients improved slightly with training. However, there were no differences in change from baseline among patients undergoing exoskeleton training compared with treadmill-based training with manual assistance,¹² treadmill-based training with electrical stimulation,¹² overground ambulation training with or without electrical stimulation,^{8,12,14} therapist-assisted body weight-supported treadmill training (BWSTT),¹⁴ no training,¹⁰ treatment with tizanidine (dose = 0.03 mg/kg),¹⁰ or the Gait Trainer GT1 with conventional therapy.⁹ One crossover trial found that fast walking velocity improved significantly more after strength training versus exoskeleton training.¹⁵

A subgroup analysis of Duffell et al comparing exoskeleton training to no intervention found that patients classified as high walking capacity at baseline (high 10MWT velocity and Timed-Up-and-Go [TUG] test times; high 6MWT distance) had more improvement in 10MWT times with exoskeleton rehabilitation compared with no intervention at 4 weeks of follow-up; patients with baseline low walking capacity (low 10MWT velocity and TUG test times; low 6MWT distance) showed no difference for either treatment (p for interaction = 0.02).^{10,16} A subgroup analysis of Alcobendas-Maestro et al comparing exoskeleton training with standard physical treatment to conventional overground training with standard physical treatment found that patient baseline upper or lower motor neuron injury did not modify treatment effect for 10MWT velocity at 8 weeks of follow-up.^{8,11}

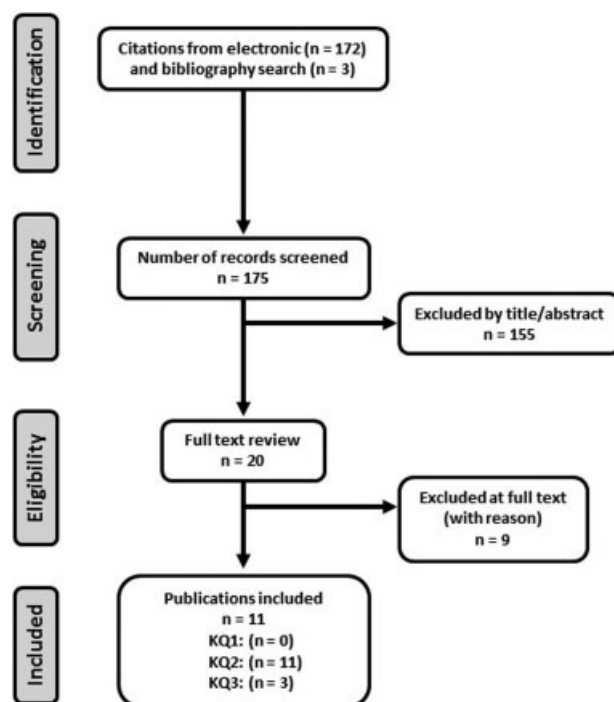


Fig. 1 Flow diagram showing results of literature search. Abbreviation: KQ, key question.

Table 1 Spinal cord injury studies characteristics table

First author (year), study design	Patient characteristics	Study purpose	Inclusion and exclusion criteria	Intervention (A) ^a	Comparator (B)	Length of F/U; % F/U (n/N)	Risk of bias	Funding
Alcobendas-Maestro (2012), ⁸ RCT	No. randomized A: 40 B: 40 Age (y) A: 45.2 ± 15.5 B: 49.5 ± 12.8 Males A: 77.5% B: 78.8% Months from SCI: 4.2 (median) Injury level Levels C1–C8 A: 59% B: 61% Levels T1–T6 A: 19% B: 13% Levels T7–T12 A: 22% B: 26%	To compare a walking re-education program using exoskeleton to conventional OGT among individuals with iSCI of both traumatic and nontraumatic etiology	Inclusion: C2–T12 SCI; ASIA C or D; traumatic or non-traumatic, non-progressive lesions; onset <6 mo; age 16–70 y; achieved assisted standing for minimum of 1 wk previously Exclusion: Unstable orthopedic injury; osteoporosis; lesions or ulcers where exoskeleton harness or straps are fitted; joint rigidity; leg length >2 cm; pulmonary heart disease; body weight > 150 kg; previous SCI	Standard physical treatment + robotic-assisted locomotor training via exoskeleton ^b (30 min) Training duration: 40 sessions/8 wk	Standard physical treatment + OGT (60 min) Standard PT: joint mobilization, strengthening of supraspinal musculature and re-maining motor functions, muscle stretching and postural relaxation techniques, trunk stabilization, and practice of self-care skills	8 wks of F/U; 93.8% (75/80)	Low	Grant from Fondo para la Investigación Sanitaria en Castilla la Mancha-AN/2006/27
Benito-Penalva (2012), ⁹ RCT	No. randomized A: 46 B: 84 Age (y) ^d A: 45 B: 45 Males ^b A: 66.7% B: 68.1% Months from SCI ^d <6 mo: 77.1% 6–12 mo: 7.6% >12 mo: 15.2% Injury level: NR	To report the clinical improvements in patients with spinal cord injury associated with intensive gait training using electro-mechanical systems according to patient characteristics	Inclusion: motor incomplete (ASIA C or D), and select motor complete SCI (ASIA A or B) when voluntary movement was present at segments L2 and L3; 18+ y of age; able to tolerate the standing position without orthostasis Exclusion: cardiorespiratory instability, pressure ulcers that interfered with mechanical components of gait devices, spasticity	Conventional therapy + robotic-assisted locomotor training via exoskeleton ^b (20–45 min) Training duration: 5 d a week, 8 wk	Gait trainer GT 1 + conventional therapies Conventional therapy: details NR	8 wks of F/U; 80.8% (105/130)	Moderately high	NR

(Continued)

Table 1 (Continued)

First author (year), study design	Patient characteristics	Study purpose	Inclusion and exclusion criteria	Intervention (A) ^a	Comparator (B)	Length of F/U; % F/U (n/N)	Risk of bias	Funding
Duffell (2015), ¹⁰ RCT	No. randomized A: 27 B: 29 C: 27 Age (y) A: 46.6 ± 12.6 B: 47.8 ± 13.1 C: 47.4 ± 11.6 Males A: 70.3% B: 65.5% C: 70.3% Months from SCI: 113 ± 111 (mean ± SD) Level of injury: above T10: 100%	To investigate the effects of locomotor treadmill training and tizanidine on gait impairment in people with incomplete motor SCI, and to understand whether functional levels affect recovery with different interventions	Inclusion: age 18–50 y, motor incomplete SCI (ASIA C or D); level of injury above T10; >12 mo postinjury; able to ambulate; medical clearance; spasticity in the ankle (Modified Ashworth Score ≥1); lower limb PROM within limits for ambulation Exclusion: sitting tolerance <2 h, existing infection, severe cardiopulmonary disease, concomitant neurologic injury, fractures post-SCI, orthopedic or peripheral nerve injury in the LL	Robotic-assisted locomotor training via exoskeleton ^b (30–45 min) Treatment duration: 3 times a week for 4 wk	B: no training or C: tizanidine (0.03 mg/kg per dose) Treatment duration: 4 times a day for 4 wk	4 wk: A versus B F/U: 95.4% (54/56), A versus C F/U: 98.1% (53/54)	Moderately high	Supported by the National Institutes of Health and the Craig H. Neilsen Foundation awards to M.M.M.
Esclarin-Ruz (2014), ¹¹ RCT	No. randomized UMN A: 22 B: 22 LMN A: 22 B: 22 Age (y) UMN A: 43.6 ± 12 B: 44.9 ± 7 LMN A: 36.4 ± 12	To compare a walking re-education program with robotic locomotor training plus OGT to conventional OGT in individuals with incomplete UMN or LMN injuries having either traumatic or nontraumatic nonprogressive etiology	Inclusion: C2–T11 SCI ASIA C or D; with only UMN findings; T12–L3 SCI ASIA C or D with only LMN; traumatic and nontraumatic, nonprogressive lesions; onset < 6 mo; age 16–70 y; achieved assisted standing a minimum of 1 wk previously	Standard physical treatment (30 min) + OGT + robotic-assisted locomotor training via exoskeleton ^b (30 min) Training duration: daily sessions for a total of 40 sessions over 8 wk	Conventional OGT (30 min) + standard physical treatment (30 min) Standard physical treatment	8 wk of F/U (no training): UMN: 95.4% (42/44), LMN: 93.2% (41/44)	Low	Supported by the Founding for Research of Castilla La Mancha (grant no. PI 2006-45)

Table 1 (Continued)

First author (year), study design	Patient characteristics	Study purpose	Inclusion and exclusion criteria	Intervention (A) ^a	Comparator (B)	Length of F/U; % F/U (n/N)	Risk of bias	Funding
	B: 42.7 ± 18 Males UMN A: 71.4% B: 61.9% LMN A: 70% B: 80.9% Months from SCI: (mean ± SD) UMN: 4.4 ± 1.8 LMN: 3.6 ± 1.3 Level of injury UMN Levels C1–C8 A: 57.1% B: 57.1% Levels T1–6 A: 19% B: 19% Levels T7–11 A: 24% B: 24% LMN Levels T12–L1 A: 67% B: 76% Levels L2–L3 A: 33% B: 24%		Exclusion: orthopedic injuries that are unstable; osteoporosis with high risk of pathologic fracture; cutaneous lesions and/or pressure ulcers in areas in which the exoskeleton harness or thigh straps are fitted; joint rigidity; asymmetry of lower extremity length > 2 cm; pulmonary or heart disease requiring monitoring during exercise; body weight > 150 kg; history of spinal injury	A: robotic-assisted locomotor training via exoskeleton ^b (60 min) Treatment duration: 5 d/wk for 12 wk; mean number of training sessions completed was 49 ± 7 (range, 27–58)	B: treadmill-based training with manual assistance (60 min) C: treadmill-based training with stimulation to common peroneal n (60 min) D: OGT with stimulation to common peroneal n (60 min) Manual assistance through step phase	4 wk of training, 6 mo F/U; 86% (64/74)	Moderately high	Funding provided by National Institutes of Health grant R01HD41487 (to Dr. Field-Fote) and The Miami Project to Cure Paralysis
Field-Fote (2011), ¹² RCT	No. randomized A: 15 B: 19 C: 22 D: 18 Age (y) ^d A: 45 ± 8 B: 39.3 ± 14.6 C: 38.5 ± 12.7 D: 42.2 ± 15.7 Males ^d A: 85.7% B: 82.3%	The objective of this study was to compare changes in walking speed and distance associated with 4 locomotor training approaches	Inclusion: chronic (≥1 y) SCI; ASIA C or D at or above T10; ability to take at least 1 step with 1 leg; ability to rise to a standing position with moderate assistance (50% effort) from 1 other person Exclusion: current orthopedic					

(Continued)

Table 1 (Continued)

First author (year), study design	Patient characteristics	Study purpose	Inclusion and exclusion criteria	Intervention (A) ^a	Comparator (B)	Length of F/U; % F/U (n/N)	Risk of bias	Funding
Gorman (2016), ¹³ crossover RCT	C: 77.8% D: 73.3% Months from SCI ^d : ≥12: 100% Injury level: above T11: 100%	To assess the effectiveness of robotically assisted BWSIT for improving cardiovascular fitness in chronic motor fSCI	Inclusion: traumatic SCI ≥ 1 y prior to enrollment, age 18–80 y, injury between C4–L2, AIS A C or D, able stand at least 30 min Exclusion: uncontrolled hypertension, unstable angina, CHF, COPD, symptomatic PAD, or recent hospitalization (within 3 mo) for medical problem; severe contractures or frequent uncontrolled bouts of autonomic dysreflexia; BMD T-score ≤ -3.5	Robotic-assisted locomotor training via exoskeleton ^b (20–45 min) Treatment duration: 3 times a week for 3 mo	Home stretching program (20–25 min)	3 or 6 mo ^c ; 67% (18/27)	Moderately high	Funded by Department of Veterans Affairs Rehabilitation R&D Service Merit Review Award B4027; study registered at clinicaltrials.gov with the identifier NCT00385918
Hornby (2005), ¹⁴ RCT	No. randomized A: NR B: NR C: NR Total: 35 Age (y): NR Males: NR Months from SCI: 0.5–0.9 (range) Level of injury: above T10: 100%	To study the effects of robotically assisted BWSIT on individuals with subacute SCI	Inclusion: traumatic or ischemic SCI above T10; injury within 14–180 d; ASIA B, C, or D; required physical assistance from at least one PT to ambulate over ground Exclusion: secondary neurologic injuries, including traumatic brain	A: robotic-assisted locomotor training via exoskeleton ^b (30 min) Treatment duration: 3 sessions/wk	B: Therapist-assisted BWSIT (30 min) C: OGT with mobile suspension system (30 min)	8 wk training and F/U; 85.7% (30/35)	Moderately high	NR

Table 1 (Continued)

First author (year), study design	Patient characteristics	Study purpose	Inclusion and exclusion criteria	Intervention (A) ^a	Comparator (B)	Length of F/U; % F/U (n/N)	Risk of bias	Funding
Huang (2015), ¹⁸ RCT	No. randomized A: 12 B: 12 Age (y) A: 41.7 ± 3.3 B: 38.4 ± 2.3 Males A: 75% B: 58.3% Months from SCI: NR Level of injury: lev- els T8–L2 A: 100% B: 100%	To compare the ef- fects of BWSTT and robot-assisted reha- bilitation on bowel function in patients with spinal cord in- jury with respect to defecation time and defecation drug dose (enema)	injury or peripheral nerve damage Inclusion: NR Exclusion: NR	Robot-assisted loco- motor training via exoskeleton ^e + manual therapy (20 min) Treatment dura- tion: 4 times a week for 4 wk	BWSTT + manual therapy + standard rehabilitation train- ing (20 min)	4 wk; % F/U NR	Moderately high	Research on Design Theory and Compliant Control for Underactu- ated Lower-Ex- tremity Reha- bilitation Ro- botic Systems, Code 51175368
Labruyère (2014), ¹⁵ crossover RCT	No. randomized A: 5 B: 4 Age (y) A: 59 ± 11 B: 59 ± 11 Males A: 55.6% B: 55.6% Months from SCI: 50 ± 56 (mean ± SD) Level of injury Cervical A: 56% B: 56% T1–T6 A: 11% B: 11% T7–T12 A: 33% B: 33%	To compare changes in a broad spectrum of walk- ing-related out- come measures and pain between robot- assisted gait train- ing and strength training in patients with chronic iSCI, who needed walk- ing assistance	Inclusion: age 18– 70 y, chronic iSCI > 1 y; sensorimotor incomplete ASIA C or D; motor level of the lesion C4–T11; walk with at most moderate assis- tance; cognitive ca- pacity to follow verbal instructions Exclusion: contrain- dications for train- ing in the exoskeleton system, had injuries limiting training, as well as orthopedic, psychi- atric or neurologic diseases, except for the iSCI	Robot-assisted loco- motor training via exoskeleton ^b (45 min) Treatment dura- tion: 32 total ses- sions over 8 wk, 16 sessions of each treatment	Strength training (45 min)	4 wks of each inter- vention for a total of 8 wk of training, F/U to 6 mo; 100% (20/20)	Moderately low	International Spinal Re- search Trust (Clinical Initia- tive Stage 2, London, UK; grant number CL106), the Henry Smith Charity (Lon- don, UK), and the EMDO Foundation (Zurich, Switzerland)

(Continued)

Table 1 (Continued)

First author (year), study design	Patient characteristics	Study purpose	Inclusion and exclusion criteria	Intervention (A) ^a	Comparator (B)	Length of F/U; % F/U (n/N)	Risk of bias	Funding
Niu (2014), ¹⁶ RCT	No. randomized A: 20 B: 20 Age (y) A: 42.2 ± 12.6 B: 49.7 ± 7 Males A: 65% B: 70% Months from SCI: 8.2 ± 7.7 (mean ± SD) Level of injury: above T10: 100%	To characterize the distinct recovery patterns of gait impairment for SCI subjects receiving exoskeleton training, and to identify significant predictors for these patterns	Inclusion: NR Exclusion: NR	Robotic-assisted locomotor training via exoskeleton ^b (45 min) Treatment duration: 3 times a week for 4 wk	No interventions	4 wk; F/U NR	Moderately high	National Institutes of Health (R01H-D059895) and the Craig H. Neilsen Foundation awarded to M.M.
Shin (2014), ¹⁷ RCT	No. randomized A: 30 B: 30 Age (y) A: 43.2 ± 14.4 B: 48.2 ± 11.5 Males A: 74.1% B: 53.8% Months from SCI: 3.0 ± 2.0 (mean ± SD) Level of injury Cervical A: 51.9% B: 61.5% Thoracic/lumbar A: 48.1% B: 38.5%	To determine the effect of robotic-assisted gait training compared with OGT	Inclusion: nonprogressive traumatic or nontraumatic SCI, onset <6 mo, ASIA D, age 20–65 y Exclusion: pressure ulcers, severe limitation of ROM of hips and knees, severe cognitive impairment, cardiovascular disease requiring monitoring during exercise, LMN lesion, previously undergone robot assisted gait training	Regular PT (60 min) + robotic-assisted locomotor training via exoskeleton ^b (40 min) Treatment duration: 1 exoskeleton + 1 conventional treatment session/d, 3 times a week for 4 wk; 2 conventional treatment sessions/d, 2 times a week for 4 wk	Conventional OGT + regular PT (60 min) Treatment duration: twice a day, 5 times a week for 4 wk	4 wks; 88.3% (53/60)	Moderately high	NR

Abbreviations: ASIA, American Spinal Injury Association; BMD, bone mineral density; BWSTT, body weights-supported treadmill training; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; F/U, follow-up; ISCI, incomplete spinal cord injury; LL, lower limb; LMN, lower motor neuron; NR, not reported; OGT, overground training; PAD, peripheral artery disease; PT, physical therapy; RCT, randomized controlled trial; ROM, range of motion; SCI, spinal cord injury; SD, standard deviation; UMIN, upper motor neuron.

^aUnless otherwise noted, training duration is the same for intervention and comparator.

^bLokomat (Hocoma, Switzerland).

^cThree months of follow-up for the robotic group, 6 months of follow-up for control group; the control group crossed over to exoskeleton training after 3 months of home stretching.

^dData only for those with data at final analysis.

^eMBZ-CPM1 (ManBuZhe [Tianjin] Rehabilitation Equipment Co. Ltd., PR China).

Table 2 Differences between groups for primary outcomes at various follow-up periods^a

First author (year), F/U, and groups	10MWT (m/s)	6MWT (m)	WSCI II (0–20 [best])	FIM-L (2–14 [best])	SCIM (0–100 [best])
Alcobendas-Maestro (2012), ⁸ 8 wk A: exoskeleton + PT B: OGT + PT	Median (IQR) at 8 wk Velocity unclear A: 0.40 (0.20, 0.60) B: 0.30 (0.20, 0.50) p = NS	Median (IQR) at 8 wk A: 169 (69, 228) B: 91 (51, 179) p < 0.05	Median (IQR) at 8 wk A: 16 (9, 19) B: 9 (8, 16) p < 0.05	Median (IQR) at 8 wk ^b A: 10 (6, 12) B: 7 (5, 10) p < 0.05	NR
Benito-Penalva (2012), ⁹ 8 wk A: exoskeleton + CT B: Gait Trainer GTT + CT	Mean Δ from baseline Self-selected velocity A: 0.19 ± 0.03 B: 0.18 ± 0.18 Mean diff (95% CI): A versus B: 0.0 (-0.04, 0.05)	NR	Mean Δ from baseline A: 5.3 ± 0.7 B: 5.1 ± 0.5 Mean diff (95% CI): A versus B: 0.2 (-0.1, 0.4)	NR	NR
Duffell (2015), ¹⁰ 4 wk A: exoskeleton B: no training C: tizanidine	% attained MID ^c Fast velocity A: 15% (4/26) B: 23% (6/26) C: 8% (2/25)	% attained MID ^c A: 8% (2/24) B: 13% (3/23) C: 12% (3/26)	NR	NR	NR
Esclarín-Ruz (2014), ¹¹ 8 wk ^d A: exoskeleton + PT B: OGT + PT	Mean Δ from baseline Self-selected velocity UMN A: 0.06 ± 0.19 B: 0.03 ± 0.19 LMN A: 0.22 ± 0.17 B: 0.17 ± 0.25 Mean diff (95% CI) UMN, A versus B: 0.03 (-0.10, 0.16) LMN, A versus B: 0.05 (-0.09, 0.19)	Mean Δ from baseline UMN A: 65.2 ± 70.8 B: 26.1 ± 56.6 LMN A: 74.8 ± 59.7 B: 51.3 ± 79.1 Mean diff (95% CI) UMN, A versus B: 39.1 (-7.4, 85.6) LMN, A versus B: 23.5 (-23.1, 70.2)	Mean Δ from baseline UMN A: 7.6 ± 3.4 B: 6.1 ± 3.1 LMN A: 6.5 ± 2.5 B: 5.8 ± 2.7 Mean diff (95% CI) UMN, A versus B: 1.5 (-0.5, 3.4) LMN, A versus B: 0.7 (-0.95, 2.25)	Mean Δ from baseline UMN A: 3.9 ± 1.8 B: 2.1 ± 1.8 LMN A: 2.9 ± 1.8 B: 3.7 ± 1.7 Mean diff (95% CI) UMN, A versus B: 1.8 (0.8, 2.9) LMN, A versus B: -0.8 (-1.8, 0.3)	NR
Field-Fote (2011), ¹² 12 wk A: exoskeleton B: TT with manual assist C: TT with stimulation D: OGT with stimulation	Mean Δ from baseline Fast velocity A: 0.01 ± 0.06 B: 0.05 ± 0.10 C: 0.05 ± 0.11 D: 0.09 ± 0.17 Mean diff (95% CI) A versus B: -0.04 (-0.10, 0.02) A versus C: -0.04 (-0.10, 0.02)	NR	NR	NR	NR

(Continued)

Table 2 (Continued)

First author (year), F/U, and groups	10MWT (m/s)	6MWT (m)	WSCI II (0–20 [best])	FIM-L (2–14 [best])	SCIM (0–100 [best])
	A versus D: $-0.08 (-0.17, 0.01)$				
Hornby (2005), ¹⁴ 8 wk A: exoskeleton B: therapist-assist BWSTT C: OCT	No significant differences	No significant differences	Mean Δ from baseline ^{e,f} A: 5.8 ± 2.0 B: 5.2 ± 2.0 C: 6.5 ± 2.2 Mean diff at last F/U (95% CI) ^e A versus B: $0.6 (-1.2, 2.4)$ A versus C: $-0.72 (-2.6, 1.1)$	Mean Δ from baseline ^f A: 1.8 ± 0.9 B: 1.9 ± 0.6 C: 2.0 ± 0.5 Mean diff at last F/U (95% CI) A versus B: $-0.1 (-0.9, 0.6)$ A versus C: $-0.2 (-0.9, 0.4)$	NR
Labruyère (2014), ¹⁵ 8 wk A: exoskeleton B: strength training	Mean Δ from baseline Self-selected velocity A: 0.04 (SD NR) B: 0.06 (SD NR) Mean diff (95% CI) ^g : A versus B: $0.02 (-0.04, 0.08)$, $p = NS$ Mean Δ from baseline Fast velocity A: 0.01 (SD NR) B: 0.14 (SD NR) Mean diff (95% CI) ^f : A versus B: 0.13 (0.01, 0.25) $p = 0.04$	NR	Mean Δ from baseline A: 0.8 (SD NR) B: 0.4 (SD NR) Mean diff (95% CI) ^g : A versus B: $-0.4 (-1.5, 0.6)$ $p = NS$	NR	Mean Δ from baseline A: 0.8 (SD NR) B: 1.3 (SD NR) Mean diff (95% CI): A versus B: $0.5 (-2.1, 3.2)$ $p = NS$
Niu (2014), ¹⁶ 4 wk ^{h,i} A: exoskeleton B: no interventions	Mean Δ from baseline, class I ^j Velocity unclear A: 0.03 ± 0.01 B: 0.01 ± 0.15 Mean diff (95% CI): class I: $0.02 (-0.08, 0.12)$ Mean Δ from baseline, class II ^j Velocity unclear A: 0.12 ± 0.32 B: 0.02 ± 0.13 Mean diff (95% CI): class II: $0.10 (-0.10, 0.29)$	Diff between groups' rate of change over 4 wk (m/wk) Class I: 0.8 , $p = NS$ Class II: 2.3 , $p = NS$	NR	NR	NR

Table 2 (Continued)

First author (year), F/U, and groups	10MWT (m/s)	6MWT (m)	WSCI II (0–20 [best])	FIM-L (2–14 [best])	SCIM (0–100 [best])
Shin (2014), ¹⁷ 4 wk A: exoskeleton + PT B: OGT + PT	NR	NR	Median (IQR) at 4 wk A: 11 (0, 19) B: 9 (0, 20) p = 0.01	NR	Median (IQR) at 4 wk A: 10 (0, 26) B: 9 (0, 33) p = NS

Abbreviations: 6MWT, 6-minute walk test; 10MWT, 10-meter walk test; BWSTT, body weight-supported treadmill training; CI, confidence interval; CT, conventional training; diff, difference; FIM-L, Functional Independence Measure–Leg; F/U, follow-up; IQR, interquartile range; LMN, lower motor neuron; MID, minimally important difference; NR, not reported; NS, not significant; OGT, overground training; PT, physical therapy; SCIM, Spinal Cord Independence Measure; SD, standard deviation; TT, treadmill training; UMN, upper motor neuron; WSCI II, Walking Index for Spinal Cord Injury II.

^aUnless otherwise indicated, all values are reported as mean ± SD.
^bFIM-L evaluated for only walking and stair tasks.

^cThe MID was defined using control group data; this was calculated using the following formula: $(1.96 \times \sqrt{2} \times \text{standard error of the mean})$. Participants who achieved a change from baseline equal to or greater than the MID for that test, after 4 weeks of training, were classified as “MID achieved.”

^dEsclarín-Ruz et al (2014)¹¹ is a subgroup analysis of Alcobendas-Maestro et al (2012).⁸

^eAuthors reported WSCI scores (1–20 [best]).

^fThese values were estimated from Fig. 4.

^gThe 95% CIs were estimated from Fig. 4, point estimates were calculated using values in Table 2.

^hNiu et al (2014)¹⁶ is a subgroup analysis of Duffell et al (2015).¹⁰

ⁱClass I (“low walking capacity class”) included subjects with longer 10MWT and Timed-Up-and-Go (TUG) test times, and shorter 6MWT distances at baseline; class II (“high walking capacity class”) included subjects with shorter 10MWT and TUG test times and longer 6MWT distances.

^jValues on 10MWT were estimated from Fig. 1.

6-Minute Walk Test

Three trials in five publications assessed endurance using the 6MWT at 4 or 8 weeks of follow-up. Two found no difference in 6MWT distance among patients undergoing exoskeleton training compared with therapist-assisted BWSTT,¹⁴ overground ambulation,¹⁴ no training,¹⁰ or tizanidine.¹⁰ One trial reported a statistically significant median distance following 8 weeks of training in favor of the exoskeleton group compared with overground training plus standard physical therapy.⁸ With the data provided, it is unclear whether this difference is functionally meaningful.

A subgroup analysis of Duffell et al comparing exoskeleton training with no intervention found that baseline low or high walking capacity did not modify the treatment effect for 6MWT distance at 4 weeks of follow-up.^{10,16} A subgroup analysis of Alcobendas-Maestro et al comparing exoskeleton training with standard physical treatment to conventional overground training with standard physical treatment found that baseline upper versus lower motor neuron injury did not modify treatment effect for 6MWT distance at 8 weeks of follow-up.^{8,11}

Walking Index for Spinal Cord Injury I and II

Five studies in six publications evaluated the level of walking impairment via Walking Index for Spinal Cord Injury I (WSCI) or II (WSCI II) scores at 4 or 8 weeks of follow-up. One trial found no difference in WSCI scores among patients undergoing exoskeleton training versus therapist-assisted BWSTT or overground ambulation.¹⁴ Another found no difference in WSCI II scores among patients undergoing exoskeleton training with conventional therapy versus patients undergoing Gait Trainer GT1 training in conjunction with conventional therapy.⁹ A third study—a crossover trial—found no differences in WSCI scores comparing exoskeleton training to strength training.¹⁵ Two studies found that exoskeleton training in conjunction with regular physiotherapy or standard physical treatment significantly improved WSCI II scores more than conventional overground training in conjunction with regular physiotherapy or standard physical treatment; median scores were 11 and 16 in the exoskeleton group plus physical therapy groups compared with 9 and 9 in the overground training plus physical therapy groups.^{8,17}

A subgroup analysis of Alcobendas-Maestro et al comparing exoskeleton training with standard physical treatment to conventional overground training with standard physical treatment found that baseline upper versus lower motor neuron injury did not modify treatment effect for WSCI II at 8 weeks of follow-up.^{8,11}

Functional Independence Measure–Locomotor

Two trials in three publications assessed locomotive function via Functional Independence Measure–Locomotor (FIM-L) scores at 8 weeks of follow-up. One trial found no difference in FIM-L scores among patients undergoing exoskeleton training, therapist-assisted BWSTT, or overground ambulation training,¹⁴ but another trial found that patients undergoing exoskeleton training in conjunction with standard

physical treatment significantly improved their FIM-L scores compared with patients undergoing conventional overground training in conjunction with standard physical treatment; median scores at last follow-up were 10 (interquartile range [IQR]: 6 to 12) compared with 7 (IQR: 5 to 10), respectively ($p < 0.05$).⁸

A subgroup analysis of Alcobendas-Maestro et al found that patients with upper motor neuron injuries had improved FIM-L scores from treatment with exoskeleton therapy with standard physical treatment compared with conventional overground training with standard physical treatment at 8 weeks of follow-up; patients with lower motor neuron injuries at baseline had no improvement with either treatment (p for interaction = 0.013).^{8,11}

Spinal Cord Independence Measure

Two trials evaluated independence via the SCIM at 4 or 8 weeks of follow-up. There was no difference in SCIM scores between exoskeleton training with regular physiotherapy and conventional overground training with regular physiotherapy at 4 weeks of follow-up in one trial.¹⁷ In the second trial, there was no difference between exoskeleton training versus strength training in a crossover design after 4 and 8 weeks.¹⁵

Lower Extremity Motor Score

Five trials in six publications evaluated lower extremity motor function via the lower extremity motor score (LEMS) at 4 or 8 weeks of follow-up (→ **Table 3**). The results were mixed. One trial found no difference in LEMS between exoskeleton training with regular physiotherapy or conventional overground training with regular physiotherapy.¹⁷ A second trial reported that use of the end-effector exoskeleton Gait Trainer GT1 in conjunction with conventional therapy resulted in a greater improvement in the LEMS compared with exoskeleton training in conjunction with conventional therapy; the difference between the mean change scores was -2.17 (95% confidence interval [CI], -2.6 to -1.74).⁹ However, these results are in contrast to a third trial, which reported exoskeleton training with regular physiotherapy significantly improved LEMS compared with conventional overground training with standard physical treatment; the median score was 40 (IQR: 30 to 45.5) compared with 35 (IQR: 29.7 to 40; $p < 0.05$).⁸ Two crossover trials reported no difference between exoskeleton training and strengthening exercises or home stretching exercises.^{13,15}

A subgroup analysis of Alcobendas-Maestro et al comparing exoskeleton training with standard physical treatment to conventional overground training with standard physical treatment found that baseline upper versus lower motor neuron injury did not modify treatment effect for LEMS at 8 weeks of follow-up.^{8,11}

Defecation Measures

A single trial reported defecation measures via defecation time and enema volume at 4 weeks of follow-up (→ **Table 3**). Exoskeleton training in conjunction with manual therapy resulted in better defecation times and enema volumes

compared with BWSTT in conjunction with manual therapy and standard rehabilitation; the defecation time difference between mean change scores was -14.0 minutes (95% CI, -21.4 minutes to -6.6 minutes), and the enema volume difference between mean change scores was -18.5 mL (95% CI, -24.9 mL to -12.0 mL).¹⁸

Safety of Wearable Exoskeletons

Adverse events were rare. Two trials reported no adverse events at 8 weeks' follow-up among patients receiving exoskeleton training with conventional therapy,⁹ exoskeleton training alone,¹⁵ Gait Trainer GT1 training with conventional therapy at 8 weeks' follow-up,⁹ or strength training.¹⁵ One randomized, crossover trial with follow-up at 3 and 6 months found that skin irritation or abrasion occurred in 11% (2/18) of subjects completing the trial.¹³ The sites affected included the hip, groin, penis, back, wrist, glutei, and scapula. The authors indicated that this issue was resolved by adding additional padding to the parachute harness setup. The remaining included trials made no explicit mention of adverse events.

Evidence Summary

Exoskeletons as Assistive Devices

There were no studies comparing exoskeletons as assistive devices to currently used orthotics.

Exoskeletons as Rehabilitation Devices

There were no differences in the 10MWT and 6MWT comparing exoskeleton versus non-exoskeleton rehabilitation in patients with SCI. There were mixed results for the WISCI/WISCI II and FIM-L; the majority of studies found no difference between rehabilitation strategies with a few studies reporting significantly improved scores in the exoskeleton group. Patients with a high walking capacity at baseline (high 10MWT velocity and TUG test times; high 6MWT distance) had more improvement in 10MWT but not the 6MWT with exoskeletal rehabilitation compared with non-exoskeleton rehabilitation, and patients classified as low walking capacity showed no difference between treatments. The overall strength of evidence for these findings is low or very low (→ **Table 4**).

Safety of Exoskeletons

Adverse events were rare; however, they were reported inconsistently.

Illustrative Case

A 29-year-old female acrobat suffered from traumatic SCI after a fall from a 3-m height during an artistic performance. She was instantly unable to move upper and lower limbs.

Diagnosis in the first hospital providing care revealed fractures and fracture dislocation of cervical vertebrae C3 and C4. At the day of admission, she received a decompression operation via laminectomy of the C3 and was immobilized with a cervical collar. On the third postoperative day, the patient was transferred to a level 1 trauma center with an affiliated rehabilitation facility for SCIs.

Table 3 Differences between groups for secondary outcomes at various follow-up periods^a

First author (year), follow-up, and groups	Score at follow-up	Difference between treatments
LEMS 0–50 (best)		
Alcobendas-Maestro (2012), ⁸ 8 wk A: exoskeleton + PT B: OGT + PT	Median (IQR) at 8 wk A: 40 (35, 45.5) B: 35 (29.7, 40) <i>p</i> < 0.05	
Benito-Penalva (2012), ⁹ 8 wk A: exoskeleton + CT B: Gait Trainer GT1 + CT	Mean Δ from baseline A: 7.1 ± 1.2 B: 9.3 ± 0.9	Mean diff (95% CI), A versus B: −2.2 (−2.6, −1.7)
Esclarín-Ruz (2014), ¹¹ 8 wk ^b A: exoskeleton + PT B: OGT + PT	UMN, mean Δ from baseline A: 8.33 ± 6.64 B: 5.28 ± 6.94 LMN, mean Δ from baseline A: 6.15 ± 6.81 B: 2.57 ± 6.6	UMN, mean diff (95% CI), A versus B: 3.05(−1.06, 7.16) LMN, mean diff (95% CI), A versus B: 3.58 (−0.53, 7.69)
Field-Fote (2011), ¹² 12 wk A: exoskeleton B: TT with manual assist C: TT with stimulation D: OGT with stimulation	Mean Δ from baseline, left leg ^c A: 1.2 ± 4.3 B: 1.7 ± 3.5 C: 1.2 ± 3.8 D: 1.1 ± 4.4	Mean diff (95% CI), left leg ^c A versus B: −0.5 (−3.28, 2.28) A versus C: 0.0 (−2.84, 2.84) A versus D: 0.1 (−3.06, 3.26)
Gorman (2016), ¹³ 3 or 6 mo A: exoskeleton B: home stretching program	Mean Δ from baseline ^d A: 0.3 ± 7.06 B: −0.4 ± 5.18	Mean diff (95% CI), A versus B: 0.7 (−5.05, 6.45)
Hornby (2005), ¹⁴ 8 wk A: exoskeleton B: therapist-assist BWSTT C: OGT	Mean Δ from baseline ^e A: 12.8 ± 2.4 B: 12.6 ± 4 C: 10.8 ± 2.4	Mean diff at last F/U (95% CI) A versus B: 0.2 (−2.7, 3.09) A versus C: 2.0 (−0.1, 4.1)
Labruyère (2014), ¹⁵ 8 wk A: exoskeleton B: strength training	Mean Δ from baseline A: 0.7 (SD NR) B: 1 (SD NR)	Mean diff (95% CI), ^f A versus B: 0.3 (−0.9, 1.55) <i>p</i> = NS
Shin (2014), ¹⁷ 4 wk A: exoskeleton + PT B: OGT + PT	Median (IQR) at 4 wk A: 37 (20, 49) B: 37 (20, 48) <i>p</i> = NS	
Bowel function		
Huang (2015), ¹⁸ 4 wk A: exoskeleton + manual therapy B: BWSTT + manual therapy + standard rehabilitation	Defecation time (min), mean Δ from baseline A: −28.5 ± 8.8 B: −14.5 ± 9.8 Enema volume (mL), mean Δ from baseline A: −29.3 ± 7.5 B: −10.8 ± 8.7	Mean diff (95% CI): −14 (−21.4, −6.6) Mean diff (95% CI): −18.5 (−24.9, −12.02)

Abbreviations: BWSTT, body weight-supported treadmill training; CI, confidence interval; CT, conventional training; diff, difference; F/U, follow-up; IQR, interquartile range; LEMS, lower extremity motor score; LMN, lower motor neuron; NR, not reported; NS, not significant; OGT, overground training; PT, physical therapy; TT, treadmill training; UMN, upper motor neuron; SD, standard deviation.

^aUnless otherwise indicated, all values are reported as mean ± SD.

^bEsclarín-Ruz et al (2014)¹¹ is a subgroup analysis of Alcobendas-Maestro et al (2012).⁸

^cRight leg lower extremity motor score data also reported, not statistically different from left leg lower extremity motor score data.

^dIt is unclear if authors evaluated the control group after the initial control treatment (12 weeks) or if they were evaluated after crossing over to robotically assisted body weight-supported treadmill training (24 weeks).

^eThese values were estimated from Fig. 4.

^fThe 95% CIs were estimated from Fig. 4, point estimates were calculated using values in Table 2.

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Table 4 Quality of evidence evaluating exoskeletons as assistive or rehabilitative devices in incomplete or complete SCI

Outcome	Follow-up	Studies (N)	Serious risk of bias	Serious inconsistency	Serious indirectness	Serious imprecision	Conclusions	Quality
Key question 1: exoskeletons as assistive devices								
							No comparisons available	No data
Key question 2: exoskeletons as rehabilitative devices								
Exoskeleton versus nonexoskeleton rehabilitation strategies ^a								
10MWT	8 to 12 wk	5 RCTs ^{8,9,12,14,15} (N = 319)	Yes (-1)	No	No	Yes (-1)	No significant difference between groups except for 1 high risk of bias crossover study that reported strength training improved speed more than exoskeleton Subgroup analyses: patients with higher versus lower baseline walking capacity ^b improved more with exoskeleton versus non-exoskeleton rehabilitation; LMN versus UMN did not modify the effect of exoskeleton rehabilitation	Low
6MWT	8 wk	2 RCTs ^{8,14} (N = 115)	No	Yes (-1)	No	Yes (-1)	No significant difference between groups Subgroup analyses: neither higher versus lower baseline walking capacity ^b nor LMN versus UMN modified the effect of exoskeleton rehabilitation	Low
WISCI/ WISCI II	4 to 8 wk	5 RCTs ^{8,9,14,15,17} (N = 314)	Yes (-1)	Yes (-1)	No	Yes (-1)	Mixed results; a majority of included studies (3/5) found no statistically significant mean difference in scores between exoskeleton and non-exoskeleton rehabilitation; two studies found that median scores were significantly improved in exoskeleton groups Subgroup analyses: LMN versus UMN did not modify the effect of exoskeleton rehabilitation	Very low

Table 4 (Continued)

Outcome	Follow-up	Studies (N)	Serious risk of bias	Serious inconsistency	Serious indirectness	Serious imprecision	Conclusions	Quality
FIM-L	8 wk	2 RCTs ^{8,14} (N = 115)	No	Yes (-1)	No	Yes (-1)	Mixed results; one study found no significant difference in mean FIM-L scores between exoskeleton and non-exoskeleton rehabilitation groups, and the other study found that median FIM-L scores were significantly improved in the exoskeleton group Subgroup analyses: patients with UMN versus LMN improved more with exoskeleton versus non-exoskeleton rehabilitation	Low
SCIM	4 wk	2 RCTs ^{15,17} (N = 69)	Yes (-1)	No	No	Yes (-1)	No significant difference between groups	Low
Exoskeleton versus tizanidine								
10MWT, Fast velocity	4 wk	1 RCT ¹⁰ (N = 83)	Yes (-1)	Unknown	No	Yes (-1)	No significant difference between groups	Low
6MWT	4 wk	1 RCT ¹⁰ (N = 83)	Yes (-1)	Unknown	No	Yes (-1)	No significant difference between groups	Low
Exoskeleton versus no training								
10MWT, Fast velocity	4 wk	1 RCT ¹⁰ (N = 83)	Yes (-1)	Unknown	No	Yes (-1)	No significant difference between groups	Low
6MWT	4 wk	1 RCT ¹⁰ (N = 83)	Yes (-1)	Unknown	No	Yes (-1)	No significant difference between groups	Low
Key question 3: safety of exoskeletons as assistive or rehabilitative devices								
Exoskeletons as rehabilitative devices								
Skin irritation or abrasion	3 and 6 mo	1 RCT ¹³ (N = 66)	Yes (-1)	Unknown	No	Yes (-1)	Skin irritation or abrasion associated with exoskeleton use was rare	Low
No adverse events	8 wk	2 RCTs ^{9,15} (N = 139)	Yes (-1)	No	No	Yes (-1)	No additional adverse events occurred in the two studies that mentioned adverse events explicitly	Low

(Continued)

Table 4 (Continued)

Outcome	Follow-up	Studies (N)	Serious risk of bias	Serious inconsistency	Serious indirectness	Serious imprecision	Conclusions	Quality
Exoskeletons as assistive devices								
							No comparisons available	No data

Abbreviations: 6MWT, 6-minute walk test; 10MWT, 10-meter walk test; FIM-L, Functional independence measure- leg; LMN, Lower motor neuron; RCT, randomized controlled trial; SCIM, Spinal Cord Independence Measure; UMN, upper motor neuron; WISCI, Walking Index for Spinal Cord Injury.

Note: Baseline quality rated as follows: high = majority of articles are observational; upgrade: large magnitude of effect (one or two levels), dose-response gradient (one level), plausible confounding decrease magnitude of effect (one level); downgrade: risk of bias (one or two levels), inconsistency of results (one or two levels), indirectness of evidence (one or two levels), imprecision of effect estimates (one or two levels).

^aRehabilitation strategies included overground training with physical therapy, gait training with the GT1 end-effect device with conventional training, treadmill training with manual assistance, treadmill training with stimulation, overground training with stimulation, overground training alone, therapist-assisted bodyweight supported treadmill training, and strength training.

^bHigh walking capacity defined by high 10MWT velocity and Timed-Up-and-Go (TUG) test times, and high 6MWT distance at baseline. Low walking capacity defined by low 10MWT velocity and TUG test times, and low 6MWT distance at baseline.

The neurologic status at the time of admission was American Spinal Injury Association (ASIA) B. Further radiologic diagnostics showed a dislocated fracture and led to dorsal spinal fusion of C2 through C4; additional figures can be seen in the online supplementary material (►Figs. S1 and S2).

Due to expected prolonged dependency on respiratory support, the patient received a percutaneous tracheostomy. Subsequent to fracture consolidation and weaning from the respirator, the patient was started on BWSTT using an EMG-controlled exoskeleton (HAL) using the protocol of Aach et al.¹⁹

The neurologic status at the time of enrollment was ASIA C; an additional figure can be seen in the online supplementary material (►Fig. S3).^{19,20}

Throughout the 12-week intervention, treadmill performance improved significantly in terms of speed, distance, and time on the treadmill. Video demonstration can be seen in the online supplementary material (►Video 1). Assessment of functional walking abilities without the exoskeletal device measured by the 10MWT improved significantly as measured by time needed to ambulate a 10-m distance and the assistance needed (WISCI II; ►Video 2, online supplementary material). The patient regained important motor functions as assessed via LEMS, leading to an improved walking ability that enabled her to ambulate short distances and even over everyday obstacles (e.g., stairs) without personal assistance; a video showing the performance on stairs can be found in the online supplementary material (►Video 3). The neurologic status after 12 weeks of HAL BWSTT improved to ASIA D; an additional figure can be seen in the online supplementary material (►Fig. S4).^{19,20}

Discussion

In the 1960s and '70s, initial research was conducted in the field of motorized exoskeletons. Due to the size and weight of the technology, it was deemed unfeasible compared with conventional KAFOs. Therefore, the research was discontinued.^{21,22}

However, SCI remained a devastating and disabling condition often resulting in significant gait limitations. To restore mobility, a weight-bearing locomotion training system was introduced into SCI rehabilitation programs. Over the past 15 years, fixed exoskeletons, primarily the Lokomat, emerged as a relatively frequent technology in SCI rehabilitation.

We looked for but were unable to find any studies evaluating exoskeletons as an assistive device compared with conventional KAFOs. With respect to evaluating exoskeletons as a rehabilitation device, we found nine RCTs. Though there was heterogeneity with respect to comparison groups, co-interventions, outcomes, and study design, these nine studies revealed no significant differences in velocity on the 10MWT and SCIM scores comparing exoskeleton to conventional locomotion rehabilitation. There were mixed results among some of the studies with respect to the 6MWT, WISCI, WISCIII, and FIM-L scores.

Table 5 Control and purpose of exoskeletons used with patients with spinal cord injuries

Exoskeleton	No. of case series	No. of patients	Purpose
Joystick control			
Rex-Bionics (Rex-Bionics, Auckland, New Zealand)	None	0	Assistive mobility device
Lokomat (Hocoma, Switzerland)	8 ^{30–37}	159	Rehabilitation
WPAL (Fujita Health University, Japan)	2 ^{38,39}	11	Assistive mobility device
Kinesis (Technaid, Madrid, Spain)	1 ⁴⁰	3	Rehabilitation
Posture control			
Re-Walk (Argo Medical Technologies Ltd, Yokneam Ilit, Israel)	7 ^{41–47}	66	Assistive mobility device
Ekso-Bionics (Eksobionics Ltd, Richmond, California, USA)	2 ^{26,27}	10	Rehabilitation
Indego (Parker Hannifin Corp., Macedonia, Ohio, USA)	2 ^{48,49}	21	Assistive mobility device
EMG control			
HAL (Cyberdyne, Tsukuba, Japan)	5 ^{3,23–25,28}	30	Rehabilitation

Abbreviations: EMG, electromyographic; HAL, Hybrid Assistive Limb; WPAL, Wearable Power-Assist Locomotor.

As new technologies enabled the development of motorized wearable exoskeletons, several types have been introduced to SCI rehabilitation. The available exoskeletons can be subdivided according to their control mode into joystick, posture, and EMG controlled (► **Table 5**).

Different applications are possible depending on the control mode of operation. Joystick- and posture-controlled exoskeletons enable the patient to regain mobility while wearing the device to compensate for the functional loss of the lower limbs. In contrast, EMG-controlled devices integrate the patient's voluntary drive in the walking pattern, because it requires an active contribution of the patient's lower limbs. This neuronal feedback may lead to or implicate neuronal plasticity and normalizes cortical excitability. Furthermore, some believe this mechanism leads to increased patient mobility when not wearing the exoskeleton, even in patients with chronic SCI.^{3,23}

There is a certain optimism that exoskeletons, primarily mobile exoskeletons used as rehabilitation devices (e.g., HAL, and to some extent, Ekso-Bionics), have potential to improve walking patterns after the device is removed.^{3,23–28}

In our study, adverse events were infrequently reported in literature, with only one trial indicating skin irritation or abrasion from exoskeleton training. There were no reports of falling or pressure sores.

Although case series provide some optimism with respect to the use of exoskeletons in locomotion rehabilitation for SCI (► **Table 5**), this optimism has yet to be validated in randomized trials. Studies of newer exoskeletons comparing them to current rehabilitation strategies are needed.

Conclusion

There is no data to compare locomotion assistance with exoskeleton versus conventional KAFOs. There is no consistent benefit from rehabilitation using an exoskeleton versus a variety of conventional methods in chronic SCI patients. Trials comparing later-generation exoskeletons are needed.

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Editorial Perspective

Over the last 30 years, the treatment for acute SCI has largely focused on three areas:

- Optimizing patient retrieval and resuscitation during the postinjury phase
- Timely decompression and surgical stabilization where appropriate
- Rehabilitation with efforts concentrating on returning patients to functional independence, relying largely on wheelchairs or bracing with mobilization aids in some patients

Additional areas of SCI care have largely focused on pharmacologic interventions, such as use of high-dose steroids as a powerful anti-inflammatory medication aimed at decreasing expansion of the secondary injury zone. Continued controversy remains about the role of this medication. Further pharmaceuticals and hypothermia, all largely with similar intent to limit secondary injury zone damage, are currently undergoing prospective trials. Taken together all of these efforts have led to improvements of patient survival but have shown to be limited in their potential for further SCI recovery.

Emerging experimental modalities for potential spinal cord repair attempt to stop neuronal apoptosis or induce cell regeneration through stem cell implantation or molecular interventions. Although these therapeutic concepts have raised substantial public interest through sensationalistic media coverage, there is little actual scientifically confirmed evidence that these treatments work in the lab using large mammals or in patients. For the foreseeable future, this important arm of research will need to grapple with a number of overwhelming foundational obstacles prior to providing SCI patients with veritable hope for meaningful SCI recovery.

Robotic devices that augment paralyzed or paraparetic lower extremity function have been a long-held dream of futurists and part of some attempts of patient care since the 1970s. With mainstream treatments as well as cellular treatments having arrived at somewhat of an impasse, there has been a renewed interest in utilizing robotically driven technol-

ogies for mobilization and perhaps even as a neurorehabilitation tool. To our knowledge, this is the first systematic review of the current evidence base for use of these devices and categorizes them into more conventional passive mobilization assistive devices versus active neurorehabilitation technologies.

The enclosed assessment provides an important insight into the difficulty of proving recovery in patients with incomplete SCIs. Designing a prospectively randomized trial is challenging due to the limited number of patients and the high degree of variability in their circumstances. Doubters will always be able to challenge any recovery claims by asking about the natural recovery potential of patients if they had not been treated. That said, the investigators and patients appear to be very excited about the potential for improved mobility or even functioning in an upright position.

On a positive scientific note, there seems to be increasing consistency in measuring the function of patients with incomplete SCIs. In addition to the conventional lower extremity motor score, the 10-meter walk test, and the 6-minute walk test, as a general functional measure, WISCI II appears to be more commonly used as an objective performance assessment. Unfortunately, important additional factors such as spasticity, urinary control, sensory recovery, and defecation measures apparently are not yet part of the routine assessments to measure rehabilitation progress. Similarly, patient satisfaction and other patient-reported outcomes were not assessed in these presented studies. To date, the reported results are inconsistent compared with conventional therapy. Longer-term outcomes of affected patients such as osteoporosis, pathologic fractures, or skin breakdown are yet to be assessed. Similarly, the persistence of any motor function gains has yet to be established. Nonetheless, these more recent advances in robotics and their human interface in terms of “neurorobotics” stand to offer far more near-term real-life hope for recovery of function and upright mobilization than current established treatment or neuronal cell regeneration therapies. The other main option is based on using robotic devices such as used in form of motorized braces (“exoskeletons”).